The documents affixed to this article were removed from our data base of neurodegenerative issues that were identified using our quantum biology algorithm.

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https://medicalxpress.com/news/2019-05-method-parkinson.html

MAY 3, 2019

New method developed to target cause of Parkinson's

by University of Oxford

The discovery of a new way to target and treat the leading genetic contributor to Parkinson's may open the way for a potential new clinical treatment.

Researchers from Oxford's Department of Physiology, Anatomy and Genetics (DPAG) have identified how the dysfunction of a key protein, LRRK2, causes the neurons affected in Parkinson's to lose their ability to effectively clear out cell components that have been damaged. This discovery has enabled the team to find a new way to target and correct this issue, paving the way for a potential new clinical treatment.

Parkinson's is a motor disorder caused by the loss of a specific sub-set of neurons located in the midbrain. Although the underlying mechanisms leading to the death of these neurons is still not well understood, one of the leading theories is that they die as they accumulate protein aggregates.

Evidence from recent years points to lysosomes, the cellular organelle in neurons responsible for clearing out waste, as a leading culprit for the progression of Parkinson's. The lysosomes do not work well enough in those with the condition, which causes damaged cell components to build up and clump together.

About 10% of Parkinson's is genetic, and lysosomes are implicated in the progression of both the inherited condition and in those with no family history of disease. Mutations in the gene LRRK2 are the most common genetic cause of Parkinson's, and these mutations have been heavily implicated in causing the lysosomes to stop working properly. However, researchers have been trying to ascertain exactly what LRRK2 does for some time and the mechanism by which LRRK2 regulates lysosomal function is still not clear.

In a new study, the Wade-Martins Group has identified for the first time both an important role of LRRK2 and a new way to target its dysfunction therapeutically. Lysosomes need to be acidic to work properly and effectively degrade the waste proteins, and the team's research demonstrates that LRRK2 regulates the way that lysosomes are acidic. In Parkinson's, the mutated LRRK2 is not able to perform this function, so lysosomes lose their acidity as a result of LRRK2 dysfunction.

They also found that a drug called clioquinol, currently used as an anti-parasitic drug, overcomes the effect of the mutant LRRK2 and restores the acidity of the lysosome and clears out the protein aggregates. Consequently, the team was able to restore the ability of the lysosomes to "chew up this pathological protein burden" (Prof Wade-Martins) and clear out the protein aggregates that are killing the neurons.

This data identifies a novel mechanism of LRRK2 mutations and ultimately demonstrates the importance of LRRK2 in lysosomal biology, as well as the critical role of the lysosome in Parkinson's.

Professor Richard Wade-Martins of Oxford's Department of Physiology, Anatomy and Genetics (DPAG), said: 'As the population in the United Kingdom gets older, we're all ageing, the incidence of Parkinson's is going to increase. We urgently need a better understanding of what causes the disease and then apply that knowledge to develop new therapies, and that is what our work has done. Our work identifies for the first time the very important role of LRRK2 in regulating the acidity and the normal function of the protein recycling centre, the lysosome, and identifies a new way to target this therapeutically in Parkinson's.'

The successful use of clioquinol to reverse the effects of this mutation highlights the potential of drugs targeting the lysosome in future therapeutics of not only Parkinson's, but also other neurodegenerative diseases where lysosome dysfunction has been implicated.

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MCFIP – Our modeling of the biomarker LRRK-2 in relation to Parkinson’s disease is outlined for verification in the document affixed to this article.

Parkinson's disease biomarker found in patient urine samples

July 5, 2016 by Jeff Hansen in Medicine & Health / Parkinson's & Movement disorders

For more than five years, urine and cerebral-spinal fluid samples from patients with Parkinson's disease have been locked in freezers in the NINDS National Repository, stored with the expectation they might someday help unravel the still-hidden course of this slow-acting neurodegenerative disease.

Now, research by Andrew West, Ph.D., and colleagues at the University of Alabama at Birmingham has revealed that the tubes hold a brand-new type of biomarker—a phosphorylated protein that correlates with the presence and severity of Parkinson's disease. West and colleagues, with support from the National Institutes of Health, the Michael J. Fox Foundation for Parkinson's Disease Research and the Parkinson's Disease Foundation, are digging deeper into these biobanked samples, to validate the biomarker as a possible guide for future clinical treatments and a monitor of the efficacy of potential new Parkinson's drugs in real time during treatment.

"Nobody thought we'd be able to measure the activity of this huge protein called LRRK2 (pronounced lark two) in biofluids since it is usually found inside neurons in the brain," said West, co-director of the Center for Neurodegeneration and Experimental Therapeutics, and the John A. and Ruth R. Jurenko Professor of Neurology at UAB. "New biochemical markers like the one we've discovered together with new neuroimaging approaches are going to be the key to successfully stopping Parkinson's disease in its tracks. I think the days of blindly testing new therapies for complex diseases like Parkinson's without having active feedback both for 'on-target' drug effects and for effectiveness in patients are thankfully coming to an end."

A biomarker helps physicians predict, diagnose or monitor disease, because the biomarker corresponds to the presence or risk of disease, and its levels may change as the disease progresses. Validated biomarkers can aid both preclinical trial work in the laboratory and future clinical trials of drugs to treat Parkinson's. West and others are paving the way for an inhibitor drug that prevented neuroinflammation and neurodegeneration in an animal model of the disease, as reported last year by West and colleagues.

The new biomarker findings were published in *Neurology* in March and *Movement Disorders* in June. The biomarker, LRRK2, has been shown to play a role in hereditary Parkinson's, and the most common of these mutations—called G2019S—

causes the LRRK2 kinase to add too many phosphates to itself and other proteins. Why this leads to Parkinson's disease is not yet clear.

The key to West's biomarker approach was the recognition that LRRK2 can be purified from a new type of vesicle called exosomes found in all human biofluids, like urine and saliva. Cells in the body continually release exosomes that contain a mixture of proteins, RNA and DNA derived from different kinds of cells. West and colleagues were able to purify exosomes from 3- or 4-ounce urine samples donated by patients, and then measure phosphorylated LRRK2 in those exosomes.

The findings

In the *Neurology* study, they found that elevated phosphorylated LRRK2 predicted the risk for onset of Parkinson's disease for people carrying a mutation in LRRK2, which is about 2-3 percent of all Parkinson's disease patients. These findings were first tested with a preliminary, 14-person cohort of urine samples from the Columbia University Movement Disorders Center. That was followed by a larger replication study of 72 biobanked urine samples from the Michael J. Fox Foundation LRRK2 Cohort Consortium. All samples were provided to UAB in a blinded fashion to ensure the approach was rigorous.

The follow-up *Movement Disorders* paper—the first study of its type—expanded the scope to people without LRRK2 mutations, which is most Parkinson's disease patients. Using 158 urine samples from Parkinson's disease patients and healthy controls enrolled in the UAB Movement Disorder Clinic as part of the NIH Parkinson's Disease Biomarker Program, West and colleagues found that approximately 20 percent of people without LRRK2 mutations but with Parkinson's disease also showed highly elevated phosphorylated LRRK2 similar to people with LRRK2 mutations, and this was not present in healthy controls. The study speculates that people with elevated phosphorylated LRRK2 may be particularly good candidates for future drugs that reduce phosphorylated LRRK2.

Next steps

Questions remain for this evidence of biochemical changes in LRRK2 in idiopathic Parkinson's disease. One is finding out where the urinary exosomes come from. Given a suspected role for inflammation in Parkinson's disease, it is interesting that LRRK2 is highly expressed in cells of the innate immune system. A possible explanation for the phosphorylated LRRK2 in patients with more severe disease may be an increased inflammation in those patients who have aggressive progression of disease.

In May, West was awarded a new U01 collaborative grant from the National Institute of Neurological Disorders and Stroke to further explore urinary exosomes and extend the observations to cerebral-spinal fluid as a marker for disease prediction and prognosis.

Besides West, authors of the Neurology paper, "Urinary LRRK2 phosphorylation predicts parkinsonian phenotypes in G2019S LRRK2 carriers," are Kyle B. Fraser and Mark S. Moehle, of the Center for Neurodegeneration and Experimental Therapeutics and Department of Neurology, UAB School of Medicine; and Roy N. Alcalay, M.D., Columbia University Department of Neurology.

Provided by University of Alabama at Birmingham

"Parkinson's disease biomarker found in patient urine samples" July 5, 2016 http://medicalxpress.com/news/2016-07-parkinson-disease-biomarker-patient-urine.html

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MCFIP – These researchers will be shocked to learn that LRRK-2 has numerous designations for epigenetic signaling molecules associate with recycling of lipids; i.e. autophagy. The following are several examples that, when physical science modeling is used, can be verified by anyone with expertise in biology 101.

Autophagy Signaling Molecules

The following are examples of designations for the signaling molecules that perform the "disassembly" portion of autophagy for lipids; i.e. phase 2.

LRRK1	--- SKP-1A	--- SREBP1	--- GSK-1	--- ApoE-2
LRRK2	--- SKP-1B	--- SREBP2	--- GSK-2	--- ApoE-3
GABA-T	--- SKP-2	--- SCAP	--- GSK-3	--- ApoE-4

When mutated, this family of 3 signaling molecules cannot stop aggregation of signaling molecules (currently referred to as the aggregation of proteins) in the brain that forms plaques. Research will be necessary, however, with near certainty, the retardation of the neural firing (metabolic) rate is a primary factor in the disruption of autophagy in addition to the mutation of the signaling molecules.

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Researchers Set Sights On New Era in Neuroprotection

ScienceDaily (Oct. 15, 2012) — For decades, patients with Parkinson's disease (PD) have had the same experience. Their hands start to shake uncontrollably, their limbs become rigid and they lose their balance. Years before those movement problems set in, many begin struggling with fainting, incontinence, sexual dysfunction, anxiety and depression. Most patients are still treated with a 42-year-old drug called L-DOPA, which temporarily staves off symptoms but can itself cause heart arrhythmias, stomach bleeding and hallucinations.

This punishing experience may explain in part why patients with PD die at twice the rate of those without the disease in the years after their diagnosis. In this light, it's best to tread carefully when talking about early study results that promise something better. That said, a team of researchers at the University of Alabama at Birmingham is excited.

The team has identified a set of experimental drugs called LRRK2 inhibitors that may go beyond symptom relief to directly counter the inflammation and nerve cell death at the root of Parkinson's. At least, these effects have been suggested in mouse and cell culture studies meant to approximate human disease. UAB researchers reported on these findings today in a presentation at Neuroscience 2012, the annual meeting of the Society for Neuroscience in New Orleans.

"We don't yet know what percentage of patients might benefit from LRKK2 inhibitors, but LRRK2 is without a doubt the most exciting target for neuroprotection to have ever been identified in Parkinson's disease," says Andrew West, Ph.D., associate professor in the Department of Neurology within the UAB School of Medicine, who gave the presentation at Neuroscience 2012. "We will repeat our experiments many times before drawing final

conclusions, but our ultimate goal is see our compound or something like it enter toxicology studies, and ultimately, clinical trials as soon as is prudent."

While West's compounds are promising, they still face many crucial tests that will decide whether or not they reach human trials. But the field is excited, because this is the first time such a drug target has been found for any neurodegenerative disease. Along with evidence that LRRK2 plays a crucial role in the mechanisms of Parkinson's disease, it is a protein kinase, the same kind of enzyme (although not the same one) that has been safely and potently targeted by existing treatments for other diseases, including the cancer drugs Herceptin, Tarceva and Erbitux.

Why LRRK2?

LRRK2 stands for leucine-rich repeat kinase 2. Kinases are enzymes that attach molecules called phosphates to other molecules to start, stop or adjust cellular processes. Past studies found that the most common LRRK2 mutation, called G2019S, makes LRRK2 slightly over-active. The idea is to dial LRRK2 back with drugs.

Whether it's a bad version of a gene, an unlucky flu infection, a head injury or just age, something makes a protein called alpha-synuclein build up in the nerve cells of Parkinson's patients, contributing to their self-destruction. Unfortunately, alpha-synuclein and proteins like it are not part of a traditional set of "drug-able" targets. Once alpha-synuclein builds up, the question becomes whether the brain will handle it well or amplify the disease. MCFIP – LRRK-2 is one of the family of 3 signaling molecules for autophagy. If mutated or if the metabolic rate is retarded a variety of signaling molecules cannot be “disassembled” and will aggregate in the brain; alpha-synuclein is one of those signaling molecules. Along with its other family members; alpha and gamma, the amino acid cascade is phenylalanine (α), tyrosine (β) and tryptophan (γ).

In other works, disruption of the mechanism for autophagy (due to aberration of the appropriate signaling molecule or the retardation of the rate of activity) will enable signaling molecules to aggregate in the brain to form “plaques.” Outcomes will vary but, using Alzheimer’s as an example, dementia will be the result.

LRRK2, to West's mind, is a critical decision-maker in the body's answer to that question. He thinks it operates at the intersection between alpha-synuclein, neurotransmission and immune responses, which fight infectious diseases but also create disease-related inflammation when unleashed at the wrong moment, or in the wrong place or amount. Not everyone who has a LRRK2 mutation develops the disease, but West's team thinks it becomes important when combined with other factors.

Past studies have shown that alpha-synuclein build-up in nerve cells activates nearby immune cells of the brain called microglia, and that these microglia express high levels of LRRK2. Recent cell studies in West's lab suggest that mutated, overactive LRRK2 strengthens inflammatory responses in microglia and that inhibiting LRRK2 reduces them. Preliminary data also suggests LRRK2-driven inflammation raises the rate of nerve cell death. It's worth noting,

however, that neither these mechanisms nor their relationships with each other and Parkinson's disease have been fully confirmed.

"The beauty is that we don't necessarily need to confirm an exact mechanism to move drugs into clinical trials," says West. "One could argue that human PD is too complex to fully model in other animals. Many predict that we will not know if we understand Parkinson's disease until we get safe, potent, specific drugs into human studies and until one of them halts or reverses the disease process."

Toward a new treatment

In West's view, the perfect drug would get past the barrier that keeps toxins (and many drugs) in the bloodstream from entering the brain, and then past the proteins that pump toxins out of the brain if they slip through the first barrier. This ideal drug would have its effect and then clear out of the body in a reasonable timeframe to avoid building up in any one organ. It also would dial down the activity of LRRK2 alone, and only enough to reduce its signaling to normal.

West's presentation at the meeting described how his team's lead compound has achieved these goals in some preclinical disease models. Specifically, the team has identified potent inhibitors that affect only LRRK2 in a test involving more than 300 kinases. The researchers have increased the potency of candidate compounds that show good solubility, stability and brain penetration. Moving forward, they will re-test their best compound in the best rodent model, conduct toxicology studies, and then -- should all go well -- seek permission from the U.S. Food and Drug Administration to start a clinical trial.

While West leads the ongoing UAB effort, Robert Galemmo Jr., Ph.D., leads a group of collaborators at Birmingham's Southern Research Institute, together with Joseph Maddry, Ph.D., director of the Medicinal Chemistry Department there. Making this research possible have been UAB- and SRI-related entities like the Alabama Drug Discovery Alliance and the Center for Clinical and Translational Science, which supported West's LRRK2 work with an early pilot grant. The partnerships have allowed UAB researchers to move drugs closer to clinical trials by taking on roles once shouldered exclusively by pharmaceutical companies.

The research also has been funded by private philanthropists within the Birmingham community who are dedicated to advancing new drugs to treat PD. West is the John A. and Ruth R. Jurenko Scholar at UAB, which reflects the Jurenko family's vital support of this work.