A fortuitous discovery of a molecule that can differentiate between normal and abnormal levels of brain cells that bear dopamine transporters may hold the key to more accurate and early diagnoses of Parkinson’s disease and attention deficit hyperactivity disorder.

Imagine waking up one morning with a sudden and unexplained twitch in your little finger. Too persistent to ignore, you go to your general practitioner where you learn that you may have some kind of movement disorder. The twitches, tremors and shakes may not go away — in fact they may get worse. Even scarier, there is a good chance that your condition will be misdiagnosed, and the treatment you really need is not necessarily the one that will be prescribed.

Welcome to the frustrating world of movement disorders. Doctors who treat patients with these symptoms face this conundrum every day. Patients with Parkinson’s Disease — a highly debilitating neurodegenerative disease — as well as patients with other disorders that appear to be the same thing but are actually of a very different etiology suffer because of a lack of accurate and reliable diagnostic tools.
There has been a crying need for a long time now for earlier and more accurate diagnosis of Parkinson’s disease,” says Ken Rice, executive vice president and chief financial officer of Boston Life Sciences Inc., a Boston-area company that is playing a huge role in helping to solve this problem. Research into the progression of Parkinson’s disease has shown that by the time a patient is symptomatic, 70 to 80 percent of the neurons that control movement in the substantianigra part of their brain have died. Because there is no cure for the disease, all that is available to patients and their families is a plan for managing the symptoms — and even this phase is relatively short. “That is why earlier detection and intervention of PD can make a big difference,” Rice says. “It would allow for an extension of the symptom management phase and translate into better quality of life for patients.”

Understanding Diseases on a Molecular Level

That’s where Altropane®, a highly specific imaging agent presently undergoing evaluation in Phase III clinical trials, comes in. The groundwork for Altropane® was laid in the late 1980s, when Bertha Madras, Ph.D., professor of psychobiology at Harvard University, was researching the action of cocaine in the brain. Madras fortuitously discovered that a certain molecule, by virtue of selectively binding to a protein — the dopamine transporter — could accurately differentiate between particular cells in the brain. A somewhat simple concept, but the information it revealed was quite powerful. “I’ll never forget that moment,” Madras recalls. “When the lab technician showed me the results of the experiment, I nearly fell off my seat. I immediately realized the impact of these results, and it sent off a cascade of ideas in my mind.”

This binding molecule, called a tropane, was the first to accurately identify neurons in the brain that bear dopamine transporters, specialized proteins that transport the chemical dopamine into cells. Neurons that don’t have dopamine transporters on their cell surface were clearly and cleanly ignored when introduced to the tropane. The implication for Parkinson’s patients is that those with the disease have very low levels of dopamine transporter-producing cells; they mysteriously die off. So, the brains of Parkinson’s patients, compared with normal brains, as well as those with non-Parkinson’s movement disorders like essential tremor, look very different when put to this test.

The clinical application of this discovery involved joining forces with a team of chemists who specialize in modifying molecules to make them imaging agents, or proteins that become detectable by nuclear medicine tests such as positron emission tomography, or PET, scans. Collaboration with fellow Harvard scientist, chemist and inventor David Elmelah, Ph.D., helped to overcome this hurdle, and the team was ready to find a partner to support product development. They enlisted the expertise of Peter Meltzer, Ph.D., scientist and president of Organix in nearby Woburn, Mass., and the collaboration between academic and industry science led to the further development of Altropane®.

The final version of Altropane® includes a radioactive label (Iodine-123), enabling its visualization by clinicians in live humans when imaged by single photon emission computed tomography, or SPECT. SPECT imaging is more widely available and less expensive than conventional PET scans, making it accessible to most hospitals with nuclear medicine departments. Moreover, SPECT can provide imaging of Altropane® almost immediately after it is injected, enabling quick and accurate diagnoses.

Early Diagnosis Can Slow Progression of Disease

The technology transfer office at Harvard University worked with the scientists as they recognized the potential of
Altropane®, and Boston Life Sciences, headquartered in Hopkinton, Mass., acquired the rights to develop, manufacture and commercialize the agent. Following the completion of several large early stage trials, Altropane® is now in pivotal Phase III trials specifically designed to test the molecule’s ability to differentiate between Parkinson’s Disease and other non-Parkinsonian movement disorders manifested by shaking and tremors.

“We’re very excited about Altropane® and its promise in reducing the high error rate associated with the diagnosis of PD and other movement disorders,” says Rice of Boston Life Sciences. The company is very committed to bringing the product to market and has made a substantial investment in the clinical development of Altropane®. “First and foremost, the Parkinson’s community is a very dedicated group of people who want nothing more than to find a cure,” Rice says. “Anything we can do to help alleviate the uncertainty by providing a more accurate tool for diagnosis is hugely important.”

Clinicians who diagnose and treat Parkinson’s patients say Altropane® could have a significant impact. “In terms of a patient’s quality of life, it is so important to get the appropriate medicine early on,” says Burton Scott, Ph.D., M.D., associate clinical professor in medicine and neurology at the Movement Disorders Center at Duke University Medical Center. “We want to eventually use neuroprotective drugs for those patients who are susceptible to PD. That goal has been the Holy Grail in PD research for quite some time. In the foreseeable future, when we have effective therapies that can slow down the progression of PD — and I’m confident that they will be forthcoming — the correct diagnosis of the disorder will be even more critical.”

The acceptance of Altropane® also promises a more widespread means of identifying and diagnosing Parkinson’s Disease patients so that they receive adequate treatment earlier. “Altropane® allows more clinicians to make an accurate diagnosis without requiring movement disorder specialists,” says Alan Fischman, M.D., director of nuclear medicine at the Massachusetts General Hospital and an investigator involved in clinical trials of Altropane® in Parkinson’s Disease patients. “By allowing doctors who are not necessarily experts in the field of movement disorders to make a definitive diagnosis, it moves the treatment out of major academic centers and out into the community. Because of this, Altropane® can significantly augment the field.”

Attention deficit hyperactivity disorder, or ADHD, is another highly prevalent medical problem characterized by abnormal levels of dopamine transporter-producing neurons in the brain. Like Parkinson’s Disease, the level of dopamine transporters in the brains of ADHD individuals differs from those without the disorder. In the case of ADHD however, dopamine transporters levels are elevated, not reduced. Boston Life Sciences is now sponsoring Clinical trials to test the accuracy of Altropane® in diagnosing this disorder.

ADHD, which affects more than 5 million children in the United States and as many as 2 to 4 percent of adults, has been a controversial medical issue because of inconsistencies in the clinical diagnosis and concern about the reported abuse of behavior-modifying medications for the disorder.

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