UNFOLDING ALZHEIMER'S: THE ACCUMULATION OF AMYLOID AND TAU WITHIN THE BRAIN

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William Jagust, MD, *is a professor within the UC Berkeley School of Public Health and the Helen Wills Neuroscience Institute. Professor Jagust received his MD from SUNY Stony Brook and completed his residency in neurology at Boston University. His research focuses on aging and how the brain changes in response to age and disease such as Alzheimer's. Specifically, Professor Jagust's interests lie in observing the accumulation of two abnormal protein aggregates in the aging brain: β-amyloid and tau. Professor Jagust uses PET scans and machine learning in order to conduct his research. In this interview, we had the pleasure of discussing how β-amyloid and tau accumulation in the brain lead to Alzheimer's and how Professor Jagust can spark optimism for the future of combating Alzheimer's disease.*

BSJ: Much of your research centers around Alzheimer's disease. What sparked your interest in this topic?

WJ: I was not really interested in Alzheimer's when I started out. At first, I was interested in the brain and how the brain produces behavior. At the time, I had finished my training in neurology as a clinical neurologist, and I wanted to explore research. When I started my career, there was a new technology that became very popular to try to understand brain function called PET scanning. This was a technique people used at that time to understand how the brain functions and how it generates behavior. So, I joined a research group that was using PET scanning to expose me to the technology. It turned out that my supervisor was using PET to study Alzheimer's disease. I did not really want to study Alzheimer's; I wanted to study language and memory. But, since he was paying my salary, he told me that I had to study Alzheimer's. After a relatively short period of time, I got really interested in it, and I began to think of it as a really difficult, fascinating, and important problem yet to be solved. It was not exactly a straight and narrow pathway to the research I do today.

BSJ: Alzheimer's disease is a massive issue in medicine, and current treatments are still limited. Why is Alzheimer's such a difficult disease to combat, and how does your research contribute to this fight?

WJ: Alzheimer's is difficult for a lot of reasons. For most of my career, treatments were not very good. For so long, we could not measure a lot of the things happening in the brains of people with Alzheimer's. For the vast majority of my research, all we could see was the destruction this disease caused. When we looked at MRI or PET scans, we saw how the brain used glucose and how glucose metabolism decreased in afflicted patients. But, the reduction in glucose metabolism and the shrinkage of the brain are, in reality, nonspecific – they occur in almost every neurological disease. Thus, these indicators were not telling us much about how Alzheimer's disease really happened. This was certainly one of the things that made it very difficult to treat. For so long, you could only diagnose Alzheimer's disease postmortem. We also did not have good animal models. Things began to change in the '90s when people discovered genes that cause this disease, such as autosomal dominant mutations. These discoveries led to transgenic models of Alzheimer's, which then increased the availability of animal models. Admittedly, the transgenic animal models are imperfect, but they have enabled a lot of new innovations to happen. For example, they have helped us generate new therapies for Alzheimer's.

BSJ: Are there any biomarkers that can be used to identify Alzheimer's disease in a human brain? Could these biomarkers be used to attack the disease?

WJ: In the Alzheimer's-diseased brain, there are two proteins of interest – β-amyloid and tau. For decades, we were not able to see them until autopsy; but in the early 2000s a type of PET scan was introduced which allowed us to image amyloid in live patients. Then, in the early 2010s, a way to image tau with PET came along. These tools transformed the field. These biomarkers that can measure amyloid and tau aggregates in the brain, allowed us to see the progression of the brain and track how Alzheimer's

develops and spreads through the brain. The transgenic models were models of amyloid because all autosomal dominant mutations that cause Alzheimer's disease increase the amyloid in the brains of humans. These mutations were then put into mice, and these mice began to make a lot of amyloid; this allowed researchers to experiment with ways to reduce the protein. This resulted in a category of drugs called immunotherapies, which use the immune system or passive antibodies to reduce the amyloid in the brain.

You can imagine that when you couple the ability to give antibodies that might lower amyloid with the ability to track the pathology during life, you start to gain a pretty good approach to developing therapies – and that is exactly what has been happening for the last five years. However, I should note that Alzheimer's is probably more complex than simply amyloid and tau. There are lots of other variables affecting the disease, including inflammation, changes in blood vessels, and all kinds of other physiological processes that we do not yet understand very well. So, what makes Alzheimer's so difficult to treat? For a long time, it was a lack of tools; now, it is because of the disease's sheer complexity.

BSJ: You have already talked a lot about amyloid and tau buildup and how that relates to Alzheimer's disease. What exactly are amyloid and tau and how do each play a role in Alzheimer's?

WJ: The protein amyloid, otherwise referred to as β-amyloid, is a cleavage product from a larger precursor protein aptly named the amyloid precursor protein (APP). The amyloid precursor protein is a large protein spanning the cell membrane that we believe is involved in signaling between cells. When metabolized, it is cleaved to form this β-amyloid protein, which is usually 40 or 42 amino acids long. It is a smaller protein that floats around as a monomer. It then aggregates to form dimers, trimers, and polymers, ultimately forming these plaques that occur in the brain.

The consensus is that these soluble polymers are toxic, and they affect synapse structure and function. When this protein is either over-produced or inadequately cleared, it seems to accumulate in the brain, causing these amyloid plaques.

The tau protein is associated with microtubules in the neuron and neuronal skeleton, acting as a stabilizer for these microtubules. What happens in Alzheimer's disease is that the tau protein becomes abnormally phosphorylated. For reasons we do not understand, it then seems to disassemble from the microtubules and aggregate within neurons. This aggregation of tau seems to be associated with neuronal death and dysfunction. So, in Alzheimer's, you have these two proteins that, when they aggregate, cause problems with neuronal structure and function and probably many other things in the brain, as well.

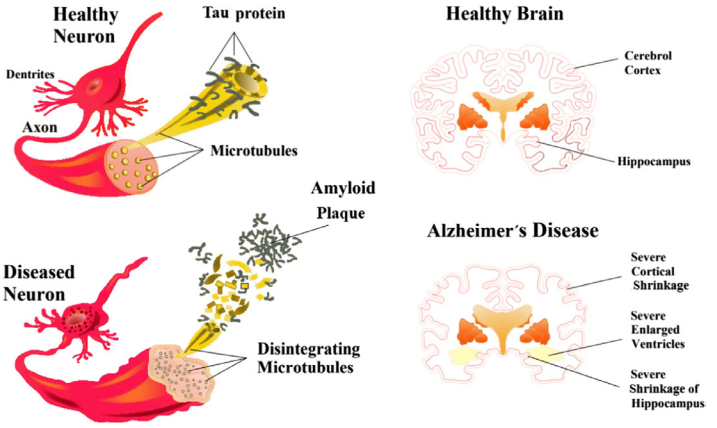

Figure 1: Tau Accumulation and its Effects on Neurons. *The top half of this model shows a healthy neuron with normal levels of tau protein, highlighting that with normal levels of tau protein, the brain is unharmed and neurons are stabilized. The bottom half shows an abundance of tau and thus the disintegrating of microtubules and the resulting impacts on the neuron and shrinkage of the brain.*

BSJ: Do tau and amyloid interact with each other? If so, how and could these proteins be an area of interest for creating treatments for Alzheimer's disease?

WJ: When tau aggregates, it forms these structures called neurofibrillary tangles that occur within the neurons. As humans age, we all develop these neurofibrillary tangles – specifically in the temporal lobe. If you autopsy the brains of people in their 80s, virtually everyone has this tau pathology in the medial temporal lobe of the brain. But, it seems to be benign in regard to dementia for most individuals. However, in Alzheimer's, when amyloid comes along, we think it does something to tau to make it spread out of the medial temporal lobe and throughout the rest of the brain. Serious cognitive decline starts to happen when tau spreads throughout the brain.

There is much we do not understand about this process, but we do know that you can have a lot of amyloid in your brain and not have cognitive problems. However, you cannot have an abundance of tau in your brain without cognitive problems. Also, we never see large amounts of tau spread throughout the brain unless amyloid is present. Thus, in unaffected individuals, we hypothesize that although amyloid may be present in the brain, unless it is interacting with tau, people do not develop Alzheimer's-associated dementia. What we still do not understand is how amyloid interacts with tau to cause it to spread and become malignant.

As for treatments, there are a number of different approaches to treating Alzheimer's. One of these approaches is to lower tau, but current methods are not yet that good at doing so. However, we are getting better and better at being able to lower amyloid accumulation through pharmaceuticals. The idea is, if you can reduce amyloid aggregation, maybe you can prevent this process of tau accumulation from initiating. That is what the majority of

clinical trials are focusing on right now. In only the past week, a clinical trial was reported in the New England Journal of Medicine for a drug that lowered brain amyloid and improved cognitive function in patients with Alzheimer's disease. This is a very exciting finding.

BSJ: It was mentioned that Flortaucipir-PET and Pittsburgh Compound B (PIB)-PET imaging were used to investigate how regional amyloid accumulation progressed in cognitively normal adults. How do these technologies work, and how significant are they for your research?

WJ: They are critical for my lab's ability to understand how Alzheimer's disease evolves. In PIB imaging, we rely on Pittsburgh Compound B, a molecule that is engineered to bind to amyloid. It is labeled with the radioactive Carbon-11 atom, which allows us to track where it goes in the brain using our PET scanner. We inject PIB into the vein of a person, where it circulates around the body, some of it reaching the brain. When it enters the brain, it binds to an amyloid molecule. The PET scan consists of scintillating crystals that detect and map the radiation in 3 dimensions. Therefore, by using PET scanners, we can construct a three-dimensional map of where amyloid is in the brain. Flortaucipir-PET is exactly the same idea, except we use flortaucipir molecules labeled with the radioactive atom Fluorine-18, which bind to the tau protein instead.

A lot of the Alzheimer's "story" that I have discussed thus far is derived from work we and other labs have done using PET imaging. These scans are really safe and noninvasive. Although people get exposed to radiation, it is at a relatively low dose, which allows us to repeat the procedure over time and analyze how amyloid and tau spread across the brain every two to three years.

Thinking back to the early days of my career, when I was at the Alzheimer's Disease Center at the UC Davis School of Medicine, we would follow people over time and measure their memory. However, we only got a chance to see the amyloid and tau in their brain with an autopsy after they died. Now, we can gain a living picture of the pathology in the brain and how it evolves. Currently, my lab follows a cohort of healthy older people who live in the East Bay. These folks are in their 70s, 80s, and 90s, and we often see these little clusters of tau in the medial temporal lobe. In some, we see amyloid; it is in those patients that we often see evidence of the tau starting to spread over subsequent years. We have been doing this style of research now for 15 years, so we have a lot of data, which has really contributed to our model of disease progression. We could not do any of it without PET.

BSJ: You have discussed the presence of amyloid and tau in Alzheimer's patients. Would you be able to provide more insight into how exactly amyloid and tau spread throughout the brain in Alzheimer's disease patients?

WJ: One of the things that Alzheimer's disease has taught us is that amyloid and tau proteins aggregate very similarly to prions.

If you are unfamiliar with them, prions were a Nobel Prize-winning discovery by Stanley Prusiner at UCSF. Prusiner essentially showed how proteins could be transmitted from one animal to another and act like a virus or an infectious agent, even though it was not an infectious agent in any sense. They did not have any DNA or RNA; they were just proteins, but they could be transmitted and cause disease. This idea that a protein can change the conformation of another protein is called templated protein misfolding. Now we see that this seems to happen in every neurological disease. To be clear, these neurological diseases are not infectious. What happens is a misfolded protein approaches a new, normal protein, the new protein becomes misfolded. This cycle of misfolding continues until large amounts of these proteins become aggregated, leading to toxicity.

Amyloid was one of the first proteins that was shown to induce this templated protein misfolding. We now understand that tau also behaves in this way. In fact, pretty much every neurological disease that is a degenerative disorder is associated with these protein aggregates formed from templated protein misfolding.

This is a major way through which amyloid and tau aggregates spread in the brain. However, tau has another trick up its sleeve. As I mentioned, we gain information about how neural networks are structured from the MRI, and from these, we can gather that tau seems to be transmitted from one neuron to another across synapses. It actually seems to spread through the brain by neural connections.

BSJ: Machine learning has recently emerged as a powerful tool for medicine and has even been used in your research. How is it that machine learning can predict tau accumulation, and do you see machine learning as a widespread tool to combat Alzheimer's disease in the future?

WJ: People use machine learning for lots of things in neurological research because of all the PET and MRI scans neurological researchers conduct. These scans result in digital, numerical quantitative data that one can use to train a machine learning algorithm. So, people are using machine learning to interpret patient scans as normal or abnormal. One of the things we have used machine learning for is to predict how much tau will develop over time in a patient's brain. With baseline information, one of the postdocs in my lab trained a machine learning algorithm to predict not just how much tau would accumulate, but where the tau would be over the next several years. This worked out pretty well. One reason it worked is because the way in which tau spreads is fairly predictable. Tau spreads through neural connections, and connections are pretty similar across a population.

I believe machine learning could be very useful in the future. If you give a person a drug that lowers amyloid, you have to ask the question: "Is this going to work if the tau has already spread

everywhere throughout the brain?" If you have ever seen the brain of a person with Alzheimer's disease under a microscope, the destruction is just devastating. The brain has lost neurons, it has lost synapses, and there are axons that are disrupted; it is a disaster. The idea that you can repair such devastation seems pretty far-fetched, at least as of today. As a result, the consensus is that you have to intervene before too much damage has occurred. But, if you are testing a drug, you cannot test the drug on a person who is cognitively perfect, because then you have nothing to follow. It turns out that one approach involves researchers finding people with just a moderate amount of tau – just a little bit of tau at the earliest stages of Alzheimer's. A lot of people believe this is the best way to test drugs, and we think machine learning can find those people.

BSJ: At the moment, the treatments for Alzheimer's disease are very limited. What do you see in the future of Alzheimer's disease treatment?

WJ: There is a lot of contention about the idea of lowering amyloid. There have been a whole series of drugs developed that bind to β-amyloid and seem to remove it from the brain. However, there have also been a number of other drugs that cleared amyloid out of the brain, but people did not get any better; this is where the skepticism stems from. A brand new drug was just released that has shown positive results and it will likely be approved by the FDA. This shows a new way of attacking Alzheimer's by creating disease-modifying drugs that could create massive differences over time in brain structure between those who take the drugs and those who do not. I think this is the most promising thing right now.

There are other promising strategies as well. There is a project in the United States involving lifestyle interventions, including monitoring diet, exercise, blood pressure, lipids, and all kinds of multidomain lifestyle interventions. Evidence from another large study out of Finland indicates that multidomain lifestyle interventions could be beneficial. It may be that this kind of multidomain lifestyle intervention will be effective. As I said, Alzheimer's is really complicated. There are lots of things happening: changes in the vascular system, changes in inflammation, and so forth. Thus, multidomain lifestyle interventions are another thing that we anticipate hearing about in the next few years.

BSJ: With that said, can you provide any insight into the future trajectory of your research?

WJ: My lab is trying to understand things at a fundamental level. I want to understand more about how tau is spreading and whether there are better ways to understand how it is affecting memory. We are also focused on trying to understand differences between people that may lead to disease progression. For example, two people can have similar amounts of amyloid, or even tau, and yet be very cognitively different. Some people, when they get to be 70, 80, or 90, are doing great, while others are

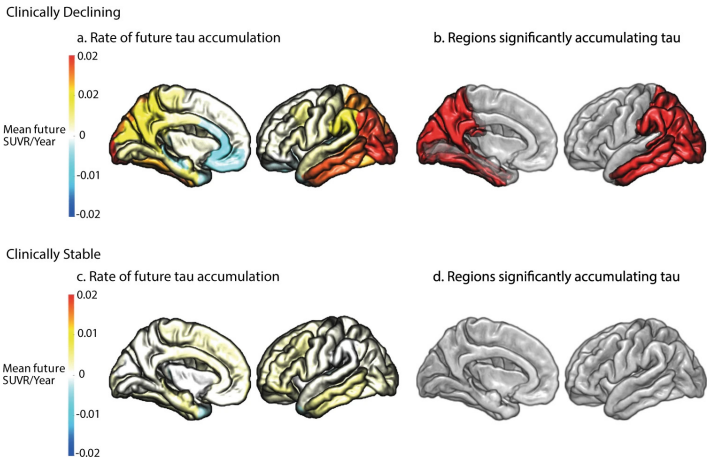

Figure 2: Rate of Tau Accumulation in Clinically Declining and Stable Brains. *This diagram illustrates the relative rate of tau accumulation in clinically declining and clinically stable brains. Tools like these, generated by machine learning, allow researchers to predict where and when Tau will accumulate. This figure represents a key feature of Professor Jagust's research by showcasing the buildup and spread of tau in the brain.*

affected by cognitive decline relatively early. We are attempting to answer questions like this; how does lifestyle affect Alzheimer's, how do genetics affect Alzheimer's, how do amyloid and tau appear in the brain, and how do they spread throughout the brain? Those are all major questions we are interested in studying. It really comes down to understanding the mechanisms that are driving the way amyloid and tau spread and how it differs between people.

BSJ: You mentioned that there are many pharmaceuticals under development aimed at preventing amyloid buildup in the brain. However, it seems tau buildup can be an even bigger problem than amyloid. Is there any research targeted toward preventing tau buildup?

WJ: The way I think about it is, amyloid initiates the process of Alzheimer's, but after a while, the spread and aggregation of tau may not even be dependent on amyloid. If you want to control the disease early on, you probably have to lower amyloid. But, if you cannot diagnose Alzheimer's early, it may be too late to treat amyloid. We have seen that in many cases, the rate of amyloid accumulation slows down without any therapy, yet people are still getting worse. Admittedly, we do not know when it is too late to target amyloid, but we believe that at some point tau becomes the driving force of disease.

BSJ: You recently attended the 15th annual Clinical Trials on Alzheimer's Disease (CTAD) conference. From this experience, would you be able to shed light on the future of Alzheimer's therapeutics?

WJ: Results presented at this meeting included the final readout of a phase III trial of an anti-amyloid immunotherapy, Lecanemab. The results were very exciting,

showing that the drug had a strong amyloid-lowering effect. Most importantly, patients on the drug showed significantly less decline in cognitive function, as well as activities of daily living. These results are very exciting and provide support for the approach of lowering amyloid to treat the disease.

BSJ: You have mentioned various Alzheimer's therapeutics that help to lower Amyloid aggregation. What makes Lecanemab different, and why is it so promising?

WJ: The main difference, of course, is Lacanemab's clinical success. At the same meeting, another drug, Gantenarumab, had results presented that were not as promising. People on that drug did not show clinical improvement. However, Gantenarumab also did not lower brain amyloid as much as Lecanemab. So one thing that seems very important is the strength of the amyloid lowering effect.

BSJ: You say clinicians will have to catch Alzheimer's early. Do you think any kind of screening will become routine for patients based on age or lifestyle to help catch Alzheimer's early?

WJ: Yes, I think it could. There have been blood tests that can pick up amyloid and tau, but they still are not great. At this time, the blood tests are not standardized and the sensitivity is not clear – but they have potential. Reasonably, you are not going to get a PET scan on your 65th birthday as it is just too expensive. However, what if, when you start getting cholesterol tests, you could start getting a blood test for amyloid? If your blood test was positive, you might then get a PET scan and receive treatment accordingly before you have any symptoms. Therapies right now are also very expensive because they are intravenous. There are some companies experimenting with subcutaneous injections of these Alzheimer's drugs. If we create a blood test and a subcutaneous pharmaceutical, we may be able to scale treatment to the point where it is not cost-prohibitive. All in all, I think there is cause for optimism for sure. I'm an optimist.

AFTERNOTE

Following the completion of this interview, the Food and Drug Administration (FDA) approved Lecanemab, a drug that targets amyloid beta in Alzheimer's Disease. Lecanemab is a landmark drug as it has shown that it can slow cognitive decline by up to 27% in Alzheimer's patients, a 26% decline in the slowing of key secondary cognitive functions, and a 37% slowing of decline in daily living measurements.[5] This drug highlights the importance of research, such as Professor Jagust's, as well as illustrates the optimism present in the future of Alzheimer's treatment.

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