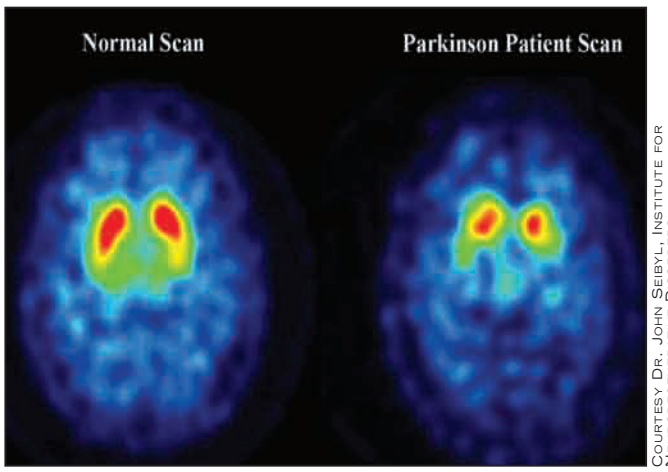
# Projects Will Search for Parkinson's Biomarkers

BY MICHELE G. SULLIVAN

Private and public sources are launching two massive efforts to identify biomarkers for Parkinson's disease – an effort they say will speed drug research, providing more efficient ways to track disease progress and monitor therapeutic response.

In late September, the Michael J. Fox Foundation kicked off its Parkinson's Progression Markers Initiative (PPMI) and the National Institute for Neurological Disorders and Stroke sent out a request for applications to create the Parkinson's Disease Biomarker Identification Network (PD-BIN). The 5-year PPMI is the first large-scale clinical study to focus exclusively on identifying and validating both chemical and imaging biomarkers of the disease. The multiproject PD-BIN will be similarly devoted to identifying biological markers that contribute to an individual's risk for Parkinson's disease, as well as its onset and progression.




COURTESY DR. JOHN SEIBYL, INSTITUTE FOR NEURODEGENERATIVE DISORDERS

**PPMI will use single-photon emission CT scanning to track dopaminergic neurodegeneration in Parkinson's patients.**

"We expect that the biomarkers we discover will help us better understand the disease and accelerate therapeutic trials, with the goal of assessing whether a drug can modify the progression of Parkinson's," PPMI primary investigator Dr. Kenneth Marek said in an interview. "In a way, this is much more complex than a clinical treatment trial. We are not testing a drug, but ideally, we will find markers that can pave the way to accomplish more effective drug testing, and speed the development of much-needed therapies for this disease."

Speaking from the World Parkinson Congress in Glasgow, Scotland, where he unveiled the PPMI to the scientific community, Dr. Marek stressed the need for objective, measurable disease markers in diagnosis and disease progression, as well as in research studies. The diagnosis of Parkinson's disease remains solely based on clinical signs and symptoms, with no concrete diagnostic measure. And with no objective clinical measurements in hand, researchers are "shooting in the dark" when assessing response to candidate drugs, he said.

"We have been conducting these clinical trials, but we there is no way to assess when a drug is ineffective, or how to get a better sense of whether the next one will actually work," said Dr. Marek, who also is president of the Institute for Neurodegenerative Disorders in New Haven, Conn.

Having a set of biomarkers will speed research in a way that is not now possible, said PPMI co-investigator Dr. Tanya Simuni, director of the Parkinson's Disease and Movement Disorders Center at Northwestern University, Chicago.

"We have many ongoing clinical trials of potential disease-modifying agents, but they are slow to progress because clinical assessment is the primary efficacy measure," Dr. Simuni said in an interview. "Because of this, these studies take a long time and need a large number of patients – and they still sometimes end up with inconclusive results. If we had an objective measure of disease progression, that would speed drug development by reducing the duration of the studies and the number of participants needed for each one."

The discovery of a biomarker could also help clinicians identify patients in the very earliest – perhaps even prodromal – disease state, she said. "By the time symptoms of Parkinson's appear, patients can have lost up to 70% of their dopamine-producing cells, which tells us that there is a prodromal or preclinical phase during which damage is occurring without clinical signs. Biomarkers could not only help us develop better interventions but also screening tools. It's conceivable that in the future, we could screen for Parkinson's in the same way that we now screen for breast cancer or other medical conditions."

PPMI will be conducted at 14 U.S. centers and at centers in Innsbruck, Austria; Kassel and Tubingen Germany; and Naples, Italy. It aims to recruit 200 healthy control patients and 400 patients newly diagnosed with Parkinson's disease who are not yet receiving medication.

The absence of Parkinson's disease medications is one key to a successful biomarker hunt, said Dr. Simuni, the principal investigator for the Midwestern region of the United States. "We want to make sure there is no over-signal of the therapy – that we are looking at the progression of disease unmasked by interventions."

This should not be a problem with this patient population – at least initially. "For many patients with a new diagnosis, symptoms don't interfere with their function, so it's quite common not to start treatment at this time," Dr. Simuni said. "At the point when the patient needs treatment, of course, it will start. They can remain in the study and count toward the follow-up. But our aim is to recruit patients early enough that we get at least 6 months of data without medication."

Funding for the $40 million PPMI study will come from the Michael J. Fox Foundation, private contributions, Pfizer Inc., and – Dr. Marek hopes – federal grants.

In fact, he said, PPMI leaders hope to become involved in the PD-BIN.

Although the request for applications for the PD-BIN was just released (http://grants.nih.gov/grants/guide/rfa-files/RFA-NS-11-005.html), Dr. Mark Hallett, chief of NINDS' Medical Neurology branch and its Human Motor Control Section, anticipated that the project could be up and running within 1 year.

"The deputy director of NINDS [Dr. Walter J. Koroshetz] made it clear that the goal of this project is to bring as many resources as possible to bear on advancing neuroprotective therapy for Parkinson's," Dr. Hallett said in an interview.

Although not officially connected, the PD-BIN and the PPMI may join forces, Dr. Marek said.

"We'll be applying for [the federal project] and we would love for these processes to be complementary. We would be delighted to have the government, through NIH, partner with us."

Both projects were largely inspired by the Alzheimer's Disease Neuroimaging Initiative (ADNI), a public-private collaboration launched in 2004. ADNI discoveries have shown that cerebrospinal fluid carries disease-specific biomarkers that change with disease progression, including levels of phosphorylated and unphosphorylated tau protein and amyloid-beta-42. The project also investigated new imaging compounds which allow, for the first time, visualization of amyloid plaques and tau neurofibrillary tangles in the brain and how they change during disease progression.

Like the ADNI, both the PPMI and the PD-BIN could amass an enormous biobank of samples, which will be available without cost to scientists with approved research projects. In fact, Dr. Marek said, PPMI data sets will be maintained by the same lab that administers ADNI data: the Laboratory of Neuroimaging at the University of California, Los Angeles.

"In addition to accessing the data, researchers will be able to apply for PPMI's imaging and samples of CSF, blood, and urine from a biorepository we intend to maintain," Dr. Marek said.

PPMI already has specific biomarkers targeted for research. Preliminary data indicate that alpha-synuclein, urate, and expression of the Parkinson's genetic marker DJ-1 change according to disease stage. Some data suggest that total tau, phosphorylated tau, and amyloid-beta might change as cognitive function is altered. Therefore, each of the 12 study visits will include blood, cerebrospinal fluid, urine, and DNA sampling as well as motor, neuropsychiatric, and cognitive assessments.

## How to Get Involved in PPMI

"Recruitment is the first, second, and third issue in a study like this," said PPMI lead investigator Dr. Kenneth Marek. "We know we are asking a lot of our participants, but from what we have seen so far, a lot of patients with Parkinson's, and their friends and families who could be controls, understand the need for this approach and are willing and excited about participating in it."

Both Dr. Marek and his coinvestigator Dr. Tanya Simuni admitted that the repeat lumbar punctures the study calls for could intimidate potential subjects. "It's important that they know that for most people, the possible side effects of a lumbar puncture are just about the same as for a blood draw," Dr. Simuni said.

The first stop for information is the PPMI website, www.ppmi-info.org. From here, physicians, researchers, and participants can learn about the scope of the project, the inclusion and exclusion criteria, and even see a schedule of visits and tests that each participant will need to fulfill.

By clicking on the "For Physicians" button, doctors can download the Physician Tool Kit, which includes brochures about the study; a poster; a pocket card with the study overview; and research referral forms (www.ppmi-info.org/about/for-physicians).

Researchers who are interested in working with biological samples from the study also can find information about submitting requests for potential projects (www.ppmi-info.org/for-researchers). The site contains a wealth of information for patients and families as well (www.ppmi-info.org/about/for-pd-and-control-participants).

Both Dr. Hallett and Dr. Marek noted that the PPMI investigation and any others that join the federal program may uncover additional biomarkers. "The constant concern about looking for things that you know is that you might overlook something that you don't know, which could turn out to be something even better," Dr. Hallett said.

Dr. Simuni has served as a consultant and received honorarium from GE Healthcare. She has received research support from the NIH and the Michael J. Fox Foundation. Dr. Marek is a member of the scientific advisory board for the Michael J. Fox Foundation and has been a consultant for Pfizer and GE Healthcare. He has an equity interest in Molecular NeuroImaging LLC. Dr. Hallet has no relevant disclosures. ■