

# Drug Development in Alzheimer's Disease — Challenges and Opportunities

Hi everyone. We will try to touch on the most important points in developing drugs for Alzheimer's disease today. As you can imagine, this is a very large topic to be covered in 30 minutes, but we will try to talk about the most important concepts in that area. Of course we cannot talk about developing drugs for Alzheimer's disease without talking very briefly on what causes Alzheimer's disease or what are the pathological changes in that disease.

What we know is that Alzheimer's disease is a degenerative disease characterized by a number of findings. Degenerative disease as you know is a wastebasket term. It doesn't mean much except that we don't really know what causes it. But the observations that are very clear are that there is loss of neurons, there is accumulation of different types of proteins, the most prominent two of them are the amyloid protein that accumulates outside the cells, and the tau protein that accumulates inside the cells and form something called neurofibrillary tangles. At the same time, of course, you will see atrophy of the brain. And I have some pictures to show on that. So these four changes, please keep them in mind, because that would be the target of therapy, really, is to stop this process and halt these changes.

There are certainly genetic factors to Alzheimer's disease because we know that having certain genes accelerates the disease or makes the disease worse in some families, or even start early in some families. But it's not enough by itself. So it's not totally a genetic disease, but there is genetic predisposition. To make things even more complex, these same changes that we mention here can be seen in aging "normal" individuals, without being diagnosed with Alzheimer's disease, but of

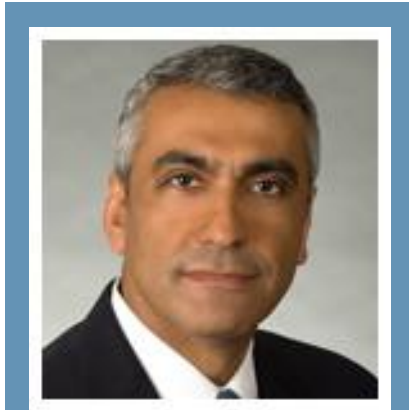
course the amount and the location of these changes may vary a little bit from actual Alzheimer's disease.

So without being too technical, this is just to put a face with the name if you will, so plaque, amyloid plaque, very common term in Alzheimer's, outside the cells, and neurofibrillary tangles inside the neurons.

The brain atrophy, again, this is a normal brain; this is Alzheimer's disease brain. I guess I don't have to say that, right? The same age, patient is the same age. And you can see the generalized atrophy here, and how the what we call the sulci are much wider here, for example, compared with those. This is much fuller, happier brain.

So what leads to these changes? And the simple fact is that we don't know exactly. We know some pieces of a big puzzle. And we know that the important pieces are these three categories. We know that there is accumulation of abnormal proteins as we mentioned, beta amyloid and tau proteins. We know that there are some synaptic changes. So in addition to the loss of cells, and accumulation of proteins, the cells don't talk very well to each other.

What synaptic means is like the ends where neurons talk to each other - where nerve cells talk to each other. So we know that there's also abnormality in neurotransmitters, and there was some success in terms of symptomatic therapy, by modulating these neurotransmitters. And we know now, more recent data indicate that there is a little bit more of inflammation than we thought. There is even possibly some vascular effect that early on can be responsible for setting the whole process in motion. There are some changes in the insulin-signaling pathway inside the brain itself, etcetera. So there are all kinds of theories ongoing in terms



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of what's causing the disease. As is the case with all these complex neurological diseases and degenerative diseases, there are early processes, and then there are late processes. Basically, the goal is to find the earlier processes, because the endpoint where you see all these proteins and atrophy, that's not really what we're trying to treat. Because by the time these changes are there, it may be too late to do anything for the patients. The goal is to try to go up in the cascade of events to know what's happening early on in the process.

The clinical presentation of Alzheimer's disease can vary from patient to patient, but the most common things, the most, very prominent changes, you're all familiar with, you've seen it probably in family members, on TV, and it's the most prominent one: is short-term memory, registration. Early on the long-term memory is not affected. They can tell you stories from 50 years ago, but they can't remember what they did this morning. So short term memory, very selective. Confusion is very common. They can't conduct very complex conversations. If two people talk to them at the same time, they get totally confused, things like that. Although, I do that sometimes. Then you have the decreased visual spatial orientation, and what we mean by that is like the concept of space and location and direction is not as normal. And that can present itself with getting lost a lot, even inside the house, or in relatives' houses. And this is an example - this clock here - this is part of what we call mini mental status exam, or MMSE, which is part of the battery of tests we do on Alzheimer's disease patients. And one of the questions is to draw this clock, and sometimes we present the patient with it, or just say, from memory, draw a face of a clock. And that's typical for Alzheimer's disease patients. See how it's missing all the side, and the numbers are not distributed evenly and stuff. It just illustrates the visual spatial orientation decline. Of course, verbal skills go next.

We cannot underestimate the importance of behavioral changes. So these are the cognitive symptoms. But also there are behavioral changes. And this can be very subtle in the beginning; personality and mood changes. They can be just a little depressed, just a little withdrawn. Close family members will notice that he is not the same. Or

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he is not himself. Or she is not herself. But later on, they become really prominent. They turn into agitation, into frank psychosis. Also, the motor symptoms are very important. They become slow. They do everything slowly and their movements become sluggish. And the sleep disturbance is very prominent. They switch cycles. They wake up at night and they'll sleep in the day.

Back to drug developments, that's what we're talking about today. When you think of treating Alzheimer's disease, that's in general true for lots of neurological diseases, you think of treating the symptoms or symptomatic management; and disease modifying therapies, which are therapies designed to halt the actual progression of the pathology itself, the disease itself. Off the bat, I have to tell you there are no disease modifying therapies approved or available for Alzheimer's disease at this point of time. And that's why, as you can imagine, the race is on to find these treatments. Now the target, as I said earlier, is to find the earlier changes; that if you stop these steps, or these events, you can stop the disease from getting bad enough to cause the full-blown syndrome of Alzheimer's disease. Early treatment is crucial.

In terms of symptomatic treatment, it's mostly targeting neurotransmitters and chemistry of the brain, which is a little easier target to address, and all existing therapies that you find on the market now are symptomatic therapy. So just a few words on symptomatic therapy, because from now on I'm going to talk only about disease modifying drugs and the challenge in developing these drugs. So in terms of symptomatic, you probably recognize some of these names of the drugs on the slide. Basically, you can think about it as cognitive enhancers that work to enhance thinking and memory and stuff like that, and general symptomatic treatments to modify the behavior. So modifying behavior, things like - if they get psychotic, you give them some anti-psychotics; if they have problems sleeping, you give them sleeping aids - things like that. More importantly, the cognitive enhancers are so far two classes. Cholinesterase inhibitors that increase acidity of cholin in the brain that is important for the memory processes, and there are like three, actually four drugs. Cognex, we forget about it, this was the very first drug that was approved in Alzheimer's disease. And it's still available. It has some problem with hepatic

toxicity, so it fell out of favor for the newer agents. And of course Namenda, that has a different mechanism of action and it acts on glutamate receptors to improve, also, cognition.

Okay, so what about disease modifying drugs? Well, I have to say there's tremendous effort, tremendous resources are being thrown at that, needless to say. Appropriately so, because you hear all the news about aging population, and how common the disease would be, more even than it's common now. So imagine that there are thousands of people working in different institutions all around the world, trying to crack the code and to figure out what are the initial processes that lead to the events that ultimately end with Alzheimer's disease. So imagine that what we see now in a patient with Alzheimer's disease has started at least ten years earlier, or sometimes probably twenty years earlier. So that's why it's very important to trace these processes and initiate therapy as early as possible.

So despite all this effort, and all the resources thrown at this, the discovery of new drugs has been very slow - and for lots of legitimate reasons. One of them, the most important one, is that the disease itself is very complex. It's multifactorial, and it happens over a long time. So whatever you know about a disease in a certain patient may not apply to the next patient because they are simply in two different stages of the disease. So tracing the disease in a longitudinal way is important, but on the other hand we don't have the appropriate tool for that, simply because you can't just keep on biopsying someone's brain every few years to see how their Alzheimer's disease is progressing. So we are limited in the amount of data we know to collecting pieces of information here and there to try to put the puzzle together.

We can also identify other specific reasons why this is being a slow process in coming up with disease modifying drugs for Alzheimer's. The first one we mentioned is difficulty identifying the therapeutic targets to start with, but there's also sub-optimal collaboration with academia. And there are lots of combined conferences now that try to link academia with drug developers and pharma-

ceutical companies, because there are all kinds of issues that need to be worked out in terms of intellectual property and in terms of technology transfers and stuff to allow other companies to work on therapeutic targets identified in university settings.

The lack of adequate animal models also hampers development. As you know, in lots of diseases, having an animal model helps a lot, because this is a very helpful tool in screening early compounds. And that's absent in Alzheimer's. So lots of times it's a matter of guessing, and lots of times you have to take it to human until you realize it's not going to be effective.

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Then you have the limitations of the standard endpoints that we use now in clinical trials. Your clinical trials are as good as the tools or the instruments that we use to measure efficacy or drugs, or changes in the disease activity. And ADAS-Cog and other measures we use in clinical trials are certainly with limitations. One of

the big needs in developing drugs in Alzheimer's disease is the need for biomarkers of disease activity and tissue injury. And that's of course not unique to Alzheimer's disease, but because of the importance of Alzheimer's disease, this has really, I would call it a critical need there. And I don't think we're exaggerating if we say that most of the resources really have to focus on that area to identify these biomarkers that by which first we confirm the disease; second, we know if the disease is active or not and pick our patients correctly for clinical trials; and third, this is the marker that would allow us to judge a drug if it's working or not. Then you have the tactical challenges in Alzheimer's disease trials. And again, we can't underestimate that. Lots of times, the concept is sound and the drug may be effective, but the execution of the trial has a major impact on the success or failure of clinical trials, and how clean the data is, and how appropriately the rating scales are applied, etcetera. And of course, that's where the need for very experienced and therapeutically focused CROs like Medpace and other companies who are really in tune with what's going on in the field.

Of this list of challenges for why things are slow in Alzheimer's disease, I'm going to, of course, focus

on one or two because we don't have time to go over all of them, so let's talk a little bit more about biomarkers of Alzheimer's disease. As I mentioned earlier, these would be very instrumental in early development to provide surrogate measures for evaluating compounds early on, and making early go/no-go decisions, so we don't waste resources and time on drugs that are not likely to work later on in clinical trials. So early development, they can have a value. They can have a value also in later development by confirming eligibility of patients by making the group of patients as homogenous as possible, which is important for the success of any trial, and by providing more objective endpoints to corroborate the clinical impressions and sometimes even to be more objective than the clinical evidence.

Finally, biomarkers of tissue injury, which is not necessarily the same as biomarkers of disease activity, are also very critical. Because once you're talking about disease modifying therapy, you will have to make sure that the alteration of the patient's symptoms is due to actual halting of the disease process, not just improving the symptoms, right? I mean that's the hallmark of the difference between these two therapies. So your symptomatic therapy can make the patient better, cognitively and behaviorally, but you stop your drug and the patient goes back to the usual symptoms. Disease modifying therapy may improve the symptoms also early on, but the difference is that they are improving the symptoms by stopping the disease or slowing the disease process. So you need the tools, these markers or imaging techniques that will allow you to see that the effect here is not only on the symptoms level, but also on the process itself.

What biomarkers are available or being developed at this time? The focus is, of course, as you can imagine, on brain imaging, on biological testing, or on electrophysiology techniques. Brain imaging is the big one, and MRI is providing of course a great tool so far. Looking at the MRIs, you can look at the volumes of generalized brain atrophy or specific brain atrophy in certain areas, and functional MRI is becoming more and more popular and more validated in this area. Nuclear medicine is coming to the helm also with PET scanning, either using FDG or specific amyloid imag-

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ing, and then you have the biological testing for the specific proteins in the CSF like amyloid, beta A4, or tau protein or phosphor related tau in the CSF that can be markers of disease activity, at least in terms of staging the disease. Electrophysiology was much more popular probably a few years ago, and now unfortunately it's not proving to be a very valid tool, but you never know, it may come back to the forefront. And that's mostly quantitative EEG and earlier people experimented with long latency evoked potentials. I have to say at this stage, though, none of these biomarkers are ready for prime-time. Some of them are more developed than others, like functional MRI and PET scanning, and they can be very helpful in academic setting or in very specific setting. But they're not ready to be used on a wide scale, in a clinical trial, in a validated measure. And more importantly, from a drug development point of view, they are nowhere to be validated by the standards of regulatory agencies to be accepted as surrogate markers.

Just a few examples, again to put a face with the name - this is an example of quantitative EEG or brain mapping. It's basically looking at electrical activity in the front parts of the brain, and creating a map to see where the slowing is, and there are specific patterns that correlate with Alzheimer's disease. This is an example of volumetric measurements of specific hippocampal atrophy. This part of the brain here inside the temporal lobe, this is the temporal lobe, is called the hippocampus. And this is an area that is affected very early in the disease process and correlates with memory deficit, and as you can see in advanced Alzheimer's disease, you see a major shrinkage in that area, or a major atrophy in that area. So measuring the volume of the hippocampus can provide a good tool of the progression of the disease early and late, and of course you need specialized software for that. And that's where the need for really centralized imaging and people who know what they're doing here, make sure that the sites have what it takes from technical point of view, from personnel point of view, from software point of view, to really produce meaningful data. Now of course in this image also you notice the generalized atrophy. These are age matching patients. In here you see the size of the ventricles and there is some atrophy here, because it's an older person,

but still much more severe, prominent, in the Alzheimer's disease patient.

Functional MRI, it's the same idea. The concept in functional MRI is that when parts of the brain are activated, brain cells are working, they require more blood. So you see more blood supply to these areas. So in functional MRI, you exploit this fact that active parts of the brain have more blood coming to them, and you ask the patient to do certain tasks, either mental or motor, and then you do the MRI that detects blood flow in certain parts, and it tells you what's being activated. Now for this pattern of activation for a specific task, we know what is normal - we know what part of the brain should be activated with that level of activity. And in Alzheimer's disease, these patterns of activity clearly would be disturbed and different. So the effort now is to identify these best ways to look at these patterns and to create some kind of data set to be used in clinical trials. This is the most promising in terms of practicality, because this is a regular MRI machine with just a special software, and it can relatively be applied in a wide-scale clinical trial. Versus PET, if you will, because PET, as you know, is nuclear medicine technique and it requires radioactive material that has very short lifespan and has to be produced on site or has to be shipped to the site. Not every institution has a PET scanner, so this, from practical point of view, although PET scanning is very elegant in Alzheimer's disease, but applying it in a wide-scale clinical trial may be a little bit more difficult from practical point of view, and in terms of consistency of the data.

So these examples here of PET scan, you see on the left amyloid imaging using Pittsburgh compound B, that's abbreviated as PIB usually, and what you see here then, that radio labels are given that attach themselves to amyloid. So the hot areas here reflect areas where amyloid is deposited. So you see the controls, and you see the Alzheimer's disease and you see the amyloid deposits where you would expect them in parts of the brain. This is a very severe disease, very elegant example. FDG is a little different. FDG is glucose basically, and it indicates the consumption of glucose. So active parts of the brain would consume more glucose, right? So here you see the

reverse. The control is hot where there's lots of glucose consumption either at rest or associated with certain task, while in Alzheimer's disease there is a deficit in glucose utilization in very specific areas that correlate with the disease, or with the parts of the brain that are damaged most because of the disease process.

Few words on the limitation of clinical outcome measures. Because the biomarkers are not acceptable yet as surrogate measures in Alzheimer's studies, especially of course in pivotal trials and later development in registration trials, so the reliance is usually on the clinical measures. And to make sure that we're not relying on only one measure, usually regulatory agencies in US, Canada, and Europe require that the clinical benefits are shown on at least two types of measures. And these are typically the cognitive measures and the global rating scales. Sometimes they also require functional improvement. What does this mean? That means that the main outcome

measure we think of when we think Alzheimer's disease is ADAS-Cog, which is the abbreviation of Alzheimer's Disease Assessment Scale - Cognitive subscale. This measure is really different domains of cognitive functions - thinking, verbal skills, executive functions, retention, memory, things like that. So we look at all these different spheres or different domains in ADAS-Cog. And let's say you start with a patient with a certain score, and then they improve by four points at the end of the study. Well what does this mean? And that's the problem, one of the problems with ADAS-Cog. In some patients that four point improvement may translate into major improvement in their behavior and cognitive functions. In some patients you may not notice that change except on ADAS-Cog. So it doesn't always correlate with clinical benefits to the patient, palpable clinical benefits to the patient and their family. And that's why regulatory agencies, rightfully so, require a corroborating evidence from another type of scale - either the functional scales, which tell you how functional an Alzheimer's disease patient, how much they are able to do things for themselves. So let's say I improve the function by four points, and at the same time this patient goes from needing help in getting dressed and eating, to a point now that they can feed themselves, and they can put a shirt on. Well that's a very good improve-

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ment. You can't touch that improvement more than just saying, well, he improved three points on ADAS-Cog. And the same applies when you talk about the global ratings. Global ratings, of course, they have some level of subjectivity in them, but when you combine both the clinician or the interview based impression of change, if it correlates with the caretaker impression of change, then that is meaningful. Some agencies require different scales called clinical dementia rating, but these provide the same purpose, I mean the CIBIC and the CDR are global ratings scales of what the caretaker thinks of the patient's overall status. And what the clinician thinks of the overall status.

So some examples of ADAS-Cog limitations - we mentioned one already, that it doesn't always correlate with clinical improvements or observed clinical behavior. Other limitations include the ceiling and floor effects - if it's a very advanced dementia, or it's a very mild dementia, ADAS-Cog does not move much in these ranges. It's good only for moderate disease, moderate to moderately-severe disease. It's non-linear, even in the range that it changes well, it may not be linear. In other words, when you are the lower scale, you may improve faster than when you are on higher end of the spectrum. Some people are trying to tweak it in a way that, okay, you give more weight to certain domains in different stages of the disease to make it correlate better with the clinical findings. There is some work in that area. Like any other scale in neurology and psychiatry, you run in with problems inter-rater and intra-rater variability, right? Inter-rater refers to, if I score the patient, I get a score. You score the patient, you get a different score. So that's because the way you apply or you interpret the scale and how I apply or interpret the scale. And then you have the intra-rater variability. I rate the patient now a certain way, and then I go like two hours later rate the same patient, I may get totally different result. And there are all kinds of reasons for that; again, consistency in applying the scale - the patient's fatigue, time of the day - all kinds of things.

So these are the kinds of things that have to be taken into account in designing the protocol and providing training to the sites and monitoring the study. I mean, the monitors when they go to the

site, they have a very important role in looking at all this data, and making sure that all the processes are followed very strictly according to the protocol, and of course, training - greater training. No matter how experienced your investigators are, the goal of training is not to teach them how to do ADAS-Cog as much as to make sure that they are all doing it the same way, and they are all interpreting the questions the same way, etcetera. And if it's a very long enrollment process, or very long study, you have to make sure there's also no rater drift, which basically they get together in the beginning of the study, but then gradually they go back into doing it the old way, the way they've always done it. So all these issues have to be taken into account, and that's where the CRO can play a very important role also in making sure of that.

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There is also a practice effect. You can't do ADAS-Cog very frequently with patients, because they get better at it just because of practice. The last slide, there are all kinds of tactical issues, and I'm not going to

cover all of them, and of course we can expand on the imaging and the biomarkers in different talks and we can cover that later. The same applies here on the tactical challenges. I'm going to touch on them, but this can be the subject of a future talk completely.

But when I think of tactical challenges in conducting Alzheimer's disease trials, so now we are beyond the concept and strategy of identifying therapeutic target and developing drugs. Now we're talking about applying certain principles in conducting the clinical trial to make sure that the trial is successful itself. And when you think of the challenges in conducting these trials in Alzheimer's disease, I like to split it into difficulties with early disease, moderate disease, and advanced disease, that can be a little different from each other. For example typically, most trials done to date were done in moderate disease, especially when you think of cholinesterase inhibitors and memantine and stuff. And difficulty in conducting these trials is first, of course, finding treatment naïve patients, because now there are drugs for that level of disease, and almost every patient you would see would be on treatment of some sort. Then you have the need for a reliable caregiver. You can't rely on the patients to drive themselves to the site, to remind themselves to take the drug,

to call IVRS. You have to have a really reliable caregiver, and you have to be careful that the caregiver is not demented as well. Because the data shows that unfortunately, lots of demented patients are being taken care of by another less demented patient. So you can't rely much on the memory if the caregiver cannot really comply with that. So there are all kinds of screenings that you have to do when you're doing the study to make sure that your data is meaningful at the end. Comorbidities, these are older patients.

Now in early disease, which we will see a trend now towards most of the studies will seek early disease, because as we discussed, disease modifying drugs would be way more effective if you apply them early.

So the move is more towards what we call MCI, which is minimal cognitive impairment, which is simply a word to say this is an early Alzheimer's disease. So these are patients who have a little bit of cognitive decline, and they are destined to become Alzheimer's disease over time - for the most part, not 100 percent, but probably most of them. The difficulty in these studies, which would become more prominent the more studies we conduct in these patients, is of course finding the patients, because again they may not accept therapy, because they don't see themselves as demented yet. They have some memory problem, but so what? It's not a big deal. I don't want to go on a trial for that. The motivation, I mean they may go on the study, but then they're not motivated to stay on it, because again, they perceive themselves as relatively normal. Then you have the need for long-term follow-up. Because the endpoint here is not really improvement or stabilization on ADAS-Cog or other measures; the endpoint here is the rate of conversion to probable Alzheimer's disease. So in other words, you take a patient who does not fulfill the criteria of Alzheimer's disease yet, and then you take the point of time when now they meet the criteria of Alzheimer's disease, and that's your measure. How long it takes these patients and what's the rate of conversion. So if you put 100 patients on the study, 50 of them are on the drug. 50 of them are not. How many of the 50 on the drug would become Alzheimer's disease at the end of one year, or two years, or three years, versus how many of the placebo patients would become Alzheimer's. And this would be your measure of how effective your drug is in preventing that conversion to full-blown

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Alzheimer's disease. So naturally, these observation periods have to be long. You can't follow these patients for six months and expect a difference, it has to be years. And that of course is to be determined, and it depends on the population you pick. I mean, this has a lot to do with the criteria you put in your protocol, and in terms of anticipating the conversion rate without any intervention in that group of patients. So there would be lots of competing trials in that area.

Finally, advanced disease clearly comes with its own set of problems. These are typically the phase four and three B studies, or lifecycle management studies, like when your drug works in this group of patients, and you want to make sure that, what does it do for more advanced disease, and then you

start conducting studies - these patients would be mostly institutionalized and they would have much more behavioral problems. They have lots of comorbidities. Of course, here your endpoints again are a little different. Here you're looking at better quality of life, less agitation, less behavioral problems that allow people to take care of them without interruption, rather than actual functioning of the patients. Because these would be fairly advanced disease.

#### About the Presenter

Dr. Kaba has extensive experience in neurology, psychiatry, and analgesia drug development. He is a board-certified neurologist with additional training in neuro-immunology (MS) and neuro-oncology. He currently serves as a Clinical Assistant Professor of Neurology at Emory University, and is an active member of the American Academy of Neurology, Society for Neuro-Oncology, and American Society of Clinical Oncology. Dr. Kaba has authored many scientific publications and book chapters.

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