Biomarker Development for Parkinson’s Disease

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Parkinson's Disease (PD) is a chronic neurodegenerative disease with no known cure, no certain cause, and no clinically available test for simple diagnosis. Research advances have been made, but there still remains a huge unmet need for diagnostic and disease progression biomarkers.

Research on this disease is focused on the changes that occur in the brain. Research has shown that the nerve cells in the brains of Parkinson's patients have abnormal protein deposits that may disrupt normal brain function and cause Parkinsonian symptoms, such as tremor, slowness of movement, and rigidity, among others.

Called Lewy Bodies, these microscopic protein clumps are made up primarily of the protein alpha-synuclein (SNCA). The general function of the SNCA protein is largely unknown, but mutations in SNCA, or excess copies of the normal gene may cause familial forms of PD.

Researchers are focusing on the possible importance of different types of post-translational modifications to SNCA, including phosphorylation. These modifications may be important in regulating the function of proteins. Phosphorylation can take place at certain specific sites along the chains of amino acids in the protein. In PD, it is suspected that certain post-translational modifications in SNCA may play a role in causing the disease or may signal progression of the disease.

In 2011, Covance began work with a client to develop an assay aimed at detecting phosphorylated SNCA. At the time, there were no published reports of phosphorylated SNCA in plasma or in the protective fluid surrounding the brain, cerebral spinal fluid (CSF).

The Covance team developed a method to study phosphorylated forms of SNCA. They characterized multiple phosphorylated forms of SNCA in CSF and plasma, measuring these sites using a technique called liquid chromatography-tandem mass spectrometry (LC-MS/MS). Liquid chromatography physically separates the components in the sample and tandem mass spectrometry determines the relative mass and charge of the target peptide.

Working with samples from non-PD subjects, the team discovered multiple phosphorylated forms of this protein in CSF and plasma. This method, which is also applicable to other low abundance CSF analytes, was presented at the
2011 Conference on Alzheimer’s Disease & Parkinson’s Disease (ADPD) meeting in Barcelona. Subsequently, other researchers outside of Covance examined how to quantify phosphorylated SNCA in biological fluids. Since the 2011 meeting, Covance scientists have used the same LC-MS/MS method to examine cerebral spinal fluid and plasma in search of other modified forms of SNCA, including, splice variants, other phosphorylated forms, and truncations. These data were reported at the 2013 Conference on Alzheimer’s Disease & Parkinson’s Diseases (ADPD) meeting in Florence. Meanwhile, Covance Antibody Products developed an ultra-sensitive SNCA ELISA kit, in collaboration with the University of Ottawa, with support from the Michael J. Fox Foundation.

What does the ability to accurately identify and measure SNCA phosphorylation mean for biomarker development? To address this, Covance is part of a consortium organized by the Michael J. Fox Foundation along with researchers at Biogen Idec, Eli Lilly and Company, and a number of academic institutions including the University of Pennsylvania, the University of Goettingen, and the Ecole Polytechnique Federale de Lausanne. As a team, they hope to determine whether there is a correlation between these modified forms of SNCA and progression of the disease. If so, phosphorylated SNCA or other post-translationally modified forms of the protein may be useful as a biomarker for PD.

The implications of biomarker identification in Parkinson’s Disease are enormous. PD takes several years to develop in patients—usually several PD symptoms must appear before a diagnosis is made. Early diagnosis could allow for earlier interventions. And, if post-translationally modified SNCA is indeed a valuable biomarker, it will speed research for developing therapies.

While great strides have been made, work in this area has only begun. This research requires collaborative teams of experts and shared resources, but will ultimately add insights and deliver a positive impact on patients’ lives.

About the author:

Robert Martone is the Neuroscience Therapeutic Area Lead for the Covance Biomarker Center of Excellence. He joined Covance in 2010 after 17 years of industry experience in drug discovery and eight years of basic research experience at Columbia University. He is working with Marci Copeland, Senior Research Associate at Covance, to develop LC-MS/MS based approaches to neuroscience biomarker discovery.

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