Welcome to the Cutting Edge Health Podcast with Jane Rogers, where we discuss science to help prevent cognitive decline.

Jane Rogers: Can a specific compound in cannabis have a neuroprotective effect? We've all heard about THC and CBD, but research from the Salk Institute finds a lesser known compound called cannabinol or CBN, for short, might help protect the brain from Alzheimer's, and the good news is that even in states where pot is illegal, CBN is okay and sold. In today's episode of the *Cutting Edge Health: Preventing Cognitive Decline* podcast, our guest is Dr. Pam Maher, a research professor and head of Salk's Cellular Neurobiology lab. Dr. Maher, thank you for being with us.

Pam Maher: Thanks for giving me the opportunity.

Jane: I'm really glad you're here. We have a lot to talk about, because the research that you've been doing at the Salk Institute is really exciting and it's into how to protect us, our brains from the process of aging using a compound in cannabis. Can you tell us about this? You were the senior author of this paper published last January.

Pam: Yes. We've been interested in using natural products to protect the brain from neurodegenerative diseases, and since aging is the major risk factor for pretty much all neurodegenerative diseases, we've been focusing on that intersection between aging and neurodegeneration. For a long time, as I said, we've been interested in natural products because there's a lot of changes that occur in the aging brain that predispose to neurodegeneration, and natural products often have multiple activities that we think could be beneficial **[00:02:00]** in the context of the aging brain.

We've looked at different types of natural products, and more recently, we turned towards cannabinoids. Medical cannabis has a millennial long history; I think there's evidence going back 6,000 years for different cultures using it for treating various problems. At least in the US, it's fairly relatively unexplored, partly because working on it can be a little tricky because a number of the components are schedule I drugs, so you have to have a DEA license.

We became interested in non-psychoactive cannabinoids, which don't require the DEA license, and also, I think have a much better potential for being useful, particularly for diseases where you have other psychological changes going on in your brain, you might not want to combine that with THC. We tested a variety of non-psychoactive cannabinoids in our primary cell-based neuroprotection assay a few years ago and identified several that were extremely active.

One of them was CBD, but there's been a huge amount of research on CBD, and so we decided to focus on CBN, which was equally or more active but really not nearly as

much as known about, and so we thought we could, by focusing on a less studied cannabinoid, get some new information and also potentially treatment of neurodegenerative diseases.

Jane: Were you surprised by how well this-- You've tried it on mice. Were you surprised how well it worked?

Pam: We're just trying it on mice. We haven't done that, we're in the middle of doing that, literally, right now, but beginning a number of years ago, we developed a battery of cell culture-based phenotypic screening assays to identify compounds that would inhibit various toxicities associated with the aging brain, and so the paper was based on that, one of those assays in particular, in a nerve cell line in culture.

It was quite a bit more potent than some of the other natural **[00:04:00]** products we'd been studying previously, but we found it had a different mechanism of action than some of the other compounds we've been working on. That was interesting and we thought was important because Alzheimer's disease, which is the major focus in my lab, is actually a pretty heterogeneous disease, and so there's not going to be a magic bullet.

It's going to take a battery of different compounds, potentially, to treat the disease, and I think some people are going to benefit from, say, one compound and other people are going to benefit from something else, depending both on what's actually driving the disease and also perhaps where they are in the course of the disease process. Having multiple compounds out there that may act through different mechanisms could be particularly valuable in order to treat a wider range of patients than if you just have a single compound that might just act through one mechanism and therefore might only be effective at a smaller subset of patients.

Jane: Could you explain the mechanism that CBN uses? It affects the mitochondria and its energy?

Pam: Yes. The mitochondria, they call them the powerhouses of cells, and that's particularly important in the brain because the brain uses a lot of energy because nerve cells, as they communicate with each other to transmit their signals and retrieve memories and do everything that they do, that takes a lot of energy. All cells need efficient mitochondria, but the nerve cells particularly in the brain, mitochondrial function is extremely important to having them perform properly.

It's known that in aging and particularly in neurodegenerative diseases like Alzheimer's disease, mitochondrial function goes down. They become not as good at producing energy. One of the model systems that we use also causes a defect in energy

production by mitochondria. We were able to see that CBN was able to prevent that decrease in energy production. **[00:06:00]**

It did so by maintaining multiple aspects of mitochondrial function, which was quite intriguing because mitochondrial function is regulated by a variety of processes, and the insult that we used adversely affected all of these processes, and CBN was able to reverse that. That was interesting because some compounds may only act on one aspect of mitochondrial function. In this case, we saw it affecting multiple aspects of the mitochondria.

Jane: Right when I read this, I got really excited and I went out to see, can I find CBN? CBN you could find it, even in a state like this in North Carolina where marijuana is illegal, but you can still sell CBN because it doesn't have any THC in it, and that's exciting for everyone, but am I jumping too quickly? You have not done this completely with mice. You haven't done it with humans yet. Did I get too excited too early?

Pam: Perhaps. I think the data out there with CBN suggests that it should be safe, and they are selling it in gummies and various things for other indications, I guess.

Jane: Like sleep.

Pam: Sleep, yes. There isn't evidence out there now, even in animals, that it would preserve memory, but as I said, it seems safe, so it might not be necessarily bad to take it. As you probably know, no drug's really out there for the treatment of Alzheimer's disease, particularly to stop disease progression. A number of groups have looked at lifestyle factors that can impact the development and the progression of the disease, even in people who are at fairly high risk for developing it.

One of the factors that they've noted is that getting good sleep is really important, so even if this only helped with sleep, and people are having trouble with sleep as they're getting older, it actually could have benefits, even if it did not have benefits **[00:08:00]** in other areas, and I think probably most people know, if you haven't been sleeping well for a while, it does affect your memory. Sometimes it makes it harder to recall things and to make new memories, even.

Even if, as I said, the only effect turns out to perhaps improving sleep, that still could have, I think, significant benefits in the context of age-related memory dysfunction and perhaps neurodegenerative diseases. Also, there's the growing body of literature, the function of sleep and dreams and everything people are still arguing about, but during sleep, one of the things that there's now evidence that happens is a lot of garbage essentially gets cleared out of your brain.

Some of that garbage is thought to potentially playing a role in Alzheimer's disease and perhaps other neurodegenerative diseases. If you're not sleeping well, that housekeeping process is not going to be happening, and so that's another potentially important aspect of getting good sleep, and so, again, even if this just helped with sleep, the CBN, it still could have benefits.

Jane: What happens, just because I haven't been in a lab, when you've been working so hard with your colleagues and all of a sudden you find something like this, that has some efficacy, that could help people? That's why you're in this, to help people. What do you do? Do you high five? Do you have a party? What happens when you realize, "Oh, my gosh, guys, we found something that could help"?

Pam: Actually, over the years, we've identified several compounds we think might have benefits, so it's tempered enthusiasm, I guess, because there's still a long way to go. As I said, the CBN work right now is just an insult culture and encouraging, but there's a long way from animal studies to see if it can improve aging associated with Alzheimer's disease. To move it further is an even more involved process because, for natural products, you may be able to take them directly into humans. I think CBN you probably could because it's generally recognized as safe, so **[00:10:00]** if it's something like that, if you could get money, take it into a clinical trial for human use.

Jane: But once you get into a clinical trial, we're talking years from now, probably, before we have the results of that, years.

Pam: Well, it depends on exactly what you are trying to do. Again, CBN is already out there, so the approach might be quite different than with a pharmaceutical company because I think the goal wouldn't be to make money off of it, it would be to just show that there was a potential for efficacy in the context of the disease. One of the problems with Alzheimer's trials is, particularly if you start with people earlier stages of the disease, some people progressing more slowly than others, but it has nothing to do with taking the compound. There are developing, new memory tests and new markers that potentially could be used to speed up trials and to get better indications that something might help.

From my point of view, for a natural product like CBN that's already commercially available, as I said, the point would be to do probably a smaller-scale trial to just see if there really was efficacy in people, much more so than these huge trials that drug companies do where the goal is to have something they can make a lot of money off of, because the point wouldn't be to be making money off of it. It would just be to see if it actually could have some benefit for patients.

Jane: CBN prevents cell death, is that right to say?

Pam: Yes. At least in our models, yes.

Jane: You said you were studying other cannabinoids. There are 150 of them. How are those doing? Are those helping brain health in any way?

Pam: Well, our focus has been on CBN. We screened a number of cannabinoids in our assays. A lot of them didn't actually work. We identified what's called a structure-activity relationship, so a core structure that was **[00:12:00]** essential for protective effects. A lot of the cannabinoids are missing parts of that structure, so they didn't work. As I said, CBD worked very well, too, but I don't have that big a lab, and we decided to focus on CBN because less was known about it and it's actually very stable. In that respect, it's a good compound to work with and, potentially, as a drug candidate.

Jane: This still doesn't give your research and your findings, which were encouraging but haven't been tested yet in humans. What do you do? It doesn't give license for someone just to go out and smoke a bunch of weed because then they're getting THC and CBN and CBD, and it's not a good idea.

Pam: No. I think, as I said, and as you noted that CBN is available in various products. Also, the CBN, it's a breakdown product of THC, so when you smoke cannabis, then the levels are going to be very different. I think the better approach would be to use some commercial source where they actually tell you how much you're getting. Our animal studies were actually trying a couple of different doses. If we do see beneficial effects, we would have a little bit better idea of what kind of dose might be potentially beneficial in humans.

Jane: How can you tell if a mouse is having the neuroprotective benefits? Do they just stand up and say, "I'm okay now," or do they run on their wheel faster, or is it a post-mortem autopsy of their brains, or how can you tell?

Pam: Well, it's a combination. We can do behavioral assays on mice. There's a number of tests we can do with mice to look at memory because memory loss is the hallmark of Alzheimer's disease, so that's what we usually focus on in our studies. One of the simplest tests that we can assay short-term memories, what you'd use when you put your cheese down 10 minutes ago and now you have to remember where you put them, and longer-term memory in mice, one of the simplest tests to explain is something called novel object recognition test.

[00:14:00] We put a mouse in a cage, and there are two identical objects. We let the mice explore for 5 or 10 minutes, and then we take them out of the box and put them in their home cage and let them relax. Then, depending on whether you're interested in short-term or long-term memory, either a few hours or the next day, you put them back

in the box, and this time, one of the same objects is there, but there's a new object that they've never seen before.

If they remember the old object, they'll spend more time with the new object because it's what we would do, too. If you come into a room and there's something you've never seen before, you'd spend more time with that than something you've seen many times in the room. If the mouse remembers the old object, it will spend more time with the new object. If it doesn't remember the old object, then it will spend equal amounts of time with both objects.

Jane: That's fascinating.

Pam: That's one of the simpler tests. It's not stressful, particularly, for the animals, and it can be repeated multiple times on the animals. It actually is a good indicator of defects in memory. There are other tests that we do as well.

Jane: Where do you think that this is going? Look down the road. Where's this headed?

Pam: Well, I think it depends a lot on how these mouse studies come out. If the data from those is encouraging-- Let me go back one step. We do also do analyses of their brains post-mortem on the mice as well. The mouse strain we're using for this study is a strain that has what's called an accelerated aging phenotype. They have a shorter lifespan, and they develop a lot of the brain changes associated with Alzheimer's disease as well as changes in other organs that are associated with aging and disease, so we'll be able to see, from the behavioral studies but also at the biochemical level, if we're maintaining various **[00:16:00]** aspects of a younger, healthier brain and potentially other organs as well.

Jane: It seems, from my learning, that slowing aging prevents age-related disease, and so you're really onto something.

Pam: Right. We've used these mice in a number of previous studies and with some other compounds we have and shown that we could make not only the brains but other organs appear younger based on various molecular and functional parameters. That's something we would look at with CBN, too. If it didn't help with memory, but we see, potentially, benefits in other organs, that might lead in a different direction, so it's a little bit hard to say right now.

Jane: It's off-topic a little bit, because I know you're not studying this, but Dr. Dale Bredesen, he was formally with the Buck Institute, he has said that there's new research out that shows if you are using cannabis in its entirety, all the spectrum of all the different cannabinoids, like smoking it or edibles or something like that, that it has an

aging component. Are you reading that research? Is that something we should be paying attention to?

Pam: Well, yes, that's a bit more complicated because the cannabis, as you pointed out, has a whole lot of different compounds in it, and it's not just the cannabinoids, there's whole other families of compounds, terpenes and things that particularly contribute to the smell but they also can be bioactive. It's quite different using the whole cannabis plant than using just a single component of the plant. Also, people have been breeding the cannabis plants to have high THC or high CBD and all of this, so there's a whole lot of different strains out there, so what different people are using can be very distinct, too. It can be hard to compare different products.

By focusing on a single compound, we're taking out a lot of those other variables. Again, the psychoactive component, I think, potentially can **[00:18:00]** have an effect. I guess there's arguments of whether that can be harmful or not in the long term. It would be something to pay attention to, but we're not presenting this in the context of the entire cannabis plant. Again, CBN is really quite a minor component of the cannabis because it's a breakdown product of THC, so the levels of CBN are generally quite low. People wouldn't actually be getting much CBN by smoking.

Jane: Well, that's interesting because it is so low. Before we close, anything else that we've missed or you would like to add about you and your colleagues' research?

Pam: Well, as I think you pointed out, I think focusing on this intersection between aging and neurodegenerative diseases is going to be critical to advancing treatments for these diseases. Aging has surprisingly been left out of a lot of discussions for many years on these disease that people have ignored the fact that it's the major risk factor for Alzheimer's as well as most other neurodegenerative diseases. I think taking that into account, what happens in the various cells in the body during aging that leaves them vulnerable to additional insults that lead to disease development, is something that's extremely important.

Both the research in my lab as well as many labs around the world looking at aging, what contributes to aging, and how that contributes to neurodegenerative disease is a really important direction that the field is starting to go in but needs to continue to go in because I think that's the way people are going to identify approaches to not only increasing your lifespan **[unintelligible 00:19:39]** not that great at-

Jane: You're sick.

Pam: -all of the extra [chuckles] **[unintelligible 00:19:42]** when you're not all that functional. Approaches to keeping people healthier longer, there's lifestyle changes that can be made, but there may be additional, particularly natural products that may be out

there that can promote the healthspan longer, and by **[00:20:00]** virtue of that, reducing potentially the development and the progression of some of these neurodegenerative diseases.

Jane: The World Health Organization has declared aging a disease. By doing that, it does speak to exactly what you were saying. We can impact our healthspans. We can slow aging and have a lot of benefits for our brains and the rest of our bodies.

Pam: We hope to be able to slow aging. We have in mice and a lot of other organisms, but whether we can do it-

Jane: In people.

Pam: -in humans is still up for debate, I think. There's trials out there and there's a variety of different viewpoints on the best ways to do that, which different labs are investigating as you probably know. Again, aging is heterogeneous as well. It may be that as with diseases, as with cancer, there's not going to be one approach for everybody. Different people are going to respond differently to distinct compounds and distinct potentially lifestyle changes, and other approaches. There may not be one single approach even to treat aging.

Jane: I'm watching from the sidelines all the funding that's being pumped into this research. Are you finding it easier to be funded now?

Pam: Well, for Alzheimer's disease, yes. The last maybe five or six years, maybe a little bit longer, NIH has started to put a lot more money into Alzheimer's disease research. For a long time, the funding was really very low and it was pretty much directed towards a single hypothesis about what caused the disease. If you were not working on that hypothesis, it was extremely difficult to get funding.

Jane: The amyloid-beta.

Pam: They just were not funding grant proposals, either the NIH or the Alzheimer's Association really were not particularly interested in ideas that were outside of that hypothesis. That's changed particularly with the drug candidates that were based on **[00:22:00]** that hypothesis, that have all failed-

Jane: They have.

Pam: -in clinical trials. Even before those failures started, they began to put more money in Alzheimer's disease. Part of that, I think the Alzheimer's Association really lobbied for that and lots of other people as well. This was a major health problem that was not being addressed adequately by the funding that the NIH was providing. That

respect, it's easier. I know there's a lot of companies out there that have jumped on funding.

They're all hoping to have some blockbuster thing, I think, to allow people to monitor their biological age and see how that corresponds to their chronological age and recommending various approaches to getting your biological age down [crosstalk] or at least lower than your chronological age, or not more than your chronological age. There's a lot of investment, a surprising amount of investment in antiaging, but I don't know what's going to come of all of that.

Jane: It's very early.

Pam: Well, it's also tied to the fact that the world population used to be a pyramid and now we're like a tower, I guess. [chuckles]

Jane: Then what does that mean for society in the future on the planet? On a personal note, my dad passed from Alzheimer's in 2004. My mother, I just visited her this weekend back in Iowa. She's just in her very final days from Alzheimer's. I just want to thank you, Pam, for what you're doing, for how you are helping families like mine because we need it. Thank you very much.

Pam: Well, we're not there yet, but anyway, thank you.

Jane: You're welcome.

Pam: I mean, we hope to have something, but as I mentioned, there are lifestyle characteristics that have been recommended to pay attention to risk of developing the disease.

Jane: Make sure your blood sugar is in order. Make sure you don't have bodily inflammation. **[00:24:00]** There's a whole list of them. Bredesen has a list of those foundational things that are just pivotal for just good health as we age. Dr. Maher, thank you. Thank you so much for your time.

Pam: Thanks.

Jane: You have a great day.

Pam: You too. Thanks.

You've been listening to the *Cutting Edge Health podcast* created and hosted by Jane Rogers. The website is cuttingedgehealth.com. We hope you enjoyed the show and would very much appreciate your writing a review. They

help a lot and we read each one. Any information shared on this podcast is for educational purposes only. Guest opinions are their own.

This podcast is not responsible for the veracity of their statements. The comments expressed are not medical advice. Do not use any of this information without first talking to your doctor. This podcast and Jane Rogers disclaim responsibility for any adverse effects from the use of any information presented. Thank you for listening and have a beautiful day.