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Brian Martin: From UPMC Children's Hospital of Pittsburgh, we'd like to welcome you back to That's Pediatrics.

Carolyn Coyne: [I'm Carolyn Coyne](#). I'm a basic scientist in the division of pediatric infectious diseases.

Brian Martin: [I'm Brian Martin](#), I'm the vice president for medical affairs here at Children's. We would like to welcome [Mioara Manole](#). Dr. Manole is the director of basic and translational research in the division of [pediatric emergency medicine](#). She is also the associate director of the Safar Center for Resuscitation Research and assistant professor of pediatrics at the University of Pittsburgh School of Medicine.

Brian Martin: We welcome her here to talk about some of her research involving vascular pathways and cerebral vascular dysregulation. It's of note that she's made significant contributions in teaching and mentoring pediatric emergency medicine fellows, undergraduates, and post-doctoral and medical students, as well as our residents and other critical care fellows here at Children's. Welcome Dr. Manole.

Mioara Manole: Thanks for happy to be here.

Carolyn Coyne: Thanks joining us. Tell us a little bit, you know, one of the things I'm always fascinated about is people's sort of back story. What brought them to the disciplines they've chosen, their area of research. I'm not a clinician, but I think about all the fields that one could choose, and I certainly don't have the brainpower, perhaps, or reaction time to do ER medicine. Tell us a little bit about how you chose that as your career path and when that became something you were interested in doing.

Mioara Manole: Sure. I went to medical school knowing that I was going to be an ophthalmologist, just because I was inspired by my ophthalmology physician as a child. Quickly, I realized that pediatrics was what I loved to do. I was in medical school in Romania for six years, and I loved working with children. I loved the impact that I can have on a child, the quick recovery that children make. That determined me to go into pediatrics.

Mioara Manole: In Romania, emergency medicine was not a specialty at that time, so when I came to the United States and I started doing my residency, my first rotation was in pediatric emergency medicine, and at that time I realized that that's the specialty I was going to pursue, the subspecialty I was going to pursue.

Carolyn Coyne: What was it that sort of drew you to that?

Mioara Manole: It was a combination of intriguing diagnoses, the fact that I was the one making those diagnoses and putting the pieces of the puzzle together, right there at the bedside. It was the diversity of patients, diversity of patient's ages, conditions that I was seeing. The combination of procedures, skills that I was using. Using the creativity in every day and in every patient interaction. Also, the fact that I was always drawn to underserved populations. I was always drawn to doing a little bit of mission work, and I felt like in the emergency department, I would see underserved children. Children who don't necessarily have a regular pediatrician and I can make a big impact. To this day, this is true.

Carolyn Coyne: When did you come to the Children's Hospital?

Mioara Manole: I came to Pittsburgh as a second-year pediatric resident, and the Children's Hospital, I did first time a rotation as a third year pediatric resident and then I did my fellowship here.

Brian Martin: At what point in your training journey did you start to think about your, from a research point of view, what you wanted to do as far as the research aspects of your career?

Mioara Manole: That is something that I love to talk about and I talk about often to my fellows and pediatric residents. It was serendipity that got me into research, and I love this. I love this serendipitous pathway. Pediatric emergency medicine fellow, we needed to do one research project. A wonderful mentor from my division, Robert was doing animal research. Well, I had heard that there is this Safar Center for Resuscitation Research, and there are brilliant researchers over there. Having never done basic research, I said, "Let me give it a try. This sounds interesting."

Mioara Manole: The first project that I did was a simple project of resuscitating newborn rats from cardiac arrest, well actually rats of two different ages, newborns and adolescent age rats. We were doing a study looking at their cardiac contractility. When do the heart stops in newborns versus older rats? We pretty much knew the answer to this, but we wanted to prove that newborn hearts are more resistant to asphyxia, and in this study, we saw that gasping was auto-resuscitative. We were amongst the first to demonstrate in an animal model that gasping auto-resuscitates the heart, and this gasping phenomenon is beneficial.

Mioara Manole: I presented at a national meeting, and then at that point I realized that the research path is something that I really wanted to combine with clinical work. Mainly because it gives me a really nice space to use my creativity. It gives me a nice place to bring any questions I had in the clinical practice to the bench side.

Carolyn Coyne: How difficult was that? You started doing basic research as a resident. You're obviously an attending now. How difficult was it and is it to just manage the time, kind of navigating time requirements between your clinical work as well as your basic science work? You know, I ask that because I'm a basic scientist and I often feel like I don't have as many hours in the day, and I don't do anything but my research, so I'm wondering how difficult that is. Certainly, being in emergency medicine, if that presents a unique time constraint in terms of the ability to do basic science.

Mioara Manole: Yes, I was very fortunate that I have been at this institution. I was a fellow when I first started doing basic research. When I expressed my interest to continue doing research, my mentors directed me towards the Safar Center for Resuscitation Research where I was fortunate enough to compete for a training award, which gave me ample protected time. It gave me pretty much 75% of protected time for research while I was doing 25% clinical work. From that point on, with the mentorship of giants like Dr. Bob Clark and Dr. Pat [Cohanick 00:07:53], my career started really taking off. I competed for a career mentor development award, at K08, which continued to give me 75% protected time, and then during my last year of the K08, I was fortunate enough to secure R01 funding.

Carolyn Coyne: Wonderful.

Mioara Manole: It's been good and it's been good because of the institution and because of excellent mentorship.

Brian Martin: Tell us a little bit about how you segued into vascular pathology. Sounded like you started off with an animal over at the Safar Center. Tell us what peaked your interest with vascular pathology and cerebrovascular dysregulation.

Mioara Manole: When we started the award, I met with Bob Clark and he was looking into different vascular pathways and gave me a couple of projects that I could delve into. One of them was a collaboration with Carnegie Mellon University's researchers looking at cerebral blood flow after cardiac arrest, and for that a new model needed to be developed. A model where we would take these 30 gram rats and we would take them into the bore of a huge MRI machine, which was an animal MRI.

Mioara Manole: We needed to develop this model so that that rat can be inside the machine, whereas our ventilator needed to be 10 to 12 feet away. We needed to infuse medications through tiny, very tiny lines into these little rats. It was a model that needed to be developed and it was something I was very interested in doing for my initial year of research. I had a wonderful time. We had wonderful results. We described for the first time that cerebral blood flow is reduced after cardiac arrest in pediatric rats. We described this in a noninvasive way, and from that point on, I started looking mechanistically at this pathway.

Brian Martin: Was that with magnetic resonance angiogram, as some previous thought from this type of research, was that the mechanism by which you were able to measure this?

Mioara Manole: It is a novel technique developed at Carnegie Mellon University called arterial spin labeling MRI.

Brian Martin: Okay.

Mioara Manole: It is a noninvasive technique where the protons in the blood at the level of the neck are inverted using a radiofrequency, and the signal is picked up at the level of the brain. Because there is no contrast agent, the contrast agent is endogenous-

Brian Martin: Yes.

Mioara Manole: This allows serial measurements of cerebral blood flow.

Carolyn Coyne: How much do pathways differ? You mentioned before the need to look and the differences that you found in neonatal rats versus adult rats. How different are these pathways and processes between sort of a more pediatric population, in this case your neonatal rat model, versus an older pediatric or an adult population?

Mioara Manole: Oh, that's excellent, and this is a question that we answered about three or four years after we developed a model in rats, we looked serially and regionally at the perfusion in adult animals after cardiac arrest and their perfusions are different. Initially, right after resuscitation, in pediatric rats there is a regional hyperemia, so the blood flow increases in certain regions. The cortex remains always with low blood flow in pediatric aged rats, whereas adult rats have a generalized hyper perfusion initially. Very intriguing.

Mioara Manole: We're still trying to determine the mechanisms of this. We're trying to determine whether this increased blood flow immediately after resuscitation is deleterious because of the burst of reactive oxygen it is just an autoregulation that is lost at that time point. Later on, in the first hour to two hours to days after cardiac arrest, the blood flow is decreased in the cortex, especially in pediatric aged rats. Whereas, in adult rats, these regions might remain hyper-perfused. There is a regional difference and a time difference between age.

Carolyn Coyne: One of the things that I always, again, because I'm a basic scientist that I found really intriguing about clinical scientists is, how much your clinical work impacts your research and vice versa, just even in terms of the questions you ask, perhaps even the methods that you use to answer those questions?

Mioara Manole: I bring many questions from the clinic back to the laboratory. Just recently, we determined that there is a hypo perfusion in the cortex, so the cortex is hypo-

profused, whereas neuronal activity remains preserved after cardiac arrest, which gives rise to this blood flow metabolism that's mismatched, which gives rise to cortical hypoxia. The cortex has low oxygenation after cardiac arrest, and we know this from the pediatric asphyxia of cardiac arrest model. Whereas, in the clinic, we cannot monitor brain oxygenation noninvasively in these patients.

Mioara Manole: I recently partnered with two scientists, one clinical scientist and one basic scientist, to develop a device that we call flow-to neural cap, a noninvasive device that will measure simultaneously neuronal activity and brain oxygenation and will give a value that clinicians will be able to use. We were fortunate enough to receive some funding from the Innovation Institute, and we're almost ready to, our prototype is constructing and we're ready to roll this out in volunteers.

Carolyn Coyne: This is sort of the true translational from your basic science and the rat model, and then actually making a device based upon those findings that you could then implement in the clinic, if a child comes into the emergency room and displaces. That's exciting.

Mioara Manole: Yeah, that's the goal.

Carolyn Coyne: That's really neat.

Brian Martin: Tell me, are there other areas in medicine where you see cross pollination of this cerebral blood flow work? What came to mind when you were speaking there were other cerebrovascular situations, maybe like migraine or other areas. Have you had any other researchers reach out to you as a result of your research and the models which you have developed which might be able to inform other areas in clinical medicine where you may have a neural and cerebro perfusion mismatch like what you described?

Mioara Manole: Certainly, certainly. Migraine is a very good condition to try to decipher with our tools. We've done some work in traumatic brain injury, trying to assess the neuro metabolic coupling and cerebral blood flow in a traumatic brain injury. Other conditions are focal ischemia. In terms of collaborations with others, we have not collaborated in other conditions. Mainly because the area that we're covering is so vast in cardiac arrest that ...

Brian Martin: There's enough work there for you.

Mioara Manole: Exactly, exactly.

Brian Martin: Understood.

Carolyn Coyne: That's good for you.

Brian Martin: Yeah.

Mioara Manole: Right.

Carolyn Coyne: What do you see, thinking about the future, where do you see your research going? What are the biggest, most exciting either questions or avenues that you see yourself going after in the next few years, or even in the next 10 years?

Mioara Manole: Yes, so I would like to decipher the mechanism of this hypo perfusion and hyperemia. A multi-modality monitoring after cardiac arrest in the clinic, multi-modality therapeutic intervention, combining vasodilation, prevention of vasoconstriction in the brain, plus preventing what we call the no reflow phenomenon in the brain after cardiac arrest.

Carolyn Coyne: What is that? I'm not familiar with what that is.

Mioara Manole: It's a fascinating finding that we were able to describe using in vivo two photo microscopy, which is this technique where you create a small window in the brain, and with a microscope and using a fluorescent marker, you're able to see a depth of about one millimeter in the cortex and we can look at cerebral micro vessels in the cortex. Using this technique, we observed that some capillaries have normal flow, whereas other capillaries have a blockage of flow. This phenomena is called no reflow phenomenon after cardiac arrest. We are targeting right now besides this, we have vasoconstriction of the bigger arterials. We are targeting right now not only the vasoconstriction but also this no reflow phenomenon.

Brian Martin: Segue over really quickly to medical education. You've been lauded here as a leader in medical education and it's well documented that trainees really enjoy working with you. How do you find the conversation goes with some of your trainees in regards to their ability to see the pathway that you've taken? Have you had any mentees? It sounds like you've had a great mentor relationship that you're well elucidated, but have you identified any mentees or others that are interested in coming along with you on your journey?

Mioara Manole: I have wonderful news in this regard, because emergency medicine is such a clinical specialty that for seven years, I've tried to enroll somebody from our division to come along with me in the clinician scientist journey. This year, we have one fellow who is ready to enroll. Until now, I have mentored mainly pediatric intensive care unit clinician scientists, neonatal intensive care unit clinician scientists, and many undergrad students. But this year, we have one of our own.

Carolyn Coyne: Great, well that is great news.

Brian Martin: Great news, congratulations.

Mioara Manole: Thank you.

Brian Martin: Thank you very much for joining us today.

Carolyn Coyne: Thank you.

Brian Martin: We greatly enjoyed speaking with you.

Mioara Manole: My pleasure, thank you.

Brian Martin: Thank you.

Carolyn Coyne: Thank you.