Steve Lewis 00:09
Welcome to Speaking of Mol Bio, a podcast series about molecular biology and its trending applications in life sciences. I'm Steve Lewis, and my guest today is Dr. Nick Meyerson, CEO and co-founder of Darwin Biosciences. Since 2020, Nick and his team have developed saliva-based diagnostic tools for infectious diseases. His work has already made a difference in the COVID-19 landscape and shows a lot of potential for a wide variety of future applications. We hope you enjoy our conversation. We begin by asking Nick about his academic background, and how he became interested in the work that led to the founding of Darwin Bio.

Nick Meyerson, PhD 00:53
My background is mostly in science and ended up doing a PhD in molecular virology. And I was really studying how viruses, in particular, are able to cross species barriers, and I really loved what I was doing. It was, there was an evolutionary slant to the study and also, it turned into something very important. Obviously, as the pandemic hit, I was able to really adapt a lot of the knowledge I learned during my PhD to start the company. And I ended up doing a postdoc at University of Colorado, Boulder, which took me from Austin to Boulder. And it was during that time that we were researching a really interesting signature in saliva. So I should say Darwin Biosciences is a saliva-based company. So we think of ourselves as experts in saliva and we're really excited about it for a lot of reasons and I'm sure we'll talk more about that. But ultimately, some of the research that I was doing during my postdoc, which was funded by the Department of Defense, led to the basic scientific discoveries that started the company. And ultimately, what that was, is very early immune signatures that your body produces in response to pathogens, we were able to find them in saliva and that motivated us to try and leverage that to create a diagnostic for infectious diseases.

Steve Lewis 02:17
We love a really diverse background on the Speaking of Mol Bio podcast. What was that transition like for you learning how to be a biologist?

Nick Meyerson, PhD 02:26
Intimidating, like so many of the other challenges that I've taken on since then. But I would say generally, during those transition phases, what has benefited me more than anything, is having the right mentors in place. So Sarah Sawyer, my PhD advisor, who I helped move her lab to Boulder to continue working with her as a postdoc, she is still a mentor to me, she's involved in Darwin, she's a co-founder, she's an advisor to me still. And she played a pivotal role in allowing me to make that transition with confidence, knowing that I could ask all the questions that I needed to, and I had the resources to not just make mistakes, but also enjoy all the benefits of learning new things. So, I think it was scary because I had no idea what I was getting into, and especially so in meeting my classmates who mostly had biology degrees and were quite fluent in a lot of the subject matter. So, it was clear that there was a huge challenge ahead of me, but I, I just loved the experimental aspect of things so much that I was very driven to know everything that I could and work as hard as I could to make sure that I could succeed.

Steve Lewis 03:42
That's phenomenal. And I had the fortune of actually going and seeing your lab and seeing your space down in Boulder, Colorado. And why don't you tell us a bit about Darwin and what you're building today and its current shape and form?

Nick Meyerson, PhD 03:56
Sure. So, I'll start by saying one of the coolest things about Darwin is that we are fully funded by the Department of Defense through one of their agencies that specializes in medical countermeasures is what it's called, that sounds scary, but don't worry, we got it covered. This agency is called the Defense Threat Reduction Agency. And we started working with them, or I did, as a postdoc in Sarah's lab, because we had a basic science grant. And they were seeing some of the things that we were working on and they had the foresight to take some of the discoveries that I was describing over dinner effectively, and asking, you know, "It seems like maybe you could take that and harness it in a diagnostic device that soldiers could use every day to just tell them if they're sick or not." What they told me next has kind of centered everything that we're doing. They said, "You know, the reason we want that is right now the state of the art in the military, and really everywhere, for determining if you're sick without knowing what you're looking for, is the thermometer." And ultimately, they said, "You know, we really need kind of like the next-generation thermometer that works better, is kind of more specific to pathogens, but not too specific. And ideally, it acts earlier, even before people have symptoms before they know they're sick, right?" So that sounds cool. It sounds like science fiction, and that's why it motivated me to do what we're doing. And ultimately, that's exactly what the immune signatures that I had been studying for over a decade at that point, that's what they do. And so just to dig in a little more on that, your body has a very early immune response called innate immunity. And it's amazing, because every single one of the cells in your body has these, they're called molecular sensors, that can detect these foreign molecules from pathogens, called pathogen-associated molecular patterns. And when they detect that it turns on this signature that kind of flows throughout your whole body as a warning system, and signatures from that early response, RNA molecules from that response, we discovered end up in your saliva. And so in our product at Darwin, we are harnessing that signature in saliva, in a device that then allows you to collect saliva, and then can amplify those RNA signatures in saliva and allow you to detect them on something we're all familiar with now, it's called a lateral flow strip, right? The one red line, two red line thing. And so at Darwin, right now, our first product is all centered around an easy-to-use device that doesn't require any electrical power, that tells you something very simple. Am I sick? And am I contagious? You won't know what you're sick with or what you're contagious with but it's really the start of the entire kind of diagnostic pipeline. And going all the way back to where I started with talking about the thermometer, we think of our product as a molecular thermometer for the future.

Steve Lewis 07:16
There's a lot of directions that we can go, I think I'm curious to understand how you came to be a company first, because not many people get that exposure or access to the Department of Defense and non-diluted capital as well, which is pretty wonderful as a startup. So I'm curious for your perspective, how did you know that working with the DoD was the right thing, and what was that moment like?

Nick Meyerson, PhD 07:45
I would say, like, pretty much everything else I've done, I kind of fell into it as strange as that sounds, but it really started with work that I was doing as a postdoc. And like I said, Sarah, my advisor at the time, had gotten a basic science grant from DTRA, this agency of the, in the DoD that deals with medical countermeasures. And that's where all the basic science happened, right? And it led us to the discovery that there are these interesting signatures in saliva. And then taking those observations to our program officers. They were the ones that saw that discovery, and asked about the ability, if we had the ability to turn that into a diagnostic the one that I described. And at the time, it absolutely was not something that had ever crossed my

mind. It's not a logical step to take, given what we were studying. So, my response to that was, "No, I've never thought about developing a diagnostic device." But the program officer kind of kept pushing that thought and opened up this whole path, right, where they said, "Look, the DOD has mechanisms to fund early research," which is what they were doing for us, they said, "but when we identify something interesting, and especially if it's the continuance of a project that we originally funded, there are ways that we would like to continue to fund that research if there's a product development goal in mind." What I realized after further conversations, and really thinking hard about what a product might look like, it was clear that they were dead serious, and they are, you know, over the course of the next two or three years, from basically 2017 to 2020, it was clear that there was a real possibility of me formulating this idea further, putting together a proposal and getting money and support from the DOD to start a company and actually try to develop this product. It ultimately ended up leading to a development contract with this organization that didn't land until 2021, we officially founded the company in March of 2020 thinking that we were close to getting a contract with the DOD. And we all know what happened in March 2020. So, the country shuts down and of course, the DoD is, their messaging immediately changes, saying, "Yep, you know, sorry, Nick, it's not exactly the best time for us, we're a little distracted." So, you know, maybe another story if you wanted to get into it. But you know, I had founded a company, I was excited. And then I realized, uh oh, I don't know what's happening next. So, there was kind of this interesting wall between March of 2020 and June of 2021, when we actually got our development contract, where we had to do something. And ultimately what we did, I quickly invented a saliva-based test for SARS-2 that ended up getting used around Colorado and Nebraska that actually bootstrapped the company and allowed us to grow a little bit to get ready for the development contract with the DOD. So that was a, quite a crazy time in the in the company history, but we survived it, you know, we got to the contract with the DOD and since then we've been developing our product, and we have multiple prototypes. So you know, I think everyone has their pandemic story, and ours was, it couldn't have been more relevant to what was going on but it was a little scary to have founded that accompany and then everything changes a couple of weeks later.

Steve Lewis 11:30
The idea that you're getting signatures from saliva, and that they are nonspecific, right, that in a way, because they look at the innate immune response is just pretty mind blowing, honestly. I know that our listeners love to dive into the science as well. So let's, let's make our way there. Do you mind describing a little bit about the actual physical device housing? And then we'll move down to the molecular level?

Nick Meyerson, PhD 11:59
Absolutely, so it's a single device. So, it's a disposable device, about the size of a, well, they're scientists listening, about the size of like a 15 mL Falcon tube is about, you know, it's like half of that kind of thing. And it comes in two pieces. So, there's one piece that we call the collection swab. And it looks like a cotton swab, essentially, that you might use at a dentist's office, and that goes into your mouth, and absorbs about 1 mL of saliva. And then ultimately, that goes into a central cartridge, that that's where all the magic happens. So, I'll start very broadly, and just say there, there's, I think, three to five important things happening. One is saliva collection. Once it goes into the device, the saliva goes through a series of filters and pads that have lyophilized in them, reagents to lyse cells and preserve RNA. So, what's interesting about this sort of point of need is we don't have time to run purification columns, for example, in centrifuges. And so, we have to do a very quick and crude extraction, which we have been able to accomplish in our device by these filter stacks that we have. And so there is again, going back to saliva collection, there's a quick processing step to liberate and preserve RNA. And that

crude extraction goes into a pad, where amplification starts occurring. At the same time that that's happening, right when the sample goes into the cartridge, a really cool thing happens. We have engineered a chemical heater in the device that gets activated and goes to a certain temperature and holds there for about 15 or 20 minutes. And that's important for a number of reasons. It obviously takes heat and energy to run an amplification reaction. But we don't have to do temperature cycling because of the kind of amplification that's going on in the device. So, the heater heats up, it holds a temperature, and it drives what's called an isothermal amplification reaction that's happening in the middle of the device with that extracted saliva sample. And there's a lot of different isothermal chemistries, and I'm sure we can dive into that. And then ultimately, once the reaction is complete, there's a mechanism on the device and those amplicons flow onto a lateral flow strip. And there's basically small molecules and antibodies that can capture those DNA amplicons, and it resolves it into a red stripe on a lateral flow strip. So all the way, this thing that's typically confined to complicated or at least medium-complexity labs, collecting a sample, purifying nucleic acid, doing an amplification with a target, and then detecting that, we've taken those things and put them in the palm of people's hands. So, and it's, I'd say, really due to a lot of different advancements that happened relatively recently, that finally allows someone like me to put all those pieces together.

Steve Lewis 15:24
 And now back to the episode. Talk to us a bit about the chemistry because that is a hot topic, a hot application area, if you will, despite the isothermal nature of if you'll pardon the pun.

Nick Meyerson, PhD 16:23
Well, some of them do still require a high temperature, there's just no cycling, right? So, getting back to the very first thing we were discussing about the magic of PCR, right, which I still think it is pretty cool how it works. The key to that technology is a couple of things. One, cycling, right, temperature cycling, because typically you need a way to make DNA come apart, and then allow things to bind to it. And then bring it back apart again to do another cycle, right? So now isothermally, the trick is how do you get the DNA apart if you can't get up to high temperatures? And this involves a word that you used earlier, actually, Steve, a recombinase, in order to unwind DNA. So this is happening all the time in your body, right, your body doesn't get up to 95 degrees Celsius to undergo replication. But somehow DNA gets unwound and it gets replicated, right? So, it's really harnessing enzymes from that process, recombinases, and something called a strand-displacing polymerase that not only do you have something that can unwind DNA and put a primer on a target, but once the polymerase takes off, it basically works as kind of like a zipper almost, just kind of blasting things in its way to continue polymerizing and replicating something. So generally, these isothermal technologies require some kind of strand displacement, recombinase, or some magic primer design that allows strand invasion to occur. And so, again, there's at least 10 to 15 different chemistries. But typically, they solve the problem somehow of displacing double-stranded DNA.

Steve Lewis 18:27
You started out this conversation, expressing your interest, in a way, around the concept of diseases that are potentially zoonotic in origin. And I'm curious what you think today, where

we're headed for the coming years with what your technology builds, or excuse me, enables today? And then what it will enable for the future both for my perhaps preventative perspective, and maybe even ultimately, from a therapeutics perspective?

Nick Meyerson, PhD 19:02
So let me start with preventative. Our product is basically measuring the activation of your immune system. Okay, so that's, again, that's why sort of this concept of molecular thermometer is so valuable to think about. Nevertheless, we're inferring based on that, that you're infected with something. In my opinion, that's more of a detection product than a diagnostic. And so from a preventative standpoint, it's going to be so valuable to have a tool like that moving forward, when we don't know what we're supposed to be looking for. I would say the response that we had in the first few months of the pandemic was incredible. It really didn't take that long to go from thinking there's something new here to having a qPCR test to detect it. You know, even its genome, the genome of SARS-2 is what I'm referring to, was available pretty quickly, within a couple of months, I think. But people will always wonder, what if we had a way of just sensing where this unknown thing was, during those two months? Would that have changed the course of the pandemic? We'll never know. There's people that would say, “100% yes,” right? I mean, even a day would have changed things. And even if there's a test available, it's not going to be immediately accessible. So even though, like, qPCR tests were available, a few months after the pandemic started, at-home tests weren't accessible for, I think, at least a year or so. And so, it's important to have something that's ready to go no matter what the pathogen is. And that's kind of what we're offering. And it's always something that I have to think through, and I don't have a very obvious answer to this. But there's always the question of, “What's the real value in knowing that you're infected, but you don't know what it is?” And I would say, from a bio surveillance standpoint, there's nothing more important than that, right? I just need to know where something is. So, I think from a preventative standpoint, our technology will be very valuable, because if you don't know what you're looking for, that's exactly what we're providing a solution for. So that's very much, you know, bio surveillance kind of application of what we're doing. But moving into the clinics, there's a lot of interesting statistics around infectious disease. And I'll give you just one that we're kind of focusing on to some extent, which is of individuals that present to emergency departments or infectious disease clinics that have what's called febrile-like illness. So, symptoms that you would normally associate with being sick, fever, runny nose, cough, etc. Only about 50% of those individuals, at best, end up getting ID'd with a pathogen. And the other 50%, you're left wondering, “Are you infected with something and if you are, is it just, is it something we don't know, we don't have a test for it, or is there like a new pathogen?” So, there's generally a need just to identify if somebody is infected with something at all, before running more and more tests on them. So then going to the last point that you touched on therapeutic application. So, I'll say just one thing about that. We think that our product could be used to the advantage of companies developing antiviral, or antibacterial drugs. And the reason is, because our device detects when your immune system gets turned on, which happens before you know that you're sick, before you have symptoms, or even in some cases before the pathogen titer goes up to a significant extent, it could be used as a tool to tell you to administer a drug sooner than you would otherwise. So, if I'm some company that's running a trial, for an anti-flu medication, typically, I would only administer that drug when people develop symptoms in my trial. But if we can use our device to say, “Well, we actually know this person is infected now, even though they don't have symptoms, let's give them the anti-flu medication here”. That would almost certainly lead to a higher effect or better health outcomes for individuals taking those drugs, than it would if you wait until, you know, later on in the disease progression.

Steve Lewis 23:51
Talking a little bit about some of your application workflows, do you mind sharing a bit about some of the molecular biology techniques that you might have used to, A, develop this technology, and then, B, what you're using today and how you may have expanded?

Nick Meyerson, PhD 24:08
The development process, I would say really, even before the company existed, how did we find these interesting signatures? And so again, the signatures are RNA based. And the study that we that I was working on as a postdoc, one of them, was in collaboration with an infectious disease clinic at CU Anschutz, and we were effectively collecting any biospecimen that we could, from people presenting to an infectious disease clinic. What we were doing was extracting RNA. So, it was my job along with another graduate student at the time that I was working with to try to figure out how do you get a good RNA prep out of things like saliva? There's not really a standard; there is for things like blood. But it really started with how to handle saliva. It's hard to work with for a lot of reasons, there's a lot of RNases, things tend to degrade. It's generally unstable. So, from a molecular technique standpoint, it was important to establish how are we extracting RNA out of saliva. And then ultimately after that, once we got that done, we were using pretty common techniques to figure out what's in it. qPCR, high throughput sequencing, all that stuff comes back to the table. So we weren't inventing anything new there. And now in the device, I will say, I mean, the isothermal chemistry that we use, we didn't invent, it's been around since 2004. It's called recombinase polymerase amplification. There's traditionally been a very small number, really one, company that's provided kits for this because of patent protections, which are very soon to be lifted. And I know a lot of companies are going to start making more RPA reagents. And it's very exciting for us and a lot of other companies because it works so well. The great thing about it is the temperature that it runs at. It can run at 37 to 42 degrees Celsius, which is really low. So compared to other isothermal chemistries, it wins out on that front. It happens to be very, very fast and effective and reproducible. Otherwise, as far as detection on the lateral flow strip, there's a number of advancements that we had to make or think about, because of the use of saliva. Saliva, and even some of the reagents involved in the isothermal chemistry, create problems for lateral flow strips either because they run so slow, or they create background signals, false positives effectively show up a lot. Just because saliva is very dirty and in RPA reactions, there's really a lot of protein, it's pretty concentrated. So, I think there were really a lot of tricks that we had to figure out based on those two things, I think more than anything. But really, there was a lot of engineering feats to accomplish to like fully integrate everything that I've been describing between saliva collection, crude extraction of RNA, preservation of RNA, isothermal amplification, chemical heating, and then lateral flow detection.

Steve Lewis 27:24
There are a lot of really interesting applications here. And earlier in our season, we spoke with Bev Wood, which is, excuse me, she is from North Carolina, and a part of some of the bio surveillance work as it relates to livestock. And the USDA, at least in the U.S., our agency, has the Foreign Animal Disease Diagnostic Laboratories. And right now, what we are seeing at the time of this recording, is that there are potential jumps of avian influenza to cattle. And that has been discovered in a few states, do you think that your technology has a role to play, also, in animal health?

Nick Meyerson, PhD 28:15
We've thought quite a bit about that. The immune response that we detect in our device in humans, is conserved in all mammals. And even beyond that to effectively anything on land. So there's no doubt that cattle and birds have this response in them. It would require a bit of

adaptation of what we're detecting, right? The genes that we're detecting in humans aren't perfectly conserved in birds and cattle. But the response is, so you could very well imagine a version of our device that's used to detect early immune responses of birds, and cattle. I think in those cases, however, given the course of action, which is typically heard culling, it's more important to detect specifically what you're looking for. You know, livestock tends to have, just like humans, some kind of pathogen landscape that's antagonizing them at any certain time, and not necessarily every infection is going, should result in the culling of a herd, so to speak. So I do think with agricultural applications, it is more important to have specific detection mechanisms, because there are things that you're really worried about in order to take that kind of severe action versus something that would be similar to say a common cold. The thing that we've thought about also, people ask this question a lot is, “Is there a market for pet health?” Right, so people are more involved in their pets’ daily lives, I would say these days dogs and cats. And would we want a version of our device just to generally tell you something about your pet? I think there's a really interesting market there. Because people do, I know plenty of people that they get pretty riled up and concerned when their animal is acting weird, right? They're like, are they sick? Are they hungry? Did they eat something bad? So, I think there's a potential market and application for what we're doing with what I like to refer to as fur-baby health.

Steve Lewis 30:31
I love it. This has been just an incredible interview where you have done a little bit of everything, I would say. You have done multiple disciplines within science, you are both an academic in experience and also an entrepreneur, and you worked in a world that not many people have. We always like to end our podcast by asking two questions. And the very first one is, what advice would you give to somebody looking to follow in your footsteps?

Nick Meyerson, PhD 31:06
I think I would say, to not get bogged down in a particular path. There's no real surefire way to end up where I am. And it's more important to work on things that you're interested in. Because I get that question all the time, “How did you end up where you are?” and we've touched on that a little bit here and there. And it's, it's really for me, it was just following curiosities. If you truly want to have ownership of an idea to push forward, then just study something that's interesting. And I would say the other important thing is to find really good mentors, people that encourage your curiosity, that answer questions that you have, and give you constructive criticism.

Steve Lewis 31:59
That's great. And our second question is somewhat similar, but more personal to you. What have been the keys to your success?

Nick Meyerson, PhD 32:09
I think there's a pretty big element of luck and timing associated with it. But I also think I've been almost I would say, obsessed again, with wanting to know what are all the cool things going on. Probably the best thing that has set me up for that is reading a lot. I still, to this day, try to read at least one scientific paper a day, it doesn't matter what field it's in. It's not always in, you know, isothermal amplification with respect to diagnostics and infectious disease. It's just like, I'll see a paper and I'm like that, I want to know more about that. And I've told that a lot to my scientific team, because you just have no idea what you're going to find. And it also allows you to have this interesting perspective with like, what drove this particular scientific team to ask the questions that they did. So frequently, when we're stuck on a problem, and this goes back all the way when I was in grad school, it would always help me reading papers to say, what how did they come up with this crazy idea? You know, that didn't just come out of nowhere, there was a whole thought process that led to something. So I would say, one thing that's really

allowed me, I think, to do what I do, and end up where I am, and continue to be creative in thinking about what our product can do is the breadth of knowledge that I've been able to gather over the years. And I don't mean just because I have a degree in physics and a degree in molecular biology, because I read as much as I possibly can. And truly everything kind of interests me, so I think, and that's things that you can do for free, right? Anyone can do that right now. Just go read about stuff that's interesting. And especially if you're if you're in a creative space, I think it's really valuable to read more about kind of what's on the periphery and things that maybe aren't directly associated with what you're doing. But they could be, and really sort of the creative process by which people came to have those ideas, I would claim is probably always going to be valuable.

Steve Lewis 34:32
Nick Meyerson, this has been just such a pleasure getting to know you and a bit more about Darwin. Thank you so much for your time today. And we're so lucky to have had you and I hope you have a great rest of your week ahead.

Nick Meyerson, PhD 34:47
Thanks a lot, Steve. It was great chatting with you.

Steve Lewis 34:52
That was Dr. Nick Meyerson, co-founder and CEO of Darwin Biosciences in Boulder, Colorado. Speaking of Mol Bio is produced by Matt Ferris, Sarah Briganti, and Matthew Stock. Join us next time for more fascinating discussion about the amazing world of molecular biology. Until then, cheers and good science.