

Seeking Parkinson's Signature

The new Parkinson's Disease Biomarkers Program.

BY TOM VALEO

By the time the conspicuous symptoms of Parkinson's disease (PD) appear—hand tremors, muscle rigidity, slowness of gait—the brain has already lost 60 to 80 percent of the cells that produce dopamine, a neurotransmitter needed for smooth body movements. Destruction of dopamine-producing cells begins years or decades before symptoms appear.

The problem is that signs of this disease process, called biomarkers, produce extremely subtle and ambiguous changes in the years before PD symptoms appear. In fact, despite more than 40 years of searching, doctors and scientists still can't interpret changes signs reliably.

As a result, treatment for PD usually doesn't start until the majority of dopamine-producing cells have died. At that point, the only recourse is to manage symptoms by providing the body with levodopa, a dopamine replacement. Over time, people taking levodopa may begin to vacillate between having too much of the neurotransmitter—which causes the involuntary movements that people may recognize from public appearances by Michael J. Fox—or too little, which results in the slowness, rigidity, and mask-like facial expression many people associate with Muhammad Ali.

Finding reliable markers will enable researchers to determine if new treatments being tested in clinical trials really slow down the disease.

MORE THAN \$5 MILLION IN GRANTS

In an effort to speed the discovery of reliable biomarkers for PD, the National Institutes of Neurological Disorders and Stroke (NINDS)—part of the National Institutes of Health—has awarded \$5.2 million to nine research teams through the new Parkinson's Disease Biomarkers Program (PDBP).

“Our idea is to cast a broad net, allow the investigators to study their data,



ON THE TRAIL

Penn State Hershey Medical Center researcher Dr. Xuemei Huang (pointing) and colleagues Dr. Guangwei Du and Dr. Mechelle Lewis review MRI data from their biomarker study.

and then make the information available to others,” says Katrina Gwinn, program director for the PDBP. “We’re focusing on biomarkers that will help in the development of treatments to prevent or slow down progression of the disease.”

This isn't the only concerted effort to find biomarkers. The Michael J. Fox Foundation, for example, has been sponsoring the Parkinson's Progression Marker Initiative, a five-year study to validate biomarkers that have shown promise, as well as the Fox Investigation for New Discovery of Biomarkers, a two-year study that

began last fall. The first focuses primarily on biomarkers that are almost ready to seek approval from the U.S. Food and Drug Administration (FDA). The second focuses on discovering new biomarkers.

“At the National Institutes of Health, we have expertise funding this kind of scientific discovery,” says Dr. Gwinn, whose father died in 2010 of PD. “The Fox Foundation's five-year study is looking at possibilities pretty close to proven, whereas we're looking at newer ideas. But our research may also feed into their process.”

THE PROBLEM WITH DOPAMINE

Dopamine, which decreases as the result of PD, might seem an obvious choice for a biomarker. However, measuring a reduction in dopamine hasn't worked because the body makes heroic efforts to compensate for the decline.

“Years ago, we thought measuring dopamine by-products in the spinal fluid would give us a useful measure of the disease, but you don't find a deficiency in the

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—ALICE CHEN-PLOTKIN, M.D.

spinal fluid, even in advanced disease,” says veteran PD researcher Peter A. LeWitt, M.D., professor of neurology at Wayne State University School of Medicine in Detroit and director of the Parkinson’s Disease and Movement Disorders Program at the Henry Ford Hospital in West Bloomfield, MI. “The reason is that in response to the loss of neurons that produce dopamine, surviving neurons increase their output, which masks the decline,” he says.

IRON AS A BIOMARKER

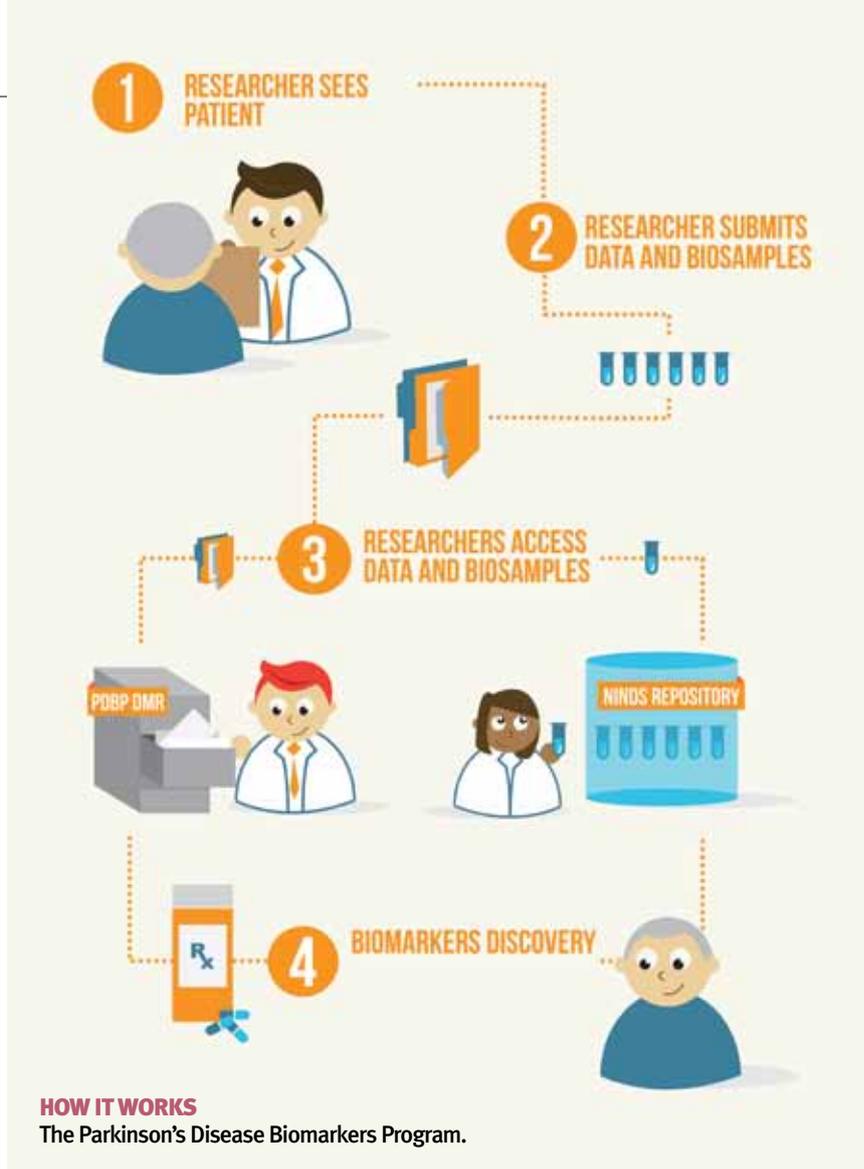
Iron may provide a better biomarker. Autopsies show that people with PD accumulate iron in the substantia nigra, a brain region that contains a large number of dopamine-producing cells. Researchers are fairly confident that iron is involved in the disease process, but they are unsure of the exact role it plays.

Xuemei Huang, M.D., Ph.D., director of the Brain Analysis Research Laboratory for Neurodegenerative Disorders at the Penn State University in Hershey, PA, has devised a way to use magnetic resonance imaging (MRI) to reveal the accumulation of iron in the brain as the disease progresses.

“Iron has been implicated in a number of neurologic conditions, ranging from restless leg syndrome to Alzheimer’s disease, and many people think disruption of iron balance participates in the death of cells in PD,” Dr. Huang says.

People newly diagnosed with PD usually don’t show excessive iron accumulation in the substantia nigra, but those who have had the disease for 10 to 20 years do. So Dr. Huang and her colleagues are using a portion of their grant money to measure iron with MRI scans in three groups: those newly diagnosed with PD, those who have had the disease 1 to 5 years, and those who have had it more than five years.

“We will measure iron concentration in each patient and compare the results to



people who don’t have PD to see if iron, as revealed by MRI, provides a biomarker for PD progression,” Dr. Huang explains.

ALPHA-SYNUCLEIN

Another biomarker under investigation is alpha-synuclein, a normal and relatively common brain protein that misfolds and accumulates as PD progresses.

Over time, misfolded alpha-synuclein finds its way into the spinal fluid of people with PD. However, obtaining an accurate measure has proved difficult for technical reasons: the needle used to draw spinal fluid must pass through skin and body tissue containing blood—and blood contains 100 times as much alpha-synuclein as spinal fluid. This means that a spinal fluid sample contaminated with blood may produce an inaccurate measure of the protein.

Jing Zhang, M.D., Ph.D., professor of pathology at the University of Washington School of Medicine in Seattle—who has received the largest of the nine grants

awarded by NINDS, at \$1.3 million—hopes to develop a biomarker based on an accurate reading of alpha-synuclein in the spinal fluid.

“We’re trying to avoid this problem of contamination by protein in the blood,” Dr. Zhang says. “That’s the technical difficulty. We’re trying to find forms of alpha-synuclein in the spinal fluid that are different from those found in blood, so that blood contamination won’t be a problem.”

Interestingly, the brain and spinal fluid may not be the only or even the best places to look for evidence of alpha-synuclein in PD.

“Some of the most exciting biomarker clues are in the lower gastrointestinal tract—the colon—where there’s evidence of accumulation of alpha synuclein,” Dr. LeWitt notes. “Aggregated protein, which seems to be central to the disease, is found in biopsies of polyps in the colons of people with PD several years before they develop motor symptoms.”

PARKINSON’S DISEASE BIOMARKERS PROGRAM

OTHER PROTEINS

Alpha-synuclein is not the only protein being investigated by these NINDS-funded researchers. A group led by Ted Dawson, M.D., Ph.D., and Liana Rosenthal, M.D., at The Johns Hopkins University School of Medicine in Baltimore, MD, plans to study other proteins found in the spinal fluid and blood of PD patients. “If we find different amounts of these proteins in individuals with PD than in those without, that would imply that the protein could be used to identify PD in its early stages,” says Dr. Rosenthal.

She notes that such biomarkers would probably not be used as the only indicator of disease, but as one clue among many. “There may not be a single protein abnormality that predicts risk of PD in everyone,” Dr. Rosenthal says. “Instead, a number of biomarkers might need to be used together to predict risk of the disease as well as progression.”

Vladislav Petyuk, Ph.D., of Battelle Pacific Northwest Laboratories in Richland, WA, and his colleagues will try to develop ways of detecting the presence of Lewy bodies, which are abnormal proteins that form in the nerve cells of PD patients. At present, those proteins can only be evaluated at autopsy by examining brain tissue. Detecting them while a patient is still alive could help determine disease progression—and gauge the effect of new drugs.

A team led by Andrew West, Ph.D., of the University of Alabama at Birmingham, will look for evidence of the protein LRRK2 in exosomes, tiny packets of molecules within cells. Mutations in the LRRK2 gene contribute to PD risk in some people.

And Alice Chen-Plotkin, M.D., of the University of Pennsylvania in Philadelphia, will look at 1,100 proteins in the blood in hopes of finding some that occur more often in PD patients. “Our hope is that in a couple of years we’ll be dealing with more than handful of potential biomarkers,” she says.

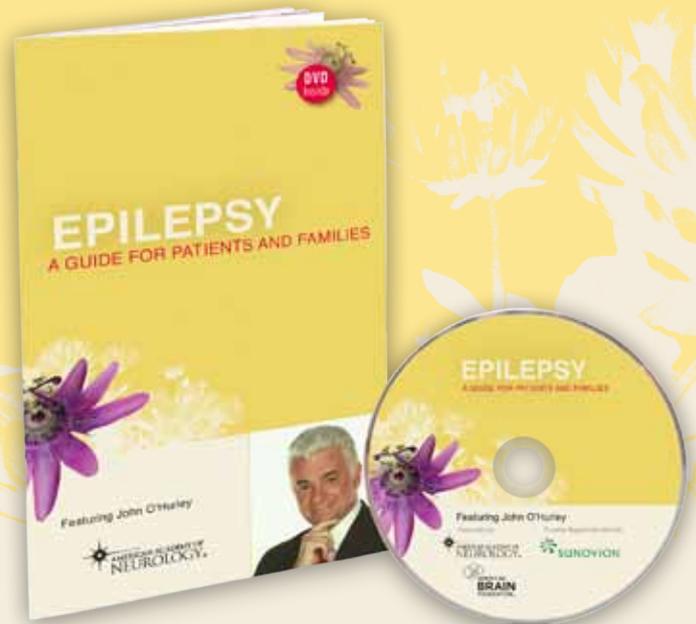
Other groups who received grants are investigating the role of the immune system in PD and developing statistical tools for analyzing data gathered in the search for biomarkers. 

FOR MORE INFORMATION

To find out more about the Parkinson’s Disease Biomarkers Program, go to <http://pdp.ninds.nih.gov>.

For the full collection of *Neurology Now* articles on Parkinson’s disease, go to <http://bit.ly/waqKob>.

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