Video Transcript: Hypertension and Cognitive Impairment: Rising Star Lecture  
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**Costantino Iadecola, MD, FAHA | Weill Cornell Medicine, New York, NY** - My name is Constantino Iadecola and I am here with Dr. Monica Santisteban to discuss her Rising Star presentation at the hypertension meeting here in San Diego. This is a special lecture which has been introduced in this particular meeting, and is aimed at early-career, mid-career investigators who are doing spectacular work in the field of hypertension that's going to set the stage for future developments, and hopefully treatment for these devastating conditions. Now, I'm going to turn to Monica to ask her what is the topic of her lecture, and what is the big deal about this new field that she's approaching? So Monica, tell us a little about your talk starting with the title.

**Monica M. Santisteban, PhD | Weill Cornell Medicine, New York, NY** - Thank you for that introduction. So my talk tomorrow at 10:45 is titled, "Hypertension and Cognitive Impairment: A Closer Look at Neuroimmune Mechanisms." So we're interested in hypertension as a major risk factor for dementia. We know that particularly mid-life hypertension is associated with late-life dementia. And for a long time, it was thought that it was only vascular cognitive impairment, but we know now that it also increases the risk for Alzheimer's disease.

**Costantino Iadecola, MD, FAHA**- And so how does hypertension do so much damage to the brain? What do you think are the factors that contribute to this effect?

**Monica M. Santisteban, PhD** - We know that hypertension has profound effects on both the structure and function of cerebral blood vessels. We've been focusing on mouse models of hypertension, looking at the function of cerebral blood flow regulation, the blood-brain barrier, and cognitive function.

**Costantino Iadecola, MD, FAHA** - And now you're going to be using an animal model of hypertension. So, what aspects of human hypertensions do these animal models reflect? And how real they are with respect to treatment opportunities that may arise?

**Monica M. Santisteban, PhD** - Right, so we've used various animal models. We've used the angiotensin II model, which recapitulates that slow, developing rise in blood pressure that's seen in patients. We've also used a BPH mouse model. This mimics that chronic long-term hypertension which is multifactorial, and has that complex ideology that's seen in the human population. And most of my work has focused on salt-sensitive hypertension, which is thought to affect up to 50% of patients with hypertension.

**Costantino Iadecola, MD, FAHA** - So in your title, there is the word neuroimmune. So, what do immune cells, which are essentially the white cells that are in the blood, but they may also get elsewhere in the organs, what is the role? You know, it's kind of surprising to see this neuroimmune link in a brain disease that leads to cognitive impairment.

**Monica M. Santisteban, PhD** - Right, so we know that hypertension is pro-inflammatory and it induces a very significant inflammatory response peripherally. What's interesting is that the cells, these immune cells, are in the circulation and can gain access to the cerebral circulation. And by releasing cytokines locally, they can affect neuronal function.

**Costantino Iadecola, MD, FAHA** - Okay. And then what part of the brain, is it where the action is that then leads to the problem with cognition?

**Monica M. Santisteban, PhD** - That is probably the most exciting part of this study. We found that the T cells that are making IL-17 are accumulating in the brain borders, specifically in the dura. We found that they're releasing IL-17 locally, which can act on another specialized immune cell in the brain, perivascular macrophages, which then contribute to an impairment in functional hyperemia, and ultimately cognitive impairment.

**Costantino Iadecola, MD, FAHA** - So we have this chemical, which is typically found in the inflammatory diseases, so-called cytokines. So IL-17 is a cytokine, and it's able to act on other cells within the brain itself. There is almost like a crosstalk. I mean, they are talking to each other ---

**Monica M. Santisteban, PhD** - Right.

**Costantino Iadecola, MD, FAHA** --- through this cytokine. And then how does this eventually lead to the neuronal dysfunction, which is the ultimate effect of high blood pressure?

**Monica M. Santisteban, PhD** - The thought is that by impairing neurovascular regulation, so the ability of the brain to regulate cerebral blood flow, it creates vascular insufficiency and the brain is not able to get the energy that it needs, and that is going to lead to cognitive impairment.

**Costantino Iadecola, MD, FAHA** - So Monica, to get into the practical aspects now, practical implications of your work, and very elegant work in this field, can you tell us what kind of therapeutic prospects this new research is unveiling?

**Monica M. Santisteban, PhD** - So even though blood pressure control is going to remain critical in attenuating hypertensive end-organ damage, it's possible that to fully protect the brain and protect cognitive health, we're going to have to, in addition to targeting blood pressure, target also meningeal immunity.

**Costantino Iadecola, MD, FAHA** - Okay, so which would mean administrating a neuromodulatory agent.

**Monica M. Santisteban, PhD** - Right, which are already being used in the clinic for other conditions.

**Costantino Iadecola, MD, FAHA** - Okay. So, do you think that by kind of inhibiting the immune system, you may have some side effects which may not be desirable?

**Monica M. Santisteban, PhD** - Yes. So it's important to identify permissible targets that are not going to increase the risk for infection, that are not going to have, like you said, side effects in patients, and potentially increase effects of immunosuppression.

**Costantino Iadecola, MD, FAHA** - This was very, very interesting. And we congratulate you on your excellent work, and we look forward to your presentation tomorrow.

**Monica M. Santisteban, PhD** - Thank you.