

Projects Begin Hunt 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 multi-project 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, with the goal of speeding disease-modifying treatments.

"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."

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. Progression, as well, can be measured only by the worsening of symptoms. 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," 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." An objective measure of disease progression would speed drug development by reducing study duration and size, she said.

The discovery of a biomarker could also help clinicians identify patients in the 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 inter-

ventions but also screening tools."

The PPMI will be conducted at 14 U.S. centers and at centers in Innsbruck, Austria; Kassel and Tübingen, 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

"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), which also is a public-private collaboration. Launched in 2004, the ADNI studied the rate of change of cognition, brain structure and function, and biomarkers in healthy control patients, patients with mild cognitive impairment, and patients with Alzheimer's disease. Discoveries made through the ADNI 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.

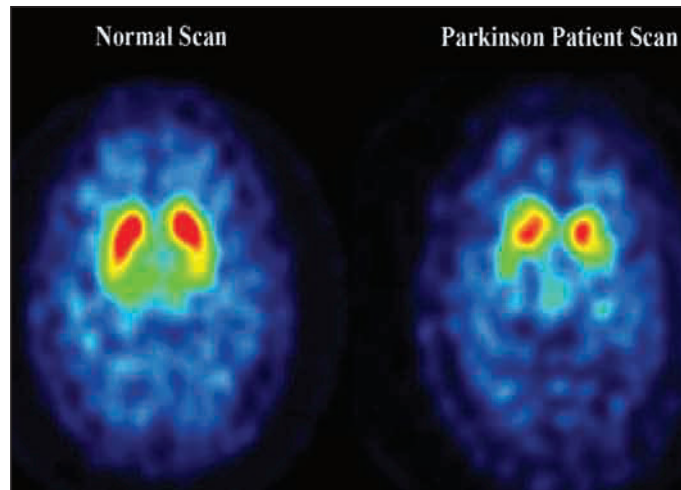
Like the ADNI, both the PPMI and the PD-BIN could amass an enormous bio-bank of samples, which will be available without cost to scientists with approved research projects. In fact, Dr. Marek said, PPMI data sets will be maintained by the same lab that administers ADNI data: the Laboratory of Neuroimaging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

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.

Single-photo emission CT with DaTSCAN (ioflupane [123I]) and MRI imaging will determine changes in brain structure and dopamine levels. Although not yet approved for clinical use in the United States, the DaTSCAN radioisotope binds to dopamine transporters in the substantia nigra, allowing researchers to study dopaminergic neurodegeneration.

Dr. Simuni has served as a consultant and received honorarium from GE Healthcare, which manufactures and markets DaTSCAN in Europe. She has received research support from the NIH and the Michael J. Fox Foundation.

Dr. Marek is on the scientific advisory board of 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. Hallett has no relevant disclosures. ■



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

COURTESY DR. JOHN SEIBYL, INSTITUTE FOR NEURODEGENERATIVE DISORDERS

How to Join the Biomarker Search

"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," she said.

The first stop for information is the PPMI Web site, 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).