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The Maternal Brain's Role in Bone Health: Exploring CCN3's Potential Power

Announcer:
You're listening to *On the Frontlines of Osteoporosis* on ReachMD. And now, here's your host, Ashley Baker.

Ashley Baker:
Welcome to *On the Frontlines of Osteoporosis* on ReachMD. I'm Ashley Baker, and joining me to discuss her research published in *Nature* that examines a maternal brain hormone that could help build bone is Dr. Nancy Lane. Not only is she an Endowed Professor of Medicine, Rheumatology, and Aging Research, as well as the Director of the Center for Musculoskeletal Health at the University of California at Davis School of Medicine, but she's also one of the study's co-authors. Dr. Lane, thanks so much for being here today.

Dr. Lane:
Thank you for having me.

Ashley Baker:
So if we start with some background, Dr. Lane, can you take us back to the early work on progesterone signaling in bone and how it helped set the stage for finding CCN3?

Dr. Lane:
Sure. Our laboratory at UC Davis, over twenty years ago, was given a mouse. This investigator said, "I think this mouse has high bone mass. We've knocked out the progesterone receptor," which is a global knockout. A long time ago, that's how we did things. We got rid of this progesterone receptor gene in the whole mouse, and sure enough, that mouse had really high bone mass.

So we studied the mouse, and we found a couple of things. It was a peak bone mass. It was a bone mass the mouse got by about the age of six or eight weeks that was maybe three times higher than normal, what we call "wild type mice." So then we went on a journey, and we found that the lack of the progesterone receptor gene in, what we called then, the "skeletal stem cells" was the reason that the skeletal stem cell made more bone, and then we stopped. We said, "Wow, we know what cell is involved," but we didn't know what else to do, so we stopped as you do sometimes in a laboratory and put things on the shelf.

And then we got a call about 10 years later from a group at UCSF from Holly Ingram's lab. They asked us if we were the people that had studied the progesterone knockout mouse that had the high bone mass, and it was related to the skeletal stem cell. We said, "Yes, we are." And they said they knocked out the estrogen receptor in the arc nucleus of the hypothalamus, which is a small part of the hypothalamus, and they also got really high bone mass, and they found that the action also appeared to be on the skeletal stem cell. So we started working and thinking together. Between Dr. Ingram's lab and myself in our laboratory, a number of experiments were done. They were able to find a molecule that showed up in the hypothalamus when the estrogen receptor was removed in the mice, and that molecule was CCN3. And then we did a lot of fun experiments, which I was a part of and watched. Instead of knocking the estrogen receptor out of the part of the hypothalamus, they would silence the gene and get high bone mass. It was just amazing.

Ashley Baker:
With all this in mind, let's zero in on CCN3 itself. What is this molecule, and how does it strengthen bone at the cellular level?

Dr. Lane:
That's a great question. What we know is when it's released from these neurons in the hypothalamus, it goes to the skeletal stem cell, which is one of the stem cells that differentiates into osteoblasts, so it connects to its receptor on the skeletal stem cell and signals the skeletal stem cell to become an osteoblast, which is a bone-forming cell.

But what we know is very important because when a mother—in this case, we're talking about mice because I don't think we've yet confirmed it in the clinic, but we're close; we're working on that—when the mouse is pregnant and then delivers these young pups, the babies need milk and the milk has calcium. And the mother has to give the calcium from her bones to the offspring. And you think to yourself, if you're getting all the calcium out of a mother's bone, then the mother's skeleton is just going to fall apart and break and become brittle. But that's not what happens because while you're taking the calcium out of the bone for the young babies to have nourishment, this molecule—CCN3—is helping the mother's skeleton build bone at the same time. So you're building bone while making milk so the mother can survive and be healthy to take care of her offspring.

So this little CCN3 molecule has probably evolved over a long time, and it's an evolution to keep the mother alive and her skeleton strong so she can take care of her offspring. So that's a very big finding and something that obviously is very important from mice and most likely all the way to men and women.

Ashley Baker:
For those just tuning in, this is *On the Frontlines of Osteoporosis* on ReachMD. I'm Ashley Baker and I'm speaking with Dr. Nancy Lane about her research on CCN3, a molecule that could transform the treatment of osteoporosis and other degenerative conditions.

Now, Dr. Lane, your team tested CCN3 in several ways, from skeletal stem cells in the lab to fracture repair in older mice. So can you highlight some of the key findings for us?

Dr. Lane:
Yeah, this was a very large effort led by Holly Ingram at UCSF. But everyone participated whenever we could help out. And at the time, Dr. Ambrosi was down at Stanford, and he was studying fractures. And so he said, "Fractures need to have bone formation." So he broke the bones in the particular fracture model and gave the animal CCN3 or a vehicle and found that the CCN3 also stimulated the fracture to repair very quickly—faster than on its own without therapy. And it was also very strong.

So that was another example of where we could stimulate skeletal stem cells to become osteoblasts and form bone in problems like fractures that heal slowly in elderly people.

Ashley Baker:
Given these findings, how could CCN3 change the treatment landscape for conditions like osteoporosis?

Dr. Lane:
The exciting thing for many of the investigators on this project is they're looking now for CCN3 to potentially be one of the most potent therapies we will ever have for the treatment of osteoporosis because right now, we have therapies to increase bone mass, but those therapies work on the osteoblast, which is a bone-forming cell, and it gets the osteoblast to make bone. PTH compounds and romosozumab help the osteoblasts make bone, but the number of osteoblasts you have depends on the number of skeletal stem cells that become osteoblasts. And CCN3 makes those skeletal stem cells become osteoblasts so you can make more bone. So if we're able to take CCN3 into the clinic, it will be a new day for the treatment of osteoporosis.

There are two big problems as we age. Women's bones get brittle, and if they break, we call it osteoporosis. Also, our joints wear out and we get osteoarthritis, or painful joints. It turns out that the same cell that makes bone—the skeletal stem cell—also makes cartilage, but there's a different cartilage for the joint. The difference is that for bone, you need oxygen, and for the joint, you can't have oxygen. And my colleagues at UC Davis and Tom Ambrosi have been able to take a joint and injure the joint and then get skeletal stem cells into the joint. And by giving the animal—because we're not into patients yet—a molecule that inhibits blood vessels, you keep oxygen out of the joint and CCN3 and you make cartilage. So not only is CCN3 able to make bone, but in the right circumstances, it also can make cartilage. So it may be a new day, not just for osteoporosis, but also for osteoarthritis. We're very excited.

Ashley Baker:
Before we close Dr. Lane, let's look ahead for a moment. What are the next steps in CCN3 research, and what could this mean for patients down the road?

Dr. Lane:
The good news from the inventors is that there's a company now that has licensed the technology, if you will, and they're working very hard to figure out the mechanism of action and to do the studies that are needed—the preclinical toxicity studies—to convince the FDA that this therapy is safe. And then if all goes well in a few years, it'll be in clinical trials. We're hopeful.

Ashley Baker:
As those forward-looking comments bring us to the end of today's program, I want to thank my guest, Dr. Nancy Lane, for sharing her insights on this exciting research. Dr. Lane, it was wonderful having you on the program.

Dr. Lane:
Thank you for having me.

Announcer:
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