Fireside Chat with Ken Marek, MD

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Highlighted Selections On the State of Parkinson's Research

I've been engaged with developing therapeutics for Parkinson's disease for 30 years. And what has happened over the past decade is really remarkable. We now have this enlarged, expanded understanding of the science underpinning Parkinson's disease from molecular biology. And there are very specific known genetic mutations that confer risk for Parkinson's disease — the most widely discussed of these are LRRK2, GBA and alpha-synuclein.

This understanding of the microbiology has led us over the last 10 years to additional preclinical work. And what is very exciting for the field is that we're now seeing the first pioneering studies where these targeted efforts are being brought forward to Phase II studies in individuals with Parkinson's disease. Ten to 15 years ago in Parkinson's research, we had this black box that had a "dopamine" label on it. Whereas now we have a lot more insight as to how we can develop targeted therapies that I hope and believe will be effective ultimately in reducing the progression of Parkinson's.

On Ongoing Trials Targeting Synuclein

Prothena, a biotech company, in collaboration with Roche is working in alpha-synuclein, testing an antibody. It turns out that all antibodies are not alike. You can develop antibodies that target different components of the alpha-synuclein protein. And it may be that there are substantial advantages to one or the other. These are sometimes difficult to ascertain without testing them. In Alzheimer's disease, a number of similar types of strategies for amyloid and a number of antibodies have been tested (see excerpt on the next page regarding June 2021 FDA approval of aducanumab). Some of them work, some of them don't work. And I would expect that's going to be the case with regard to Parkinson's disease as well. In addition to Prothena, the good news is that there is AbbVie, Takeda, Lundbeck and others who have alpha-synuclein antibody projects on their way to the clinic.

There are also a number of other pharmaceutical and biotech companies with synuclein-targeted therapies that don't involve antibodies, and in fact global biopharma UCB just began a project with a small molecule, targeting synuclein aggregation, for which they have data. An exciting number of potential therapies that are reasonably close to being in clinical trials within the next couple of years.

On Objective Measurement of Alpha-synuclein to Predict and Treat Parkinson's

We're getting closer to being able to objectively measure the extent of alpha-synuclein in people with Parkinson's disease. If we could easily do this, it would help us in a number of ways: (1) It would help us understand and predict who is affected by Parkinson's; (2) As a diagnostic agent, it would help us to track who is progressing more rapidly; (3) If we had a drug that affected alpha-synuclein, it would help us understand whether it had an appropriate effect.

So there have been enormous efforts the Fox Foundation has been leading to try to develop better tools to measure alpha-synuclein. This has been focused most on developing alpha-synuclein brain imaging agents. Imaging tools are now widely used in neurology and in other areas, such as oncology and cardiology, to target specific chemicals very precisely, in this case, in the brain.

Sadly, or maybe not sadly, there isn't that much synuclein in the brain. So it's very hard to develop an imaging tool that's going to detect this effectively. That being said, we are undaunted and a number of groups are well on their way to evaluating imaging tools, some of which already have been deployed in human studies. It's hard to predict when this type of switch will be such that these tools will evolve from being a research effort to a clinical effort. But I'm hopeful that this is something in the near-term horizon that will be a game changer in Parkinson's disease.

In the meantime, recent work has yielded ways to measure synuclein from other parts of the body. There is now a reasonably good tool to measure synuclein from spinal fluid, and that is being deployed in the PPMI study. But for those of us who don't like to get spinal fluid taken, it may be possible to do the same thing by doing something like a skin biopsy. So this is really an exciting prospect. It is not here just yet, but those techniques are being tested and hopefully we'll know more in the next, I would say, 12 months.

On the Importance of the Parkinson's Progression Markers Initiative

Companies have the challenge of ensuring that their drug has the right scientific structure to target the area of the brain to be successful. But they also have another challenge, which is to figure out how we can measure whether the drug actually has had an effect on clinical function in individuals with Parkinson's disease, or on some other measure that we believe is a sort of surrogate for clinical function.

PPMI is helping pharmaceutical firms develop the tools to conduct studies with a reasonably small number of individuals in a reasonably short period of time to say, "Okay, I feel confident that this drug has a signal that seems to work. And now I'm going to go and do a very large study to prove that point." PPMI has been very helpful in developing the clinical design tools being used by these companies. In fact, the two studies we just discussed both used clinical data from PPMI.

We now have an enormous opportunity to expand PPMI. We are expanding it in numbers because that gives us a lot more power to detect change. Remarkably, of the approximately 4,000 individuals we are working to enroll in PPMI, about 2,000 will be people who don't yet have Parkinson's disease, but who are at risk to develop Parkinson's within the next three to five years. Based on a lot of information that has been acquired over the past few years, we are confident that we can detect individuals who are more likely to be in this category.

These people will contribute first by using technology-enabled approaches such as an online, customized platform for completing questionnaires or a smart phone app. Gradually they will make their way through a process where they would get additional assessments over time. And based on those assessments they might be asked to come to a clinic, not remotely, but actually a clinic where they would be further tested. And then finally based on that some will make their way into the full PPMI study and contribute data and biosamples over many years.

This provides us with an enormous opportunity to understand what is happening to people prior to the onset of symptoms. This will be extraordinarily valuable in trying to understand, again, how to define progression and targeted therapies for individuals with Parkinson's disease. We all are aware and thinking about issues like precision medicine, targeted therapies — these are really what we would like to see happen in Parkinson's based on the data that we're collecting. Ultimately, of course, the goal is to be able to initiate treatment prior to the onset of symptoms, to prevent the onset of typical Parkinson's disease altogether.

This transcript has been condensed and edited.

> ### On the Approval of Aducanumab to Treat Alzheimer's Disease
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> (***Excerpt from "The approval of aducanumab isn't the end of the story. It's just the beginning" opinion piece authored by Ken Marek for STAT, June 15, 2021***)
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> For those in Parkinson's research, the aducanumab story should redouble our commitment to develop and test biomarkers for Parkinson's that will provide a clear understanding of the biology of this disease. This is the only way to efficiently test whether drugs slow the disease process and ultimately slow Parkinson's-related disability. Researchers need to work with pharmaceutical teams to give them these tools to ensure that their studies will meet every standard that's required, so when encouraging data emerge, they can move forward effectively.
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> I believe that the best way to put the approval of aducanumab into perspective is to see it as just the beginning of a pipeline of therapies that target the underlying biology of brain disease. This drug won't cure Alzheimer's, but it may prove helpful to alleviate suffering for many. Either way, it is giving us a road map to a therapeutic future of much more rational, targeted, and effective treatments for devastating brain disorders. Read more at **michaeljfox.org/NewsInContext**.