

## Hollywood star leads the way in Parkinson's research

The Michael J Fox Foundation is after the holy grail in Parkinson's research—disease-modifying treatments. They have launched Fox Trial Finder, which aims to get more patients involved in clinical trials, and are on the hunt for therapeutic biomarkers. Dara Mohammadi reports.

For more on Fox Trial Finder see <https://foxtrialfinder.michaeljfox.org/>

It was during filming for *Doc Hollywood* in 1990 that Michael J Fox first noticed a twitch in his little finger. At the time, he thought nothing of it, putting it down to the effects of a hangover. But a year later, at the age of 30, he was diagnosed with early-onset Parkinson's disease.

In denial over his diagnosis, the following 7 years saw him battle with depression, from which he emerged with a new determination to campaign for Parkinson's disease. The actor had turned activist, and in 2000 he launched The Michael J Fox Foundation with one explicit aim—to find a cure for the disease.

Since its formation, the Foundation has spent over US\$300 million investing in research to develop improved treatments. But, as Fox explains to *The Lancet Neurology*, they have realised that one of the biggest hindrances to research is the current set up at diagnosis. "At our Foundation we've heard a similar story from so many patients about the actual experience of diagnosis", he says. "You're reeling, the doctor writes a prescription and, basically,

wishes you luck. It's far from optimal for either party."

The Foundation wants to see more patients participating in clinical trials. Their holy grail—and that of Parkinson's research as a whole—is the development of disease-modifying treatments. Available drugs target only the symptoms, which means that as the disease continues to progress, there continues to be brain degradation, and, eventually, this degradation overcomes the ability of these drugs

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to alleviate symptoms.

Recruitment into trials for disease-modifying drugs for Parkinson's disease is notoriously difficult. Patients need to be identified and recruited early after diagnosis, before they begin symptomatic treatment, and in large numbers. Yet fewer than 10% of patients with Parkinson's disease have ever taken part in a trial. This, in the Foundation's eyes, is not good enough.

So, in April of this year, the Foundation launched a resource that it hopes will address this bottleneck in research. Fox Trial Finder, which Senior Vice President Sohini Chowdhury describes as being "a bit like match.com", is a website and online community for patients and researchers alike. Once registered, patients can locate and communicate directly with the investigators, who can also actively seek out potential participants.

Over 170 ongoing trials have thus far been registered to the site. And the number of registered volunteers is constantly on the rise (at the time of writing, 10 543 had signed up). Having surpassed their initial goal of recruiting 10 000 volunteers by the end of this year, they have set their sights on 15 000 by the end of 2013.

"Our hope", explains Fox, "is that Fox Trial Finder can help jumpstart a different conversation [after diagnosis], one about the importance of getting involved in research. It's important that patients realise that there's something they can do. And especially as a newly diagnosed patient, that they are one of a very small number who can do it."

Fox's Hollywood credentials certainly provide the pulling power needed to get this message across. But it does not stop there. The Foundation is also taking a hands-on role in speeding up the discovery of disease-modifying treatments. The staff team—currently 60 strong—is based in New York, and, as Chowdhury explains, a little of the Big Apple is also working in their favour.

"We have a real sense of urgency in how we run things; we are very proactive and very determined", she says. "It's that New York attitude in our office, in our culture—we don't wait, we try to do things there, then, and now."

But this is no foolhardy impatience. It is less the hustle and bustle of Times Square, and more the 12-hour days and 24-hour analysis of Wall Street. They understand how the drug market works. They have already invested heavily into research, but realise that their investments are a drop in the ocean compared with the amount that pharmaceutical companies have to pay to take a drug to market—health economists peg



Michael J Fox with his team

Elens Olivio/The Michael J Fox Foundation

this number at anywhere between \$1.3 billion and \$1.7 billion.

“When we think about investing money, there’s this underpinning strategy that we think about, this idea of de-risking”, explains Chowdhury. “In this economic climate, companies have a low risk tolerance. If we can get the cost and timing of drug development down, the development of drugs for Parkinson’s suddenly becomes more attractive in the industry’s eyes.”

And so, in 2010, they launched the Parkinson’s Progression Markers Initiative, or PPMI, the first-ever large-scale clinical observation study focused exclusively on identifying and validating Parkinson’s disease biomarkers.

“One of the goals for PPMI”, explains Todd Sherer, the Foundation’s CEO, “is to try and identify a biomarker, or series of biomarkers, that would be used as a gating, decision-making tool for deciding whether future clinical development should continue, and reduce some of the disincentive for drug companies to get involved.”

The Foundation is the main sponsor of the study, but 11 big pharmaceutical companies also contribute—both financially and intellectually. It is, after all, in their interest to participate because PPMI has been designed to allow a parallel process by which treatments can be developed in tandem with the discovery of biomarkers.

And the ambition of this study is matched only by its scope. Currently three-quarters the way through enrolment, they aim to recruit 600 participants—400 treatment-naïve patients with Parkinson’s disease and 200 age-matched controls—from 24 sites throughout North America, Europe, and Australia. Over the 5-year study, participants will undergo a wide range of tests, including clinical assessments, advanced imaging techniques, and collection of biological samples (blood, urine, and CSF).

Ken Marek, clinical professor of neurology at Yale University and principal investigator of PPMI, describes his team’s approach to the design and implementation of the protocol as “obsessive”. “Either myself or another member of the steering committee visited each site to present the study—it’s a lot of work for them to do, so they needed to have a particular interest in biomarkers”, he tells *The Lancet Neurology*. “We spent half a day with each team, just making sure that everyone was on the same page.”

During these visits, investigators more often than not expressed concern at one element of the protocol: they didn’t think they would be able to recruit and retain patients to a study that required extraction of spinal fluid seven times during the 5-year study period.

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“It was an interesting process”, says Marek. “Initially we needed to encourage and convince the investigators. But once they were convinced, they have in turn been able to convince the participants, simply by explaining to them why this is important. Spinal fluid assessments are an extremely valuable biomarker tool—we obviously can’t biopsy the brain, but we can look at the fluid that surrounds the brain. It’s the best surrogate we have.”

Marek’s team’s efforts have seemingly been successful. 98% of participants have given spinal fluid samples at baseline. “I think people are reasonably receptive—even to a spinal tap—if they understand that it’s critical to getting an answer at the end of the day”, he adds.

And answers are also the Foundation’s driving force. The staff team are always looking for



Biosamples collected during PPMI are freely available to Parkinson’s researchers

the best way to speed up progress towards new discoveries. “It’s not so important for us to see the credit for things”, explains Sherer. “We just want to see the progress.”

He explains how all the data from PPMI are made freely available online; their data have thus far been downloaded over 25 000 times. Biosamples obtained during the trial are also freely up for grabs for the research community—to date, 16 applications for their use have been submitted.

“The more researchers and organisations we can attract and retain in the field, the closer we are to finding a cure”, says Sherer, who is in no two minds about the value of having somebody like Michael J Fox so intimately involved in Parkinson’s research. “There is little question that Michael has done more than arguably anyone else to galvanise the Parkinson’s field—both patients and researchers—and to bring attention to the disease and the urgent need for better treatments and a cure.”

“Although none of this is easy”, adds Sherer, who is as pragmatic as he is determined. “We have to be sober about the work ahead and the effort required not only from funders, researchers, and clinicians, but also from patients. But we’re problem solvers and we’re optimistic. Whatever it takes, we’ll stay on it.”

Dara Mohammadi

For more on PPMI see <http://www.ppmi-info.org/>

Sam Ogden/The Michael J Fox Foundation