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John Williams: Hi. From UPMC Children's Hospital of Pittsburgh, welcome to That's Pediatrics. I'm one of your hosts, John Williams, Chief of Pediatric Infectious Diseases, and my co-host-

Steph Dewar: Hi. Steph Dewar, one of the members of the Hospitalist Division and Co-Director of the Pediatric Residency Program. Today we have Dr. Tom Diacovo, who is the Chief of the UPMC Newborn Medicine Program and Director of Neonatal Cardiovascular Research at the Heart Institute. Dr. Diacovo is an internationally-recognized leader in thrombosis research, and he's led the development of pharmacological agents and devices specifically designed for neonatal intensive care patients, particularly those with congenital heart disease who are at high risk for forming blood clots. Dr. Diacovo, I'm so happy that you're here today to join us on this podcast.

Dr. Tom Diacovo: Well, it is a pleasure to be here with both of you.

Steph Dewar: So, I was reading over some of your interests and background and found it so curious that a neonatologist is interested in this aspect of medicine. Could you tell us a little bit about how that came about?

Dr. Tom Diacovo: Well, it actually began with my fellowship back in Boston where we were required to do our research projects. I became very interested in understanding, initially, the trafficking of white blood cells into tissues and how they actually combat infectious agents. I found a lab that actually pioneered the development and identification of adhesions and activation pathways that promote the ability of white blood cells to get into tissues where they can carry out their immunological functions. While I was there and trying to be a diligent post-doc in that lab, and to impress my mentor, I was working on a project where we were identifying proteins on the surface of white blood cells. A colleague of mine was next to me.

Dr. Tom Diacovo: I needed to get an antibody that matched the antibodies on the surface of the white blood cells, and I took that antibody and was using it to actually characterize it on platelets and found that his antibody actually reacted when it shouldn't have reacted on the surface of the platelets. It turned out to be a new adhesion molecule that was actually important in helping the white blood cells to traffic to sites of vascular injury. So, when platelets actually stick down at sites of vascular injury they actually have to recruit white blood cells to there, and that particular protein was actually important in allowing white blood cells to get to the site of vascular injury.

Dr. Tom Diacovo: From there I guess that was serendipity and became very interested in many aspects of thrombosis, and actually went on a career in actually determining how platelets actually interact with sites of vascular injury, became interested in actually trying to understand that in vivo. And realizing that mice are not really equivalent to humans, went on to actually develop the first humanized animal model where we genetically modified proteins in the animal to make them human-like and, therefore, you can actually take human platelets and put these in these animals and recapitulate all the events that lead to a clot formation in human beings. We can use that model actually for drug development. We could actually target proteins on the surface of human platelets in this model and see how well they actually work, and that would be very equivalent to how it is in humans.

John Williams: It's really remarkable how often serendipity leads science to interesting discoveries that can lead to new treatments. I am surprised to hear that mice are not like humans. I'm going to have to take that into consideration for my own research because we use a lot of mice. How has that been for you, because as a clinician taking care of these babies, obviously that made you think early on of using humanized mice because you realized that it's hard to translate things from mice to humans? How has it been for you moving into the area that you just mentioned of actually doing research in humans when you, like I, trained as sort of a basic lab researcher?

Dr. Tom Diacovo: I think ultimately, I think as a physician scientist and what we do, you want to bring it back to the bedside. It's always been my goal, and it's taken 20 years to actually get there. Someone said to me several years ago, "How are you going to bring your research actually to the bedside of your patients?" To me it was always obvious that we're heading that direction, developing the models, the devices that are necessary to really investigate how clots form in critically ill newborns, and especially newborn cardiacs. That was always sort of on the forefront of what I wanted to do. Eventually it became ... When I went to Columbia they take care of their neonatal cardiac patients in the NICU, and it sort of was a meld of, "This is the opportunity."

Dr. Tom Diacovo: The first time I was on-call there a very important situation happened where we had a patient who had a heart defect that required putting in a little vascular graft that helped them to survive. Unfortunately, 17% of those actually clot off. I remember that it was a very complex surgery. The child did very well, great job by the surgeon, but two hours later the child was dead of a massive clot.

Dr. Tom Diacovo: I stood there and realized that we have so many medications for adults who are going to have, for instance, a stent for their coronary artery because of atherosclerotic heart disease, and yet the only drug that we ever use in our patients is something that was developed in the 1800s and that's aspirin, and it only could be administered 12-24 hours after they come back from surgery, yet over 60% of the patients are going to have a clot form before they can get aspirin. There's nothing out there that's been used. To me that was such an

injustice to see that, knowing that what's out there. That's where I said, "Enough is enough. We're going to do something about this."

Dr. Tom Diacovo: I talked to my adult colleagues and asked them what they using in the cath lab, what was on the horizon? It's just a fortunate event where we talked with them and a company was developing a new drug that was perfect for our patient population because you could give it by IV. It was already active. It doesn't have to undergo metabolism by the liver to be active and it's reversible. It's one of the first reversible anti-clotting drugs that's available. So, if you want to talk about where you have high-risk patients with potential for bleeding, you got end complications you could just simply stop the drug.

Dr. Tom Diacovo: I never had done a clinical trial in my life and my view on things is that I'm always willing to do new things. This was a grand opportunity to take this information, spent three years developing the trial, wrote the protocol with my colleagues, instituted the trial, and it has been successful. We have five more patients to do and then we're ready to go onto a National/International trial. All the patients have not had any bleeding complications, and they've achieved 100% efficacy from our perspective of the trial.

Steph Dewar: So, from a non-researcher perspective, someone who only hopes to trap mice so that they're not in her office anymore, at home, this is so really revolutionary, because I can relate a similar experience as a resident with a postop cardiac patient who had done beautifully through the procedure and within the first 24 hours had a catastrophic event from which she did not recover. As a young physician that was very impactful. I was just helpless to help this young patient. As a hospital-based pediatrician who now takes care of a lot of post-cardiac patients this is incredibly exciting. I'm just curious what's different about the babies in this trial and adults that makes this so meaningful, or useful, for that population?

Dr. Tom Diacovo: So, this drug actually has recently been approved for adults and it's been used in now close to 20,000 patients. Again, it has been one that has had minimal side effects and good efficacy. The ability now to use it in a situation where it's sort of under similar situations. The size of the little grafts that they had put in are just about the size of almost you see for a coronary artery. If you're comparing in size what happens at surgery, it's very similar types of conditions and risks for clot formation that would occur in a coronary artery would be the same thing for these particular types of shunts or grafts that are actually put in for this patient population.

Dr. Tom Diacovo: It was again ... But it took three years to make sure that we would hit the target, that it would work, and that the response would be very similar to that what we saw in adults. This was where we actually used our humanized mouse, because we could take the platelets from those babies, with the permission of the parents, and put them into this animal, cause injury, see how they actually form a clot, and then put the drug in and show that the drug is very efficacious in reducing clot formation. So, many trials go on without having this kind of

information and you're not even sure whether the drug is going to hit the target or have any effects at least in the newborn population. Many of the trials fail because there is no what we call the surrogate biomarker, something that's going to tell you whether the drug is going to work or not, before you actually go on and do the trial. I think that that's one think that we're trying to change now.

Dr. Tom Diacovo: I'm actually part of an organization called The International Neonatal Consortium where we've said, "It's time to work hand-in-hand with industry." Help them to identify areas that we want to focus on, find the targets, find the drugs, and find the biomarkers that are necessary for us to conduct the trials in a meaningful manner. Because, again, many of the things from an industry standpoint, you may get asked in a trial but they've written a protocol which doesn't really apply to the patient population. There has to be a new way that we start to approach how we do clinical trials, especially in critically ill neonatal patients where you have to have people who have boots on the ground really helping to guide industry to how a trial should be done, what trial should be done and what are the outcome measures we're looking for.

John Williams: With such an exciting approach, because I think all of us who take care of children have had this experience of the majority of the focus of research, of industry, of drug development, of the healthcare industry is all on adults. So, in all of fields we often get drugs that were tested in adults and have never been studied in kids and, therefore, we have to sort of do things kind off-label and things some more slowly. I think that's slowly changing, but it's exciting to think about happening with these very youngest of babies.

Dr. Tom Diacovo: You know, it's amazing when you talk to parents, or even to my colleagues, and you talk about hand-me-downs and off label, and 90% of the drugs we use every day in the Neonatal Intensive Care Unit have never undergone clinical testing in the patient population that we use it on. So, again, how can you expect the drug to work the same way that it works in an adult when you're talking about a younger child under different developmental conditions, different types of disease states, and then think that this is okay to do? It leads to a lot of complications and it leads to failed trials from that perspective.

Dr. Tom Diacovo: Again, when I talk about this with families and why we're doing clinical trials, one of the things I ask a rhetorical question is, "How many of you would do anything for your child?" Everybody says, "Of course we'd everything for our child." "How many of you realize that I'm using drugs that have never undergone clinical testing?" It's time to really change the way that we approach this, and I tell them, "I need your help to help change the way that we do things." I would say that what has made this trial most successful are the parents. Their altruistic behavior when you talk to them and say ... I'm going to them and tell them I want to give a drug that could potentially make their baby bleed more in the postoperative period. You can imagine if I came to you and I said that, but they understand that what they're undergoing and the complications and everything else that occur that it is important to do this, and

it is important to do this and knowing that it may not be of benefit immediately for their child but it's going to be a benefit for children in the future.

Dr. Tom Diacovo: Again, I must say that it's been touching to talk with them and their willingness to participate in a trial like this where initially it was hybrid. We had pretty good evidence that, based on the adult literature and some of the stuff that we had done, that we weren't going to have major complications, but you never know. I give them incredible credit for what they do in allowing us to conduct this type of a trial.

Dr. Tom Diacovo: With that being said, I mean it's also up to the investigator to really take charge. I think that's another area. When I do this I'm at the bedside for 10 hours for that patient. I do not leave it. I do the sampling, everything we need to do, but I watch them and I make sure that everything's going smoothly for them, and knowing that if there was something going on I could intervene and help the team to deal with it. I think that's part of the responsibility, as well at carrying out a clinical trial. If you're going to be the PI you really need to be the one who's going to be there and guarantee to the parents that you're going to make sure this is going safe and nothing is going to happen.

Steph Dewar: So, Tom, you talked a little bit about your fortuitous discovery as a fellow in Boston, and then a little bit about your time at Columbia. How was it that you ended up here in Pittsburgh, and that we're so fortunate to have you doing this meaningful clinical research here?

Dr. Tom Diacovo: Well, I got a phone call asking me whether I was interested in a Division Chief job and the answer was, I'd been wanting to be in that sort of leadership position because, again, there's a lot of things. You have to weigh what is ... When you want to change jobs you want to make sure that you're able to do things that you know are important to you and important to the field, and will you have that opportunity to do that? I think that was the impetus for me coming here was it's a phenomenal faculty, phenomenal institution, and a neonatal group that is also one of the best in the country, and a large patient population to work with.

Dr. Tom Diacovo: When I told them that I'm very interested in continuing to do this trial here there was no hesitation from my cardiac colleagues, or CT surgeon colleagues to say that, "Yeah, come and do this. We will support you 100%." That's the kind of environment you want to be in. That convinced me right on the spot that this is the right decision to make, because I can make profound changes in neonatology and for a patient population as well as have colleagues who are going to support these kinds of endeavors.

John Williams: I agree with Steph. We're lucky to have you here, Tom. I wanted to ask about another change that you've made since coming here, because this is something that is new since I was in the NICU, a few years ago as a resident, and this is something called Bubble CPAP, which I'm familiar with Bubble tea. My graduate

students have taught me about Bubble tea. I know that. It's good. Bubble CPAP is different.

Dr. Tom Diacovo: Again, you learn from all the institutions that you have had an honor to work for. One of the the things, I think, was spectacular in regards to what Columbia did is that they knew how to ventilate patient's. If you look at ... We have these networks that help sort of benchmark us where we are. For the average NICU in the United States 25-30% of the patients will develop something called chronic lung disease, which is basically due to being ventilated and intubated for a long period of time. Your lungs get inflamed and ultimately they get scar tissue development, and it makes it difficult for these babies to breathe. There's a lot of comorbidities that are associated with that. The rate at Columbia is less than 7%. Why is that? Because they've become, they developed a process about that. Not every baby needs to be intubated, even if they're 24 or 23 weeks of gestation, which is a new kind of concept. But, it's something they've been doing since the 80s.

Dr. Tom Diacovo: A lot of ... I don't know why this has not really been propagated throughout the country in understanding this is a better way to do ventilatory support. It's simply something that looks like a snorkel device that sits in the nose with these prongs. They call it a bubble CPAP because there's a container that has water in it and a little tube and you just bubble in oxygen and it creates pressure that actually helps keep the lungs inflated on these babies. Again, if you don't intubate you don't set them up for the development of chronic lung disease. For our patient population less than 750 grand we can keep 50% of those babies from ever being intubated; 1000 grand we can keep 95% of those babies from ever needing to be intubated on a ventilator.

Dr. Tom Diacovo: I must give, again ... I'm so glad to be here because the faculty, the ancillary support teams, our key nursing were all willing to get behind this and say, "We should do better, and we can do better, and we should incorporate new techniques to do this." I'm glad to say that the team came to Columbia, they learned how to do it. Columbia came to help them including nurses. They came here. We've now instituted ... It's been three, four weeks now, we've already reduced the rate of intubation by 50%; the need for ventilators by 50%, and the need to have a drug called Surfactin administration to help keeps lungs inflated by 60%. So, we've made huge ... In just three weeks we've changed the culture and, again, its because of the individuals here that really want to help improve care for our patients that we've been able to successfully improve this. I imagine over the next couple of years our rate of chronic lung disease will drop dramatically. We're already seeing the benefits of it in such a short period of time.

John Williams: That's really just amazing. It shows the benefit of having new ideas and new insight, although it wasn't new to your colleagues there. I think a lot of us would have said, "Well, this is just part and parcel of saving the lives of these extremely premature infants." Well, you just have to do it. It's part of the cost of taking care of these babies, and yet it turns out that's not the case. From an ID

standpoint less intubations and ventilation means fewer ventilator-associated pneumonias, which I'm also very happy about.

Steph Dewar: So, Tom, this has been incredibly illuminating to talk to you about some of your interests. I really do appreciate that you're here in Pittsburgh helping us take care of these smallest patients of ours. I want to thank you for joining us on That's Pediatrics. It's really been illuminating for me and, hopefully, for our listeners.

Dr. Tom Diacovo: Great. Thank you so much for your time.

John Williams: Tom, thanks for being here. We'll see you all next time on That's Pediatrics.