

Advances in Alzheimer's Disease: Early Imaging and Therapeutics

Course Chair: Dr. Ranjan Duara

Dr. Ranjan Duara:

Hello, my name is Dr. Ranjan Duara, and I am the Medical Director at the Wien Center for Alzheimer's disease and Memory Disorders at Mt. Sinai Medical Center in Miami Beach. I am also an adjunct professor of neurology at the University of Florida, College of Medicine, and Florida International University College of Medicine.

Our program, "Advances in Alzheimer's disease: Early Imaging and Therapeutics" is brought to you by Vindico Medical Education, and is supported by an educational grant from Lilly.

I am joined today with my esteemed colleagues, Dr. Neill Graff-Radford, professor of neurology, Mayo College of Medicine; Dr. Paul Rosenberg, associate professor of psychiatry and behavioral sciences at Johns Hopkins University School of Medicine; and Dr. Julie Schneider, professor of neuropathology and neurological sciences at Rush University Medical Center in Chicago.

We would like to start with describing the pathology and the pathophysiology of Alzheimer's disease and I am going to ask Dr. Julie Schneider to start discussion on some of the mechanisms implicated in the pathogenesis of Alzheimer's disease and to give us a general introduction.

Dr. Julie Schneider:

Alzheimer's disease was described by Dr. Alzheimer over a century ago now and he actually first described Alzheimer's disease in a young person, someone who is 51 years old, who had memory impairment, hallucinations, agitation, and disorientation. It progressed over about 5 years, and he was able to get an autopsy and see her brain.

The changes he found subsequently became what we now know as Alzheimer's disease. What is very interesting is that though it was originally described in someone who is relatively young, we now know that Alzheimer's disease is the most common cause of dementia in aging.

What is the age of onset of Alzheimer's disease? It is usually in the 70s and 80s. It can occur earlier, in the 50s and 60s, though less commonly. The incidence of dementia, most common cause of dementia being Alzheimer's disease, goes up with age. So even past 90 years of age, dementia is exponentially increasing.

You can see why it is a problem in our aging population. It usually begins, as most people know, with subtle memory loss that progresses over 8 to 10 years. During that time it involves language skills, visual spatial skills, and other cognitive skills.

People are often unaware of those changes. They do not actually know that they are having problems with their memory and a caregiver brings them in because of that. But we also know that some older people are aware of it. They have subjective memory problems, and they know that something is changing. We also know that there are noncognitive symptoms which are very common. Depression, anxiety, agitation, paranoia, throughout the course, and even very early on, coincident with memory problems.

We are learning a lot about the genetics of Alzheimer's disease. There are early onset cases that are genetically inherited, where if your mom or dad has the gene, you have a 50% chance of getting Alzheimer's disease. That is relatively uncommon. Most people have what we call sporadic Alzheimer's disease, where there may be a family history, but there is not an autosomal dominant pattern.

The biggest risk factor for that type of Alzheimer's disease is apolipoprotein E4, where if you have one E4 allele, your risk goes up, and your age of onset gets earlier. If you have 2 alleles, your age of onset is even earlier, and you have an even higher risk of getting the disease.

The problem with ApoE however is that if you have both of these alleles, it does not mean you are absolutely going to get the disease. It is a risk factor susceptibility gene.

Advances in Alzheimer's Disease: Early Imaging and Therapeutics

Course Chair: Dr. Ranjan Duara

Then there are nongenetic risk factors such as BMI, blood pressure, diabetes, diet, and psychosocial factors. A whole host of things that we now know appears to either prevent or delay the onset of Alzheimer's disease and those things that seem to make it more rapid in onset.

What do we see in the brain in Alzheimer's disease? We see what Alzheimer originally saw: amyloid plaques and neurofibrillary tangles. Those are the two things that he saw. He used the silver stain. We now have much more sophisticated stains to look at these molecular stains, but it is the same pathology as Alzheimer saw in this 51 year old.

When somebody has Alzheimer's disease, it is really throughout the brain that you have these tangles in the plaques. You can imagine that it is difficult to cognitively be intact, with all these problems with your neurons, the neurofibrillary tangles being within the neurons, and the amyloid plaques outside—extracellular—preventing transmission across brain areas.

You cannot use things like atrophy on a scan to make the diagnosis right now of Alzheimer's disease. Even though that is very common in Alzheimer's disease, if you see an MRI with atrophy, we do not know it is not from another cause of dementia, other than Alzheimer's disease. So definitive diagnosis, even now, still relies on brain tissue.

One of the hypotheses in Alzheimer's disease—and this is an old hypothesis, but I think evidence is now really supporting this—is that one of the first things that happens is that amyloid gets deposited in the brain, or very early on in Alzheimer's disease, and this is part of the amyloid hypothesis where there is abnormal cleavage of the amyloid precursor protein, which is a normal protein in the brain, and it gets cleaved into this abnormal protein and gets deposited in the brain.

What appears to happen is that this triggers the progression of tangles and neuronal damage and inflammation and a whole host of changes in the brain that subsequently cause damage and cause cognitive impairment.

So there are a couple of things that I think are really important to think about when you think about Alzheimer's pathology. First is that we now recognize that nearly a third of older people who are normal cognitively have Alzheimer's pathology in their brain; they are still cognitively intact and we do not quite understand why. We think perhaps they have some type of cognitive reserve, or neural reserve and they are able to stave off the changes.

But there may also be other factors. You can have the pathology without having the clinical symptoms. The other thing really important to note in older people is that often they do not just have Alzheimer's disease; often they have additional pathologies, with vascular disease such as stroke, probably being most common. These things might tip you over the edge to express your Alzheimer's pathology. So if you have vascular dementia, very commonly you are going to have Alzheimer's pathology with it as well. As you age, those mixed pathologies increase. So we are going to be seeing more of this as we see Alzheimer's disease in the older populations.

Dr. Ranjan Duara:

Julie, do you think the amyloid hypothesis is absolutely secure? Because there are these cases that are tangle-only dementias for example, and of course there is a school of thought, I think, that perhaps amyloid is perhaps a result of something else that is going on in the brain rather than causative. I do not know if you have any thoughts about that.

Dr. Julie Schneider:

Yes, I do. We do know that older people often have tangles in their brain but tangles are not specific for Alzheimer's disease. We see them in a host of other diseases, and we see them in aging. Almost all older people have these tangles. And there is evidence now to suggest that there are 2 processes going on in the brain: There is an Alzheimer's process where you have amyloid and then you have this progression of tangled pathology, and

Advances in Alzheimer's Disease: Early Imaging and Therapeutics
Course Chair: Dr. Ranjan Duara

that there is a tangled process that is an age-related process separate from the apoE4 process that may cause some memory problems.

But I think the vast majority of evidence really supports that amyloid is very early, and the tangles are coming later in the process. It is difficult to know absolutely if this is true given that these are pathologic studies. But as we have markers to look in-vivo in the brain, I think we will be able to answer these questions better than we are now. People are different in how they respond to this amyloid deposition.

Dr. Ranjan Duara:

Great. Thank you Julie. I think we would like to move onto issues relating to early diagnosis and the clinical relevance and importance of our diagnostic tools: The role of screening, for example, which can be somewhat controversial. The Alzheimer's Association has actually recommended that annual screening be done after a certain age.

And perhaps early diagnosis may have some implications towards the kinds of medications we will use in different stages of the disease. So I would like to ask Dr. Neil Graff-Radford to tell us a little bit about this.

Dr. Neil Graff-Radford:

One of the important reasons why the Alzheimer's Association recommends early screening is that there are many treatable mimics of Alzheimer's disease. Let me give you four good examples.

So the first example would be medications. Very often people may be taking a sedative medication and be complaining of memory problems. Those medications include anxiolytics and sleeping medicines and antipsychotic medicines.

A second important example is that people with depression may complain of memory problems and they may be misdiagnosed as having a degenerative dementia.

Another important area which is often overlooked is sleep disorders. So sleep apnea has been shown to cause atrophy of the hippocampus and there is a study, a prospective study, showing that treating sleep apnea actually reverses hippocampal atrophy in those who are effectively treated for the sleep apnea.

Lastly, as a good example of treatable causes that present with memory are people with normal pressure hydrocephalus. The other problem is mainly a walking problem. People are unsteady and they also may have some urinary difficulty. Initially, it is urinary surgery and they also may have memory problems. And again when that is diagnosed and treated effectively, some of the memory problem may actually be reversed.

One of the reasons why it is so crucial to screen older people is because of these other issues that are treatable.

So we anxiously wait for a treatment modification. The field has moved back earlier in the disease, especially because we now have excellent studies in biomarkers. A lot of this can be attributed to the Alzheimer's disease neuroimaging initiative, the dominantly inherited Alzheimer's Network where they have done sequential imaging in the same people with different stages of the disease.

Dr. Ranjan Duara:

Neill, I just wanted to ask you a little bit about the symptoms that actually occur in the different phases. What kind of symptoms would you expect for example in the amyloid phase, if any, before there are any degenerative changes that are seen?

Dr. Neil Graff-Radford:

So that is a really important research area as you are aware. In the ADNI Study, to look at that particular question, they put 200 people who complained of memory problems but do not have measurable memory problems, and we are going to see whether that is a clue to us being able to detect some people earlier.

There are people who complain of memory problems who have no pathology. So it is going to be hard. It will not be very sensitive or very specific but it still might be some of the symptoms that they complain about. Also there is some evidence that people may have depression at that particular time or anxiety because they feel something is going on, and so depression or anxiety may herald the actual degenerative dementia. I think those are some of the features.

Dr. Ranjan Duara:

And cognitive tests, in that stage? Do they show anything?

Dr. Neil Graff-Radford:

The cognitive tests, in a cross-sectional way, when a person comes into your office, what you have to do is compare them to the population, to the published norms. You can look at the French 3-City Study, that some of these cognitive tests start declining as a group as much as 12 years prior, even though they cannot tell it individually. But it has been a slight decline. So that is true. One other point I am going to expand upon from this point of view: In the biomarker world, they are not specific for Alzheimer's disease. There is this entity called suspected non-Alzheimer pathology, when people have positive biomarkers that are not amyloid; so they might have deoxyglucose abnormality. There's a large group of older people, who, if you are doing a biomarker study, have positive biomarkers that are not amyloid and that are other pathologies; some of these people are going to have Lewy Body Disease. Perhaps some of them are going to have vascular disease and so I think that is another important area to keep our eyes on for the future.

Dr. Ranjan Duara:

Well, that leads us into using biomarkers for diagnosis. You did mention various biomarkers, Neill, during our discussion. And currently Alzheimer's disease is primarily a clinical diagnosis. But the biomarkers, especially the imaging biomarkers, are currently used quite actively, both to rule out other conditions as well as to diagnose the disease itself.

The atrophy changes are not particularly specific, although there are certain changes that are fairly characteristic of what occurs in Alzheimer's disease. The biomarkers that we have available right now are structural, functional, and molecular. We use MRI particularly to tell us about the structure of the brain. We can use CAT scans as well. There is a particular pattern to the changes that occur structurally in Alzheimer's disease.

Brad Dickerson has done a very nice study, where he showed that there is a signature of regions where atrophy occurs, starting in medial temporal regions, lateral temporal regions, temporal pole, parietal regions, posterior cingulate, and, finally, the frontal cortex. And particularly also the signature includes the sparing of certain regions, such as the primary sensory motor cortex and the occipital regions.

And incidentally, the MRI biomarkers, the changes in structure are not only useful for diagnosis, but they seem to also tell us the extent of atrophy that occurs, what we might see in the rate of progression in those individuals, as well as the kind of symptoms they may manifest. For example, people who have more atrophy on the left side of the brain, have more language problems; people with right-sided atrophy have more visual spatial problems, and so forth.

We also have PET scans that tell us, in different ways, about what is going on in the brain. So fluorodeoxy PET tells us about glucose metabolism, which essentially measures the synaptic activity within the brain. That also shows a particular pattern of change that is characteristic of Alzheimer's disease, although not entirely specific, and, once again, the extent of change that one sees in those regions, for example, parietal temporal regions, and actually medial temporal regions, too, is often ignored on PET scans with glucose metabolism. There is a very

characteristic decrease in those regions, which you would expect. The extent of those changes, also predicts the rate of progression, disease, and also the kind of symptoms you might expect similar to what you see with atrophy.

Finally, with PET scanning, one can look at changes in the molecular composition of the brain. So amyloid PET scanning has now come into vogue, and there are a number of agents that have become available that can be used clinically because they are tagged with a fairly long half-life: Isotope fluorine-18. Unlike the original compound, Pittsburgh Compound B, we now have four compounds that have already been approved by the FDA or are currently in the process of being approved.

They all show us the amyloid composition of the brain and we use thresholds to tell us what amount of amyloid is significant for using a particular agent.

I wonder if any of you have any thoughts about the use of amyloid scanning and the kinds of clinical applications we might anticipate with amyloid in particular, and how it relates to other forms of imaging, such as fluoride PET scanning with fluorodeoxyglucose or MRI. What are the relative values for each of them, or do you think the combination is the most important thing?

Dr. Julie Schneider:

Can I just backup one second and ask you a question? We know that these scans show that there is amyloid within the brain. That has been shown by autopsy studies. How about change over time in people who have amyloid? Are we able to track the build up over time of amyloid or is it just positive or negative?

Dr. Ranjan Duara:

Yes, of course. When we use the quantitative methods of assessing how much amyloid there is in the brain, we can do longitudinal studies, and in fact, it is a very interesting question here. So far in individuals who have autosomal dominant Alzheimer's disease, the young onset cases, there is a very early buildup of amyloid in the brain, and it plateaus about several years before the onset of any clinical symptoms.

By the time a person has amyloid in the brain, it is presumably going to start the degenerative process; you have gotten the maximum amount of amyloid. It is plateaued at that level.

However in sporadic Alzheimer's disease, there seems to be a difference. There is a continuing buildup of amyloid and longitudinal studies have shown in older onset Alzheimer's disease that there is an increase in amyloid starting from the preclinical state and going on through the mild cognitive impairment stage and into mild and moderate levels of dementia.

Julie, do you think tau imaging has an application in the clinical diagnosis of Alzheimer's disease?

Dr. Julie Schneider:

Absolutely. Just like there are markers for amyloid, now there are in-vivo markers through PET scanning for the abnormally phosphorylated tau protein that makes up the tangles as well as the neuritic, or bad, component of plaques. Most studies suggest that really they are the tangles that correlate best with cognitive impairment, and when tangles start spreading through the cortex, the theory is that is really when your memory and other cognitive skills become impaired.

You can have amyloid for many, many years, with minimal, if any, cognitive impairment. But then this tangle spread really seems to herald this memory/cognitive impairment. I think if you can combine these two, if you can take amyloid and tangle imaging, I do think that it would have a role, not only for diagnosis of Alzheimer's disease, but also a role as far as being able to intervene at a time when you could actually make changes to cognition, and prevent that cognitive impairment from happening.

Dr. Ranjan Duara:

There are a couple of agents that are showing us very good cognitive imaging. We do not quite know yet how they relate to the rate of progression, state of the disease, and so forth. But those studies are being done at this point.

Dr. Paul Rosenberg:

Tau is a great target for treatment for many neurodegenerative diseases. It is, in some ways, a final common pathway for a lot of degenerative diseases. If we can find something that works...We are a long ways away.

Dr. Ranjan Duara:

Which I think leads us on to treatment in general, and so Paul, perhaps, you would like to tell us a little bit about current and emerging pharmacotherapy of Alzheimer's disease?

Dr. Paul Rosenberg:

Thank you. So I am going to talk about cholinesterase inhibitors, how they work, what agents there are, some summary of their effects and their clinical impact. You will see in your slide deck a slide that shows a cartoon with slopes. You will see one slope is the natural course of the disease, and yes, it goes down. And there are two alternative slopes. One is a onetime improvement where you take the same slope and push it up; that is what our current FDA-approved drugs seem to do for the most part. It would be preferable if we could make the slope shallower, flatten it out; that is what we are trying to do with neuroprotection, with disease-modifying agents. We are still looking for the first real hit in this area, and there is a lot of controversy whether we have one yet or not.

Cholinesterase inhibitors: They are based on very solid pathology and neurochemistry. In the Alzheimer's brain, there is increased cholinergic innervation from an area in the forebrain, the Nucleus Basalis of Meynert, to widespread areas of the cortex. Acetylcholine is a major excitatory neurotransmitter. The wires go everywhere from this one nucleus, and in Alzheimer's you lose a very substantial proportion of that.

You cannot give acetylcholine directly. You would make people crazy and you could not cross the blood-brain barrier. What you do is indirectly prolong the effect of the remaining acetylcholine with acetylcholinesterase inhibitors. These essentially inhibit the enzyme that breaks down acetylcholine.

They work very well chemically. At therapeutic doses, you can see the acetylcholinesterase activity go down by about 90% in peripheral blood and 20 to 40% in the central nervous system. These numbers are important because we might have better drugs, but they probably would be too toxic. There could be stronger agents. One that was tested more than a decade ago was metrifonate. It was a powerful and irreversible cholinesterase inhibitor.

I am impressed by the cognitive effects but some patients had some very disturbing side effects: a myasthenia gravis-like syndrome. There is some suggestion that we have kind of "maxed out" what we can do in this group of drugs.

In terms of using them, there are three that are widely-used, the fourth, tacrine, is pretty much not used any more: Donepezil, rivastigmine, and galantamine. In the slides you will see a suggested titration schedule. I have to give some opinion here. Donepezil has recently come out with a high-dose, 23 mg, which I am completely underwhelmed by. I think it is a good way to cause more side effects, but I am not impressed by the cognitive changes. And for this section, I really encourage you guys to chime in because there are a lot of opinions.

Dr. Ranjan Duara:

Well, in my experience, there has been very little positive therapeutic effect, with a lot of side effects. So I completely agree with what you have said.

Dr. Paul Rosenberg:

Adverse events are relatively common but also pretty minor. I will mention the exception a little down the line. You commonly get what are essentially cholinergic side effects, including nausea and diarrhea, and increased nightmares and sleep disturbance. That is why many of us tend to give it in the morning to minimize the sleep disturbance.

I find some minor advantages with the rivastigmine patch because there are fewer gastrointestinal (GI) side effects, and I believe in this case, the manufacturer's claim is pretty accurate. I have pretty good luck with it.

The thing about this group of medicines, the results are very consistent across different stages of the disease, and in many studies. It is a pretty replicable finding that they improved cognition. But the size of the effect is modest, in my opinion. So for instance, you will see about a point to a point-and-a-half increase in the mini-mental state exam score.

It is real and, once again, I will just give you one example for many similar trials. But whether that is clinically important is really one of those questions: Is the glass half-empty or the glass half-full?

In my clinical experience, instead of the average, what I really find in early disease is I get a small group of impressive responders. Many of whom, technically do not have dementia and have mild cognitive impairment, and they will come and say, "That really worked well." Then I also have a lot of people who really are not too impressed.

I give almost everyone that I believe has Alzheimer's disease a trial with a cholinesterase inhibitor and often a second one, but my enthusiasm and my aggressiveness is pretty modest. If I have a reason to stop, a reason not to use, I will hold back. I am not that aggressive with them because there are some risks, and this is one of the classes of drugs where it has really been down the line that we have been understanding the risks a lot more than when they first came on the market.

It makes sense since the vagal nerve tends to slow the heart rate, slow the atrial pacemaker, that you would expect bradycardia. Fine, but you also see an increased rate of syncope, pacemaker insertion, and hip fracture.

These are Phase 4 kind of data. They come out of observational pharmacoepidemiologic studies. They were not obvious in the trials. But I find them of concern, and I tend not to use these drugs when people are bradycardic, and I tend to be these days pretty sensitive to people who just are very frail: Elderly women, tiny elderly women who I am really afraid if they fall, they'll fracture their hips. I may well not use the drug.

I appreciate being asked two very interesting questions in preparation for this: When should they be discontinued and when should they be started? Is there a role for use in mild cognitive impairment, people who have memory complaints but do not yet have dementia, and should they be used in advanced dementia?

Dr. Ranjan Duara:

Well, in mild cognitive impairment, there have been some studies that seem to suggest that there may be some change in the rate of progression of the disease, but do you think that is a false indicator, that there is improvement in cognitive symptoms but there's really no change in the actual disease itself?

Dr. Paul Rosenberg:

This is an area where there has been enough studies, I think. I feel more comfortable with composite analyses, like meta-analyses because there are enough studies that you can pool and compare, and a fairly recent Cochran Review, they concluded that there was little evidence for preventing MCI progression to dementia, but also not much evidence for symptomatic change.

Advances in Alzheimer's Disease: Early Imaging and Therapeutics
Course Chair: Dr. Ranjan Duara

My own personal experience is that it is idiosyncratic. Around our group, we discussed this important question a lot, and we estimate 15-20% of patients and families come back and say, "That was great. I am improved." Sometimes you do not always see it when you measure cognition.

But on the studies that measure cognition, it is not too impressive. The prevention studies are pretty definitely null, and in fact, each of the major cholinesterase inhibitors has at least one well-powered prevention trial, with an N of 1,000 and four years duration approximately.

Now in advanced dementia, really saw something quite different in a pooled analysis of three 6-month randomized controlled trials. They saw a 4-point improvement in a cognitive measure called the Severe Impairment Battery. You are not likely to do this in the clinic. It takes 30-40 minutes. It involves a specialized toolkit of interesting plastic toys, but it is much better than the Mini-mental for measuring cognition and advanced dementia because it includes measuring apraxia and agnosia as well. They saw some improvement in activities of daily living. They suggested that there is some mild efficacy in advanced dementia, but these are the folks where you need to weigh benefits against risks because in frail elderly people with advanced dementia, you are really concerned about falls and fractures.

There's a lot of controversy about stopping. The fourth Canadian Consensus Conference on Dementia has some very useful rules of thumb for where they recommend discontinuation: One is when they seem to be declining pretty rapidly and you are very skeptical that the medicine is effective. Another one is intolerable side effects, and I would add weight loss. Very specifically, in advanced dementia, weight loss is near universal, and we do not have an effective treatment for it, despite things we could prescribe. And you should probably taper the dose.

Let us move onto one last thing. Another drug in a very different category is memantine. It is an uncompetitive block of the NMDA receptor, basically enhancing a different kind of excitatory neurotransmission. It has been approved for use in dementia in the U.S. in 2004.

It was greeted with a lot of interest because it is a very different mechanism of action. It is often used with cholinesterase inhibitors and I could sum up the evidence. I think the evidence in advanced dementia is that its effect is similar to cholinesterase inhibitors. I think in early dementia, the evidence is pretty much known. Many people are using it anyway. But I do not think it has a great role in that situation.

Dr. Ranjan Duara:

I think we should talk a little bit about disease-modifying therapy and where we are with that. Perhaps Neill, you would like to tell us a little bit about what you think about disease-modification as well as prevention of the disease.

Dr. Neil Graff-Radford:

There is a very interesting list of lifestyle modifications that might be helpful and protective of the brain. A lot of these published studies are epidemiologically-based, so you have to be cautious that the correlation may not be absolutely correct.

But there is increasing evidence, even in prospective single-blind studies on exercise. So exercise is protective of the brain in cognitively normal people. There is a study from Champaign, Illinois, from Kramer's group where 60 people did turning, stretching, and balancing. Sixty did aerobic exercise for a year. The hippocampal volume increased in size and this correlated with increased brain-derived neurotrophic factor and memory. We still do not know whether exercise is helpful at the time of mild cognitive impairment or Alzheimer's disease. So I think that needs to be studied and that hopefully in this window of secondary prevention we will hopefully have some studies done.

Dr. Ranjan Duara:

Advances in Alzheimer's Disease: Early Imaging and Therapeutics
Course Chair: Dr. Ranjan Duara

Are there any other treatments. We mentioned tau imaging earlier, and the possibility of using tau as another pathophysiological marker of Alzheimer's disease that can be modified perhaps, particularly because there is progression.

Dr. Paul Rosenberg:

So as Julie mentioned before, tau is a great target, and as you mentioned before, we are starting to have some research tools that might image tau. Our progress on actually targeting tau in treatments has been a lot slower than in targeting amyloid.

In some ways we have been drunks looking under the amyloid light. It has been easier to develop imaging tracers for amyloid. It has taken a lot longer with tau, probably because it is intraneuronal and partly because the best tracers are immunologic and antibodies do not cross the blood-brain barrier. But with that long speech, there is certainly been a lot of attempts at anti-tau drugs. Lithium, which is widely used in psychiatry for bipolar disorder. In the lab, it looks like a great drug for inhibiting tau synthesis. It did not work in people though. We have abandoned that. Currently, there is one major trial; the drug is a modified version of methylene blue. Methylene blue is an old treatment for a rare condition, oxyhemoglobinuria, and it happens to turn your urine green, because it is blue. It is hard to do a trial on it.

There was some promising early phase data presented a couple of years ago at a meeting, then this modified methylene blue is now in a nationwide trial. But we are really looking for our first hit in tau, and the pharmaceutical industry has been particularly looking into anti-tau antibodies.

Dr. Julie Schneider:

Which is interesting because I wonder if that target may be off target, meaning once you are building this tangle, something has gone wrong in your cell. It may be a tombstone of something that is happening. What we really need to do is figure out at what point and why does this cascade occur where amyloid is triggering these changes in neurons, and the death of neurons. If we can piece that together, I think that would be a real key.

Dr. Ranjan Duara:

Julie, what do you think about inflammation of the brain? Microglial activation, and its role in progression of the disease?

Dr. Julie Schneider:

I think there is intriguing evidence, genetically and in other studies to really suggest that inflammation is key here, and that your brain's response to the amyloid and to the other changes that are occurring in Alzheimer's disease is different across different individuals and plays a role whether or not you move onto express the disease.

I think that is a burgeoning field still, inflammation, and how that is working, and I think that'd be a great area for intervention.

Dr. Ranjan Duara:

There have been some studies that have been done. First, there were clinical trials that were very promising initially in the '80s and '90s, where drugs like ibuprofen, naproxen, and celecoxib were used that seemed to show a very strong benefit.

However, the ADAPT Study, a very extensive study, was done and failed to show an improvement with naproxen.

Dr. Paul Rosenberg:

Advances in Alzheimer's Disease: Early Imaging and Therapeutics
Course Chair: Dr. Ranjan Duara

There is a good chance when we use the word "inflammation" that we mean different things in the periphery and in the brain, and I think we have yet to find the right drug as a brain anti-inflammatory. Our first try, which was to literally pull nonsteroidals off the shelf or steroids, for example, did not work. I think we really need new drugs for that mechanism.

Dr. Julie Schneider:

I think there are 2 issues. I think what you just said, that there is a different kind of inflammation in the brain. But secondly, those trials were in people who already had dementia. So how far back do you need to go? Do you need an amyloid scan from a decade ago to be started on these anti-inflammatories? It may be that it was too late in the progression.

Dr. Ranjan Duara:

I believe for the mild cognitive impairment stage, we are going into some trials that are using a variety of drugs that are inhibitors of microglial activation; that may be significant. Any of you have heard about these? Not yet? It is too early.

Dr. Paul Rosenberg:

The brain is obligate for using glucose. It must have glucose to survive. And in Alzheimer's disease, there is some evidence that the brain is insulin-resistant, and has greater difficulty taking in glucose.

So that is one potential target. Another one is that insulin and amyloid are probably degraded by the same enzyme in the brain. And so that has caused some investigators like Suzanne Craft at Wake Forest to attempt to deliver insulin to the brain.

Now it is tricky. You cannot just take insulin like you do for diabetes, and in fact, you are worried about delivering insulin to the periphery. So the method she uses is intranasal insulin. Yes, you sniff insulin with a plastic device that pushes it high up into the nose, and then there's some retrograde uptake by the olfactory neurons.

As you probably know they are the only brain neurons that are outside the brain. The cells you smell with are in fact brain neurons. I am very enthusiastic about this study which is going into a pretty definitive trial right now. She has four month data showing some cognitive improvement in MCI and more importantly biomarker improvement. She shows improvement in glucose uptake.

Dr. Ranjan Duara:

Perhaps Neill, you would like to summarize what we have all said about treatments so far.

Dr. Neil Graff-Radford:

So, the dream of all of us is to delay or to prevent Alzheimer's disease. And I think now with a combination of the genetics and biomarkers, we are able to identify those at risk, and secondary prevention is now underway, and our dream may be realized soon. So let's hope.

Dr. Ranjan Duara:

Let's hope indeed. Well, this has been a great discussion and I would like to thank Dr. Schneider, Dr. Graff-Radford, and Dr. Rosenberg for their contributions, for joining me in this program today, which is "Advances in Alzheimer's disease: Early Imaging and Therapeutics."

Thank you for participating in this educational activity. Please remember to take the posttest so you may receive CME credits. Thank you.

Advances in Alzheimer's Disease: Early Imaging and Therapeutics
Course Chair: Dr. Ranjan Duara