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How DDL-920 Could Help Restore Cognitive Function in Alzheimer's Patients

Ashley Baker:
Welcome to *NeuroFrontiers* on ReachMD. I am Psychiatric Nurse Practitioner Ashley Baker, and joining me to discuss the potential restoration of cognitive function in Alzheimer's patients through the DDL-920 molecule is Dr. Istvan Mody. He is a Professor of Neurology and Physiology at UCLA Health, and in 2018 was awarded the J. Allyn Taylor International Prize in Medicine. Dr. Mody, thanks for being here today.

Dr. Mody:
Thank you for the interview.

Ashley Baker:
We'll jump right in, Dr. Mody. For some background, you conducted a study centered around a molecule called DDL-920 that was proven to restore cognitive functions in Alzheimer's model mice. What inspired this research?

Dr. Mody:
Well, we have to go a little longer back for that because we know for a fact from many studies—not just our own but many others over the past two decades, probably—that the brain actually shows oscillations that are reflections of electrical activity in the brain, and some of these oscillations have different frequencies, one of the higher ones. These are beats per second, or hertz, so between about 30 to 120 hertz. These oscillations are called gamma oscillations, and they are known to participate in laying down the traces of short-term and even long-term memories and in cognitive functions. So it's also known that these oscillations are critically dependent on a type of neuron in the brain, a nerve cell in the brain, that is called an inhibitory neuron that is fast-spiking, is a parvalbumin interneuron. We've been studying these neurons for a long time, and we have noted that they actually have some receptors on them that regulate the power of these oscillations generated by these interneurons. The way we discovered this is actually through studying hormonal effects on the brain, and the ovarian hormones end up changing the expression of certain receptors on the surface of these particular nerve cells, and as the changes in these receptors happen, so do the gamma oscillation frequencies and amplitudes or power. So for some time now we were—after finding the molecule that would be able to block these receptors in order to enhance the function of these neurons so they can increase the power of these oscillations, and finally, we came across one of these, and my colleague Varghese John from the Drug Development Laboratory in our department—hence the name DDL—we actually came about one and synthesized it, and the rest is published in this paper in *PNAS*.

Ashley Baker:
Could you tell us a little bit about the objective of the study and how it was conducted?

Dr. Mody:
So the objective was really to enhance these oscillations that I mentioned that are key elements in laying down memory traces and also in cognition. Now it has been known that in Alzheimer's patients themselves, these gamma oscillations are somehow subdued, and we were also noticing the same thing—not just us but others—in Alzheimer's model mice. These mice are modeling Alzheimer's disease by various genetic factors that are present in familiar Alzheimer's disease or in late-onset Alzheimer's disease. Our mice also had the human APOE 4 gene inserted into them, so they replicate a lot of the events that take place in Alzheimer's patients. They also have cognitive and memory problems. So we first showed that this molecule does indeed enhance gamma oscillations, does indeed block the receptors that we are intending to block on these parvalbumin interneurons, and then the next step was to use it in Alzheimer's model mice that are impeded in their memory tasks. And what we tested is the behavior of these mice on a maze called the Barnes maze.

Now the Barnes maze is a large round table with many holes on its rim, and one of these holes has a small box underneath where the mice can hide—escape, so to say. Now there are various signs on the walls around this large table, so these are the visual clues for the mice to remember where the escape hole is. So they look around the wall, and then finally guide themselves to this hole. They have about a week for this to be learned, and they do pretty well. This is the wild-type mice. They actually orient themselves with the surroundings and the visual clues in the wall, and they go immediately, and find that escape hole. Then the little box from underneath the escape hole is being removed, and 24 and 48 hours later the mice are being tested now without the escape box, and the task is to measure how quickly they go to the hole that previously had the escape box under it, how long do they spend in the quadrant of this round circle where the escape hole was, and how long of a path they can cover in order to get to the box where the escape hole used to be.

These wild-type mice, they perform pretty well, so they spend a lot more time in the quadrant where the escape box used to be. Then the 25 percent chance they find it pretty quickly, so they have a short time to reach this hole, and they also have a short path length. The Alzheimer's mice that we used, they actually spent a lot of time trying to locate the hole once the escape box was removed. They spent only the time of chance, 25 percent of the time in this quadrant and so on, so they were pretty much lost 24 hours and 48 hours after the training and after removal of this little box from underneath the hole. However, when we treated the Alzheimer's mice with our compound that was administered to them orally in a syrupy fluid, they were treated for two weeks before the entire training session started twice a day, and then once a day during the training session. So these mice that were treated with DDL-920, they behaved very much like the wild-type mice, those that found the hole quickly after 24 and 48 hours obviously, did much better than the nontreated or vehicle-treated counterparts. So this was the breakthrough discovery that what we anticipated from the increase of gamma oscillations by the drug, it actually worked in practice by somewhat curing the deficit in memory and cognition of these Alzheimer's model mice.

Ashley Baker:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Psychiatric Nurse Practitioner Ashley Baker, and I'm speaking with Dr. Istvan Mody about the DDL-920 molecule and its potential to improve cognitive function for Alzheimer's patients.

We spoke a bit earlier about your study, but now let's look ahead to what this could mean for Alzheimer's research. Now, Dr. Mody, since this study was conducted on mice, what steps need to be taken to make it a viable treatment option for humans?

Dr. Mody:
Well, obviously, that's our hope. So our hope is to move on to human patients and to really have a big impact on their life, their cognition, their memory, and for that we will need to do a whole range of studies that will take us to human-enabling studies. First, we have to do a toxicity study, obviously, with the drug to make sure that it's not toxic in higher and higher quantities or in other words, to establish an effective dose versus a lethal dose. This would be in animals. Once we establish this, we could move on to humans. And maybe we could start with just a human study in healthy volunteers, who would take the drug, and we would then monitor their brain waves with electroencephalography to show that, indeed, the target of our drug, the gamma oscillation, is engaged in just human volunteers.

Once we have those data—and hopefully, we can get there without any side effects—then the drug would be, hopefully, safe to give to patients, first to patients, perhaps, with Alzheimer's disease or who haven't moved on to Alzheimer's disease yet, maybe mild cognitive impairment patients. But we have other applications as well. In other neurological and psychiatric diseases, there is evidence for decreased gamma oscillations, and these are, for instance, schizophrenia, depression, also autism spectrum disorders. So once we establish its safety and efficacy in humans, then I think that we could move on to a variety of patients, including the mild cognitive impairment and Alzheimer's disease.

Ashley Baker:
To go just a little bit rogue here—just thinking of some questions that our audience, especially our clinical audience, may be wondering—would the future of drug development using the DDL-920 molecule and formulating a human treatment based off of the mice study, are you able to speak to at all about timing of treatment on the human population in terms of where the patient is in the disease state? How many treatments a patient may need? Or comorbidities that might rule out the treatment? Any insight there?

Dr. Mody:
Yeah. We are, obviously, a long way from finding out what potential side effects might be, what potential toxicity effects might be. We hope that they're very little. Incidentally, we did not notice any of them in the mice, so they didn't have any effects that we could actually record even with electrodes in their brains, so they weren't hyperexcitable; they weren't hyperactive; but more needs to be done, clearly. So what we're thinking if it's safe and target specific in humans, then this could be administered in early stages of Alzheimer's disease, as I mentioned, in mild cognitive impairment in patients who would go on to develop Alzheimer's disease, or perhaps, stop that process or halt that process altogether or delay it tremendously.

Another way of thinking of it is that we now know that there are a couple of antibody treatments that have already been approved for Alzheimer's disease. These are antibodies against the A-beta oligomers and A-beta plaques or fibrils that end up quite successfully clearing all the plaques from the brains of Alzheimer's patients. However, clearing the plaque may be good for stopping further damage to the cells that is caused by these plaques, but unfortunately, the circuits that are left behind cleared of the plaques may not be performing as well as they used to before the disease, so it could well be an add-on treatment to all of these antibody treatments that cleared the plaque. We don't know, by the way, whether our drug will clear the plaque by increasing the gamma oscillations, but clearing the plaques and having a cognitive enhancer or something that improves on the lost memories might be quite beneficial.

Ashley Baker:
Given how common Alzheimer's disease is and the excitement from our listening audience that is there—because I'm sure that we all know somebody with Alzheimer's disease or who has passed from Alzheimer's disease—are there any final thoughts that you would like to leave our audience with?

Dr. Mody:
We are also working on analogues of this molecule, so this is just the first step. We have a whole chemical space that we would like to fill with this. And hopefully, in a short time, pending financial support for our endeavors, we will actually be able to take this to the clinic. I want nothing more than to be able to help the patients and their relatives and their caregivers because that is also an enormous burden on society in general of what happens to the poor relatives and the caregivers of these patients who are almost helpless.

Ashley Baker:
With those forward-looking thoughts in mind, I want to thank my guest, Dr. Istvan Mody, for joining me to share his research on a molecule that could potentially improve Alzheimer's disease. Dr. Mody, it was great having you on the program.

Dr. Mody:
Thank you very much. My pleasure.

Ashley Baker:
For ReachMD, I'm Psychiatric Nurse Practitioner Ashley Baker. To access this and other episodes in our series, visit *NeuroFrontiers* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.