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Carolyn Coyne: From UPMC Children's Hospital of Pittsburgh, welcome to That's Pediatrics.

Brian Martin: I'm Brian Martin. I'm Vice President of Medical Affairs here at Children's.

Carolyn Coyne: And I'm Carolyn Coyne. I'm a scientist in the division of Pediatric Infectious Diseases.

Brian Martin: Today we'd like to welcome Dr. Dean Yimlamai. He is an assistant professor with the University of Pittsburgh School of Medicine and also a Mellon scholar here at Children's with the Richard King Mellon Institute for Pediatric Research. His research includes hippo signaling and liver growth and oncogenesis and the role of immune cells in hepatocyte activation.

Dean Yimlamai: Hi. Thanks for having me today.

Carolyn Coyne: Thanks for joining us, Dean.

Dean Yimlamai: Oh, no problem.

Carolyn Coyne: So why don't we start with a little bit of background. Tell us a little bit sort of about your training, what brought you here to Pittsburgh, and then maybe we can talk a little bit about your research.

Dean Yimlamai: Sure. I was thinking actually recently about what brought me here and I think I've always been a developmental biologist, a person who's just interested in how things grow. Gosh, it's almost 20 years ago that I worked with a person who was an MD, PhD, so today I'm an MD, PhD as well. And I took a little bit of time off after college to kind of figure out what I wanted to do. I worked with a geneticist who studied Down syndrome and Williams syndrome and I would say that I went through college enjoying my classes and doing things like biochemistry. And I was a biochemistry major, but I didn't have really I would say a great plan on how I was going to integrate these things into a career. And so I worked with a woman, her name is Julie Korenberg, she's at the University of Utah now, but at the time I lived in LA and she had a really kind of amazing life that I thought she lived.

Dean Yimlamai: First, she lived in Beverly Hills, which I still wish I could do. But she had the ability to both see patients usually once or twice a week who had Williams syndrome and Down syndrome, and also had a lab where she was trying to understand what causes the things that we know as Down syndrome or Williams syndrome. And in Down syndrome those are things people are familiar

with, things like their height or heart disease, but even things like leukemia that happens much more frequently in patients with Down syndrome. And I would say that with the patients with Williams syndrome, they are both quite delayed in their ability to relate to people and sometimes quite loquacious. I mean I think this is one of ... If one ever gets to a patient with Williams syndrome, one of the things that really drives people's interest in them is the first impression is that they're quite delayed.

Dean Yimlamai: But after you get to know them, they have some really extraordinary abilities. And the things that are always written about with such patients are their ability to sing, their ability to actually remember musical phrases, even though they may have a really difficult time with spontaneous conversation and sort of understanding what the genetic basis was. And also having basically a workshop. I mean I think that's, even today I have a lab that I think it was a workshop on trying to understand, you know, how do you build these things? And in her interest it was how do you build a brain or you know, the blood system. For me, I mean I am really interested today in how do you build organs and specifically the liver. And that's kind of where I got started. And then, you know, I spent a few years with her and then I went and got an MD, PhD in Boston at Tufts and trained in pediatrics.

Dean Yimlamai: And again, that's another thing that I sort of came back to. I explored many, many things, development of the heart, blood development. But I really wanted to understand kids and how do kids grow and you know, what makes them grow normally and obviously what's the genetic basis of some of the things that were real problems in peds.

Brian Martin: So after completion of medical school and your PhD, you did a GI fellowship right after pediatrics.

Dean Yimlamai: I did.

Brian Martin: What sort of led you in that direction? Was this a sort of hepatology kind of…?

Dean Yimlamai: It was not actually. I mean I think most of the people who were actually really attracted to doing gastroenterology, GI, are interested in the intestine. So stomach. How do you absorb? Mouth. And I would tell you that's clinically mostly what I do. From a research perspective, the liver is connected and is part of the GI tract was something I almost fell into because of to some extent just what was available when I was looking for a research project. But it is still a very connected system to me. I mean obviously we need all of these parts to digest and it still gets at the sort of basic questions that I'm interested in, which is how do you build a normally functioning system? And then when there's problems, where does it start?

Carolyn Coyne: I wonder if you could expand on that a little bit. Cause I agree with you that the liver is often overlooked when we think about your GI system.

Dean Yimlamai: Sure.

Carolyn Coyne: And so maybe tell us a little bit about what the liver does during digestion and why do we consider it part of the GI tract?

Dean Yimlamai: Yeah, so it grows as what we call an outpouching actually of the small intestine. It makes a lot of the enzymes that we use to digest our food. It also processes a lot of the blood and it's I think underappreciated. We I think see patients ... We know when people are sick with liver disease because they become jaundice, that you can see them on the street, they're yellow. You can see it in their eyes. You can see it in their face. You can see it in how they move. And I have to say that I was aware, but I didn't appreciate these things when I started out. It is one of the parts of metabolism of our growth and development that's actually really underappreciated. I mean, I think when we talk for example about diabetes, we think a lot about the pancreas, but the major place where we metabolize sugar is in the liver.

Dean Yimlamai: And you know, one of the things that really has gotten me ... Again, I started in this field almost 10 years ago and I had a sort of minimal interest if, I mean I shouldn't let my, my mentors hear this, but it's a really growing interest and appreciation. And I think that that's one of the things that drives me today. So about just the liver and things like metabolism. There's a lot of obesity in the world. We know that in the U.S. more than half of children are obese. A lot of that fat goes in the liver and that causes metabolic problems. And again, we think of fat in the skin, but we know that too much fat in the liver is toxic and that that leads to some of the things like diabetes, the inability, there's too much fat, the fat is toxic and we can't metabolize things like sugar. And then unfortunately the things that really take people are not liver problems, but things like heart attack and those issues.

Brian Martin: I'd like to segue a little bit over into liver repair and recovery from injury in cell signaling mechanisms and that kind of stuff.

Dean Yimlamai: Sure.

Brian Martin: Can you expand on how you sort of ended up going down ... To go all the way back to developmental biology, how did you sort of segue over into this, the current portion of your career in terms of working with this hippo signaling pathway?

Dean Yimlamai: Sure so I mean-

Brian Martin: Which I will admit I had to look up on Google.

Dean Yimlamai: So, I mean hippo is named for hippopotamus actually because it was discovered in Drosophila, which is a small fruit fly. People have done many what we call genetic screens. And these are ways of looking for a genes that are important in

development. And so one of the mutants in the hippo pathway, the first one was called hippo because it was quite large and had sort of a rough skin, which is what hippos have. Many of the things that we do in what we call model systems, things like Drosophila are replicated in people and we use model systems as ways of discovering new tools so that really we can change human health. I mean ultimately the NIH gives money to make basic discoveries so that then we can translate them.

Dean Yimlamai: And how I got into this pathway was I, just like many things, I was suggested by a mentor to go to a seminar. That there was a young guy who had some really interesting work, but he had a really small lab and he was giving a seminar and he was working on the hippo pathway. My mentor's name was Fernando Camargo, he was a young investigator. This was at least from the perspective of translating these things into fruit fly into humans was really early days. There'd only been one or two papers looking at what different components of this pathway did in mice. And there's more and more work nowadays. There was one or two papers just saying that the things that we saw in fruit flies, in mice was replicated in people. He put up these slides of really what we call dramatic phenotypes. And if you ever get the chance to work with Fernando or someone like him, I mean these are the words ... He's not a person who likes 10% or 20% even if it's significant.

Dean Yimlamai: I mean he's a person who we're always having to dial back in cause the words of humongous and massive are always sort of rolling out his out of his mouth. But at the same time, you know, it was really clear from the things he was showing and although he was young and he only had three or four people working with him at the time, that this was something that was really impactful. And I think, you know, as we get back to how I started, I was always looking for things that could have an impact that there's not too many people doing. But obviously, you know, if you show the right picture this is something people should work on. And so the work that I do today still focuses on the hippo pathway, but in some of those diseases that I talked about.

Dean Yimlamai: What happens in fatty liver? Is the hippo pathway activated? The shorter answer is yes. Do you get cancer? And from two big illiterate, the answer's yes. Is it through this pathway? Yes. And if we inhibit, you know, key portions of the pathway, can we reduce incidents of cancer? I would tell you the answer is yes in mice and we're still waiting to figure out if that's true in people. But that's how we sort of establish where we're going to start. And obviously this is the kind of arguments that we make when we go to places like the NIH or foundations to say that we're doing important things that affect a lot of people and why we should study these things with funny names like hippo or ...

Carolyn Coyne: Well I'm wondering if you can tell us a little bit about liver regeneration?

Dean Yimlamai: Sure.

Carolyn Coyne: Is there something unique about the liver or different about the liver? You know, people I think have this concept that you can take someone's liver and cut it in half and it's going to grow back and be completely normal. And so can you tell us a tell us a little bit about that?

Dean Yimlamai: Sure. So people are always, I think, familiar with stories, even from mythology this idea of Prometheus who is a god who was chained to a rock and as punishment had his liver chewed out and then overnight regenerated his liver. So we can do that actually in mice as well as in people. In mice they actually regenerate their liver. If you take out half their liver, they'll have an equivalent liver in seven days. And you can do the same thing in people. It takes about a month. So it's a little bit slower. But that's one of the things that allows us to do liver transplants, actually living donor liver transplants. You know we're at UPMC and just to plug why I'm even at UPMC, it's because this is one of the first transplantation places where a transplantation occurs.

Dean Yimlamai: Tom Starzl was a pioneer. He's created, you know, even though he's not with us any longer, he created a culture where people want to understand, improve transplantation. And this is one of the leading places where living donor liver transplantation occurs. And that's where you can take a piece of an adult liver and transplant it to someone else. Usually it's to someone smaller like kids. But usually what they do is take a small triangle of the left lobe of the liver and you're able to give it to kids who might have some kind of severe liver disease. So there's a lot of that kind of work going on here and there's a lot of people trying to understand different kinds of regeneration. So it's a great place to be, especially for someone like me who's still just ... I still feel like I'm just getting into the field.

Carolyn Coyne: I still feel that way about my field. So I don't know if that ever goes away.

Dean Yimlamai: Probably not.

Brian Martin: That's just about everybody. Yeah. I'd love for you to see ... I mean you just mentioned this sort of interdisciplinary community collaboration opportunities here at UPMC. Is there any particular area which really excites you about, you know, you mentioned the work that Tom Starzl and the rest of the transplant network does here?

Dean Yimlamai: Sure.

Brian Martin: Are there any other specific labs or other people that you could see as being influential in terms of where the direction that your research is going to go?

Dean Yimlamai: Well, gosh. I'll say that first, I'm involved in the Pittsburgh Liver Center, which is actually a new center that was created just two years ago in collaboration with UPMC and Pittsburgh. So Paul Monga heads that center. He is a professor of pathology. I really do consider him a mentor having moved from Boston here.

They are really interested in not only understanding sort of some of these transplant things ... There's a Starzl Institute which is devoted specifically to liver transplantation, but the Pittsburgh liver center is sort of a more expansive group of investigators. Again, I think Paul Mongo has been great. Gavin Arteel, he's a recent very senior recruit. He came from the University of Louisville. And George Michalopoulos, who's the chair of pathology has also been a great mentor to me.

Dean Yimlamai: And these are all people who are actually quite influential in the field that I work in. They have made some fundamental discoveries in what starts and stops this liver regeneration process that I touched on. But also what might be the key signaling pathways that lead to cancer development. Because on the one hand it's important to start regeneration to make a new organ, but obviously if it goes on too long, that leads to things like cancer and that's another thing that we want to understand a lot better. Liver cancer has unfortunately really terrible outcomes. If you catch it early, you can cure it by surgery. But unfortunately at five years, 80% of people won't be with us because the chemotherapy, there's really only one drug out there that's effective. And that usually only gives you a few months to live, and that's not what we expect for most of our cures, especially in something like pediatrics. And unfortunately the numbers for pediatric liver tumors is slightly but not much better than adults.

Carolyn Coyne: So can you tell us a little bit, I know some of your work looks at the immune cells in the liver and how that might impact sort of liver function and development and the liver's not often thought of something as an immune organ. And so could you tell us a little bit about the liver as it functions in immunity?

Dean Yimlamai: Sure. So the first place where nutrients absorbed that sees the body is the liver. It makes sense actually if you think about it to have immune cells to be able to react and filter if necessary, detoxify these things. So it forms a number of roles. I mean, one that we think about all the time was just filtering, but also how do you respond to infections, whether that's a diarrheal infection, whether that's a hepatitis, whether that's a an infection from your cruise trip.

Dean Yimlamai: I'm really interested actually in how regeneration occurs. And then how do you recruit immune cells to that? I mean it's important to bring in immune cells when you're regenerating to clean up dead cells, obviously to clean up things like bacteria. How do you reform these filters to keep what's inside inside and what's should stay out? And to keep those protective barriers. So we're really interested right now with respect to regeneration. What's the coordination aspect that goes on? And then in things like cancer, we know that when you have excessive regeneration that the immune cells actually can come in and reduce those cancer cells. One of the really big things in cancer therapy right now is how to reactivate the immune system. And so we know that the liver is a great model to understand that. How is it happening normally? And then, you know, when you develop cancer, how do you evade it? So we know that the hippo pathway is doing something on that side.

Carolyn Coyne: And thinking about the liver throughout life, are there differences between kids and adults in terms of how the liver functions from any sort of immune aspects or function aspects?

Dean Yimlamai: Well, we know that all of our cells age and they have the ability to regenerate more slowly. One of the good things about the liver is that hepatocytes, the red cells of the liver, probably only divide once or twice a year on average. That's about their life span is about half a year. So as compared to other cell types, they don't have to regenerate that often. But we know that when you're exposed to toxins, alcohol for example, that you have to accelerate that regeneration process. And that leads to some of the problems that we've talked about, some of the metabolic problems, some of the issues with cancer. And obviously my work sort of impacts on that.

Brian Martin: So fortunately the habits of children ...

Carolyn Coyne: Differ.

Brian Martin: Differ from in terms of the potential badness, if you will, that I've gotten from the adult population.

Carolyn Coyne: Exactly.

Dean Yimlamai: Well, I mean, I think one of the things that we're really ... Although kids don't drink, unfortunately we're seeing a lot of obesity and we know that excess fat is a toxin. We know there are toxic lipids and we know that it causes excessive regeneration. We see clearly a lot of immune infiltration, which in itself can be an inciting stress that eventually leads to things like cancer. So as we think about obesity, how do we help children? We know that right now transplantation for obesity is the third leading cause of transplantation. It's projected from obesity to be the number one reason for transplantation in about 15 to 20 years. So it's an issue. I mean it's an important issue.

Dean Yimlamai: I mean, I think we think about lots of metabolic things. We think about the cardiovascular issues, but this is another place where it clearly is going to impact us. It's going to impact the health care system and it's something we haven't really seen. So.

Brian Martin: Very interesting.

Carolyn Coyne: Well thank you very much for joining us, Dean.

Dean Yimlamai: Well, thanks for having me.

Brian Martin: Thank you, Dean.

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Dean Yimlamai: Thank you.