Video Transcript: New Insights into Monogenic Hypertension from Mouse Models

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**Alicia McDonough | Keck School of Medicine of USC, Los Angeles, CA** - I'm Alicia McDonough, from the University of Southern California, Keck School of Medicine, and I'm very pleased to introduce Dr. James McCormick from Oregon Health Science University. And I'm really pleased to congratulate Dr. McCormick on being awarded the inaugural American Heart Association, Kidney in Cardiovascular Disease Mid-Career Award. At OHSU, Jim hails from a range of departments, focusing on nephrology, hypertension, chemical physiology, and biochemistry. And he conducts research that uses all of these areas at once. So Jim will deliver his award lecture this week, entitled new insights into monogenic hypertension from mouse models. So I'm pleased to hear from Jim. And the first issue to talk about is how your scientific journey brought you to this line of investigation.

**James McCormick, PhD | Oregon Health & Science University, Portland, OR** - Morning, Alicia. Thanks so much for the introduction and also actually thank you for being one of the people that nominated me for the award. My scientific journey has been long. I'm a bit of a late comer to kidney and nephrology. I actually started out in a brain lab for my graduate work. And then I went to San Francisco to continue in that line of field with David Pierce, who's mainly a nephrologist. And then I ended up moving into kidney, that was the plan at least. And I started working on mouse models. And things, as they never do in science, they didn't go to plan. And the mice I was working with did not have any kidney defects and actually had strange hair growth. So I nearly switched to dermatology, but then the opportunity arose up in Oregon with David Ellison. I had a colleague from San Francisco who moved up here and David was looking for somebody and I wanted to go back into renal physiology. That was really my main area of interest. And I moved up here almost 18 years ago now. So that's how I ended up in Oregon. And things have taken off from there. So I gradually have learned renal physiology. As I said, I didn't start out in this sphere and David's been a great mentor for me. And what I brought was the experience with math models that David wasn't doing up here. So you know, David's been interested in the sodium-chloride cotransporter for his entire career. And that was really how I got into this area.

**Dr. Alicia McDonough** - Let me give you kind of a surprise question, which is, your work is really unraveling this monogenic disorder. Turned out to be very complicated. So for the listeners, can you explain in very simple layman's terms, your talk, what it's going to be about and also you can piggyback on there any unexpected findings you had along the way.

**Dr. James McCormick** - I'll do my best to keep it simple. But I have been working on a rare disease called familial hypercalcemic hypertension. So the two main features of this disease are high blood pressure or hypertension and high blood potassium or hypercalcemia which can have detrimental effects on your heart. So we've been interested in trying to work out the mechanism. It's been controversial. There are several genes that can be mutated that can cause this disease. And the mechanisms are quite simple for most of the other mutations but this particular mutation I've been interested in, has definitely been more complicated. And it's still controversial even after the, you know, the work that we've done. You know, people still doubt some of the findings that, you know, we've made and you know, that's science. We're always…

**Dr. Alicia McDonough** - Sure. Sure.

**Dr. James McCormick** - …arguing with each other about who's right and who's wrong. So to put it simply, so I work on this sodium-chloride, so salt transporter in the kidney. And when that's too active, your body retains too much salt causing hypertension. The mechanism of the high blood potassium is a little bit more complex. It's an indirect effect, so I won't go into that in too much detail. So this protein that brings salt back into your body when it's too active gives you high blood pressure. And exactly how that happens has been the tricky part with this particular gene mutation. So the transporter, the salt transporter is activated by a process called phosphorylation where a phosphate group is put onto the transporter. That makes it more active. The proteins that put that phosphate onto the transporter, they're degraded by a complex process called ubiquitination, where they're tagged for degradation by the cells and the kidney. And one of the components of this degrading complex when that has mutations, it can cause this disease because the protein that activates the salt transporter is no longer degraded.

So we've been trying to work out exactly how this complex gets dysregulated. And to do this we've had to employ many different math models. We've also done some experiments in test tubes and in cultured cells to kind of give us some hints as to what was going on. And I guess the ultimate findings that we've made is that the protein that's in this complex that degrades this other protein, it does two main things. So first, it causes itself to be degraded when it shouldn't be. And secondly, there's another component of this complex and this mutated protein causes that to be degraded as well when it shouldn't be. So the combined effect of these two proteins being degraded and lowering how much of them there is around, means that this target protein accumulates, and then excessively activates this salt transporting protein. So that's as simple as I can make it.

**Dr. Alicia McDonough** - That's great. That's good-

**Dr. James McCormick** - But it's complicated.

**Dr. Alicia McDonough** - That's very good. You get too much of a good thing because you reduce…

**Dr. James McCormick** - Exactly.

**Dr. Alicia McDonough** - …the degradation of it.

**Dr. James McCormick** - That's the ultimate effect. Yeah.

**Dr. Alicia McDonough** - Uh-huh. So Jim, where do we go from here? You've now elucidated this very nice signaling cascade of candidates that regulate the sodium transporter. What's the future direction for Dr. McCormick?

**Dr. James McCormick** - So yes-

**Dr. Alicia McDonough** - In this area or others.

**Dr. James McCormick** - Yeah. So actually, well, I'll give two examples. So in this particular area, I was resting on my laurels. It's like, "Yes, we've worked out the mechanism." And there have been some more recent studies that have, you know, that still suggest this may not be the whole story. There was recently a new paper in the General Hypertension which is the American Heart Association journal. So a new mutation has been identified in the same gene but it looks like it's slightly different. It looks like the mutation only causes the protein to degrade itself and not to degrade the other protein. And I was skeptical of this at first because it was all done in test tubes, but we have some new preliminary data that suggests that this may actually be the case. But what's interesting is that patients with this newly identified mutation have a much milder form of the disease. So it's similar but different. I guess to... So that's the direction that I'm interested in, is looking more at this new mutation. It's actually a bit more interesting than I thought it was maybe going to be. The second direction is I've been more interested in magnesium recently.

**Dr. Alicia McDonough** - Oh, sure.

**Dr. James McCormick** - So I've worked on potassium for many years, but I'm now interested in how the kidneys handle magnesium. You know, this is another ion that's very important for heart function and just body function in general. So, and the kidney is very important for helping your body to reabsorb magnesium, to keep the blood levels where they should be. So that's my future direction. And we'll see where it takes us. You know, there's some exciting things going on. I've just started a new collaboration with a group in the Netherlands and a group on the East Coast who are experts in this area. It's new for me. So I'm learning a lot from them. So that's one of the fun things about research and science is, you know, learning something new.

**Dr. Alicia McDonough** - And all the friends and colleagues you make to try to answer questions. I have one more short question I meant to a ask earlier, which is this transporter you're talking about, it's different in male and female rodent kidneys.

**Dr. James McCormick** - Yeah.

**Dr. Alicia McDonough** - It's more activated in females. Do you see any sex differences in the people who have this mutation?

**Dr. James McCormick** - Actually, as far as people, there have been no obvious sex differences. The effect on the transporter and this regulation is so severe and so huge that there may be differences, but they're hard to tease out. And yeah, the sex difference aspect of this is very interesting, you know, the females do differ to males with regard to how active this transporter is. And that does have a knock-on effect on blood potassium levels. And Alicia, you know, you've been doing some great work in this sphere. So you know, I'd be interested to see you know, how your work pursues the sex differences more.

**Dr. Alicia McDonough** - And the magnesium differences could be very interesting in females.

**Dr. James McCormick** - Yeah. Exactly. Yeah.

**Dr. Alicia McDonough** - Yeah.

**Dr. James McCormick** - We haven't seen any yet, but that's definitely something that we're going to be looking at as we move forward. And just to go back to the disease, so in humans, there are no differences but also in animals. We haven't seen any obvious differences in our animals. And as I mentioned, I think that's because the effects on the salt transport is so severe.

**Dr. Alicia McDonough** - Well, we could talk all day and I very much look forward to your lecture on Friday. I congratulate you again and thank you for spending the time with us.

**Dr. James McCormick** - Yeah. Thanks so much, Alicia. It's been great talking with you, and I really look forward to seeing you in San Diego as well. And it's a really great honor to receive this award from the Council on The Kidney and Cardiovascular Disease from the American Heart Association. The AHA has been very supportive of my career, my trainees' careers and, you know, I really appreciate that. Thank you.

**Dr. Alicia McDonough** - Well said. Okay. Thank you.