BRAINWISE
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The future of Alzheimer's Disease drugs

in Featured, Highlight / by Dr. Jeffrey Cummings

Few people in the world know more than Dr. Jeffrey Cummings [https://www.unlv.edu/news/expert/dr-jeffrey-l-cummings] about treating Alzheimer's Disease. Dr. Cummings is a research professor in the department of brain health at the University of Nevada, Las Vegas. He's also director of the Chambers-Grundy Center for Transformative Neuroscience at UNLV. Every year Dr. Cummings publishes a report about the number of trials for new drugs to treat Alzheimer's Disease. This means he has his finger on the pulse of Alzheimer's Disease treatment approaches. BrainWise Contributing Editor Matt Villano recently sat down with Dr. Cummings to discuss 2023 data and the future of Alzheimer's Disease treatment overall. This transcript of their conversation has been edited for clarity.

BrainWise: When we look at the landscape of Alzheimer's drugs treatments today, what would you say characterizes a lot of them and what specifically are these medications addressing?

Alzheimer's disease clinical trials. In 2021, we had the approval of aducanumab, and then in 2023 the approval of lecanemab, both of those by accelerated pathways. Now, we think that within the next probably two months, we will have standard approval of lecanemab and likely standard approval of donanemab.

Soon there will be three monoclonal antibodies on the market. A critical step in that is the review of them to determine whether they will be reimbursed, because people will take the medication only if it's reimbursed, and they can benefit from the medication only if they take it. We must establish that link in order for Alzheimer's patients with early Alzheimer's disease to benefit from this research advance. To emphasize a few of those areas, these are complicated drugs, monoclonal antibodies administered intravenously, and with a side effect called ARIA that must be carefully monitored and managed. On the other hand, they are the first disease-modifying therapies for Alzheimer's disease and almost the first disease-modifying therapies for any neurodegenerative disease. Only ALS has some disease-modifying agents, nothing for Parkinson's disease, frontotemporal dementia, any of the other late onset neurodegenerative diseases. This is a breakthrough. It's truly a breakthrough, because it's turning a corner on disease modification and our ability to impact the underlying biology of the processes that lead to neurodegeneration.

The clinical benefit is modest. There's been some criticism about this. It's about 30% slowing of cognition, about 40 percent slowing of function. I think that's fantastic. If I had MCI, which lasts about three years, and I could make my cognitive integrity last another year during that period before I became fully demented, I would want it. I think that's the human question that is worth asking. What is the value of human cognition towards the end of life? I find these worthwhile drugs, but I acknowledge the complexity that they bring, for sure.

I regard them also as a preliminary, almost proof-of-concept, advance. They show us that amyloid is a reasonable target. They're not the drugs that we want ultimately, right? We want drugs that are more efficacious. We would like them to be more convenient. We would like them to be safer. All those things are goals to be realized in the next steps in therapeutics.

There are other drugs in the pipeline, some close to coming to the end of their trials. They have reasonable hypotheses. We have evidence for these monoclonal antibody approaches. We also have, I think, pretty strong evidence for the anti-tau ASO, a drug which must be administered directly into the spinal canal. The effect of that [in trials has been] unbelievable. Again, I see real excitement in the field all around our ability to manipulate the biology.

Disease?

Dr. Cummings: This is a question I want my patients to answer. I don't want Medicare to answer it for them. I want them to be able to say, 'Yes, I want to go in for an infusion every other week with lecanemab,' or, 'Yes, I want to have those MRIs that are required to make sure that I don't get ARIA,' or 'I'm 92 and I want to live out my life now without these medical complications.' I think those are all defensible positions and I want my patients to be able to make them.

One of the things I am trying to help achieve is the availability of the drugs so that my patients can make educated choices. We're going to have to educate patients and caregivers and the world about these drugs and hopefully we're going to get simpler. There are already subcutaneous equivalents in clinical trials and there are already blood tests that look pretty good in terms of being able to replace the PET scan and the lumbar puncture to establish the diagnosis. But once we can identify the patient with a blood test and treat them with a subcutaneous injection, we're in a different world of the inconvenience that these drugs currently represent.

That's coming fast. We need to accept that we don't know what the future will bring, so we need to deal with what we have now. But if you had to forecast, how long will we be here in this space? I think we'd say a short period of time, because the subcutaneous injections look very good, and the blood biomarkers look very good.

BrainWise: What are the most important questions for drug researchers to be asking at this point, as we look to future development?

Dr. Cummings: I would say we're looking forward to combination therapies. Improvement of 30 or 40 percent is not enough. So, what do we want? Well, we would like essentially to arrest the disease progression. We'd like a combination of therapies that would come close to that. We also want to improve cognition. We want to restore them to as close to a normal level of function as we can. Only 11 percent of the pipeline is currently devoted to cognitive enhancers. Those are drugs that would improve cognition. And 78 percent of the pipeline is currently devoted to disease-modifying therapies, drugs that would slow the progression. So, one of the things I'd like to bring back into the drug development world is more emphasis on cognitive enhancement.

Other questions pertain to how we're approaching this. Recruitment is horribly slow. It's the major reason that we're not getting drugs through each phase quickly enough. The diversity of

BrainWise: To what extent are there currently trials in place that incorporate a more diverse subject group?

Dr. Cummings: One example is the Global Alzheimer Platform, which did a biomarker trial. They achieved, I think, 22 percent racial and ethnic minority representation in that study. That's pretty good. I think we're kind of pretending right now that we're going to have an answer regarding treatment in minorities if we include a representative number [of minorities in trials]. We will not.

BrainWise: What's the current landscape of trials?

Dr. Cummings: This year—the 2023 data just came out [https://brainwisemedia.com/record-number-of-alzheimers-drugs-in-development-in-2023/] —we had 178 trials and 141 unique agents in clinical trials on the index date of the study. Most of them are not viable. When we last calculated, there was a 99 percent failure rate of Alzheimer's disease therapeutics. I think it's less severe than that now but I'm sure it's at least 80 percent. Most of them still will not be viable. One of the correctable reasons that drugs fail is because they're in poorly designed trials. We want to make sure that when a drug fails, it's because the drug didn't work, not because the trial didn't test it adequately. This is a solvable problem over here. We can make those trials be great. We should require it. We can't predict which target will work, that's why we have a whole bunch of targets.

BrainWise: What trends are you seeing?

Dr. Cummings: More trials; the 2022 numbers [https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1002/trc2.12295] weren't as high. Another trend that is obvious is that the type of drug is changing. A biologic is a big molecule that must be given intravenously or subcutaneously or intrathecally (which means, into the spinal canal). Those are all called biologics. The drugs that are given by mouth are called small molecules. What you see in the pipeline over the past five years is the growth of the biologics. It's interesting. It's gone from 40 in the pipeline to 60 in the pipeline, which is about a third of the pipeline.

This is important because that's what the doctor is going to offer the patient. It also means the doctors must begin thinking about what their practices are going to look like. They're going to have to have infusion chairs, they're going to have to anticipate subcutaneous administration. Alzheimer's Disease treatment likely will become much more like cancer therapy. Practice patterns are going to have to change. Healthcare systems are going to have to change. And that's

One position that I'm taking in some of the things I write is that this is the first step. The march of science is no doubt going to yield more medications, and we [must] have social and healthcare systems that can absorb the advances in science. We haven't had much success before, so we haven't had to do much of that before. But we should see this almost like a test case. How do we begin thinking about having a system which is sufficiently flexible; [a system into which] we can introduce new medications without there being a lot of hurdles? By the way, the pharmaceutical companies must be partners here. If they make the prices very high, that's just another hurdle. But if this is a kind of collaborative arrangement so that we can get these drugs in without too much cost, then the system is likely to have the flexibility to be able to do it.

BrainWise: Tactically, what aspects of the landscape of the brain will be the targets of the next generation of Alzheimer's Disease drugs?

Dr. Cummings: I think amyloid will continue to be a target. Tau looks like a good target. The two most active areas in the pipeline are inflammation and synaptic function. We're going to see a lot of emphasis on trying to decrease the inflammatory aspect of Alzheimer's disease. There are roughly 20 drugs against inflammation in the pipeline right now. No two of them have the same target within inflammation. Is one of these more manipulable than another, in a way that we can see a therapeutic benefit or early on a biomarker benefit? Is there a combination that looks like it might work together because both have small effects?

The fact that we have so many targets within a given process is going to be highly informative. The same is true of the synaptic function. Of the roughly 15 drugs addressing the synapse, only two have the same mechanism, so it is interesting to see how diversified the mechanisms are within a single target area.

BrainWise: Five years from now, what do you think Alzheimer's Disease treatment looks like?

Dr. Cummings: It'll still be dominated by biologics, but I do believe [some treatments will] be given subcutaneously or maybe at longer intervals. We might be able to extend this so that we could give a drug, say, every three months after an initiation period where it's given every month. That'd be a great outcome so that the patient doesn't have a lifelong commitment to infusions every other week or every month as they are now, depending on the drug.

With donanemab, when [patients] get the amyloid levels to undetectable, they stop. That's interesting because, of course, that's a lot cheaper drug than the drug that must be given continuously. Already, we're seeing vastly different strategies within this therapeutic category.

follow that therapy, and maybe when therapy is interrupted, to decide when to introduce it. I think the blood tests are going to help us in a whole variety of ways.

BrainWise: Where does stem-cell development fit into this overall puzzle?

Dr. Cummings: There's a lot of excitement about stem cells. There are six stem cell trials in play right now. Five years is a short time horizon for that, because the FDA is very conservative in terms of stem cell trials. Often, they [administer] stem cells and then watch for a year to see what happens. [It ends up being] 18 months or two years to recruit the trial, and then it's a year after the last patient in before you get the last patient out. Now, you're talking about three years already.

I don't think we'll have stem cell therapy [for this] figured out in five years, but I think that's a worthy pathway to keep working on. Can we make sure they're safe? That they do what they're supposed to do once we introduce them into the body? What's the magnitude of the response and what's the durability of the response? These are the things that must be answered, and they'll be answered, I think, more slowly for stem cells than they are for biologics or small molecules, because the trials are more difficult to do.

BrainWise: How likely is it that we'll see combinations of different treatments?

Dr. Cummings: I think it's very likely, even necessary. I think manipulating one target is almost certainly not going to be enough to halt or seriously slow complex disease. At the same time, combinations are tough, because a company [would need] to have two agents at the same level that could be put into the same trial, and they almost never have that. [The way it is] now, you got to have one company with one agent and another company with the other agent, and those two companies [must] work together. These are just operational complexities that keep us from doing what we want to do.

The trials are hard, and the developmental process is hard, but we absolutely must do it. This is where, I think, federal funding is critical, because you could get two repurposed agents and put them in the same trial at the same time, and at least see whether manipulating those two pathways looks beneficial. If so, you have a whole range of ways to exploit it. But there are complexities that you don't ordinarily think of, like a company must have two drugs in order to do the trial of combinations, and it's a rare event in the company. They usually have one asset that they're advancing in Alzheimer's disease and then a bunch more that they're advancing in cancer, so they don't have two assets that they can put into the same trial.

Dr. Cummings: What I want is the AIDS discovery. You have the virus, put your person on combination therapy, and they're able to live, really, without manifestations of the infection for many years. Magic Johnson, right? The classical example of this. That's what we want. Do your blood test every year. When your PTAL 217 starts to rise, you're getting amyloid in the brain. You get put on a combination therapy and you stay on that for the rest of your life, and you follow your PTAL 217 to know whether you have ameliorated the acceleration of the neuronal processes in the brain. That's a kind of future scenario that, I think, is realistic. I think that could be done and looking forward to having it be done.

BrainWise: What other mysteries do we need to solve about Alzheimer's Disease?

Dr. Cummings: There's a part of Alzheimer's Disease that is driven by aging, and aging is pretty hard to fix. I'm not forecasting a cure, but I do foresee a time when we could prevent the disease through early detection or maybe through risk stratification of people in their fifties. Amyloid starts in the fifties, and then people become symptomatic 20 years later in their seventies. We could start testing very early. By then, maybe we will have small molecules that could be taken, so it would not be an inconvenience and we could prevent the onset of illness.

BrainWise: What are the next big questions you'll be asking in your research?

Dr. Cummings: How can we accelerate biomarkers to allow us to do great drug development? That's a huge one. Because it turns out that biomarkers have been the key to our success, That's why we have monoclonal antibodies. We also have what's called the Amyloid Tau Neurodegeneration framework, or ATN. We have biomarkers for all three of those. We need more biomarkers so we can be more informed about the impact of therapy and who should be on therapy. We also need biomarkers of health. The biomarker expansion is critical, both for the disease and also to begin to understand the biomarkers that would signal good health in individuals, because it's ultimately some sort of algebra between the brain health and the brain disease that determines who becomes symptomatic.

BrainWise: What do you want people to know about Alzheimer's Disease?

Dr. Cummings: If I had to simplify the message, I would say great progress is being made and hope is there. We're going to be able to help people. We're going to see who needs help early on. We're going to keep people at a more dignified level of function during their aging years.

At the same time, while there has been a good increase in funding for Alzheimer's disease, we

to rural communities. We've got to get everybody on this wagon. We've got to make sure we're helping everybody, and that costs a lot of money.

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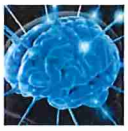

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