THE UCLA CENTER FOR THE STUDY OF PARKINSON'S DISEASE AND RELATED DISORDERS

Progress *in* Parkinson's

from understanding … to curing

Spring 2015

Parkinson Awareness Month

As Parkinson's Awareness month comes to a close, patients, caregivers and researchers alike continue our efforts towards a better quality of life, more effective treatments, and an eventual cure. Over the past decade, there have been many encouraging advances in our understanding of Parkinson's disease, from identification of genetic and environmental contributing factors, to uncovering changes in brain circuitry and at the molecular level. The availability of better scientific models has allowed us to ask more in-depth questions, to study what happens in the brain before motor symptoms manifest, and throughout progression, and to more effectively test potential new treatments which target specific aspects of the disease. But perhaps one of the most important (but subtle) advances in the field is our deeper understanding of the complexities of PD. Although PD is still diagnosed based on motor symptoms, its characterization has evolved from a "motor disorder" to a dysfunction of brain circuitry that affects a number of motor and non-motor functions. This shift also opens the possibility that the best treatment approach may not be a single magic bullet that can cure every aspect of the disease, rather, targeted therapies which will address specific symptoms for each individual patient.

We know that for patients and their families, more advanced therapies cannot come fast enough, and that every day with Parkinson's is another day too long. But for researchers, every small scientific breakthrough brings us a step closer to better solutions and a brighter future for our friends in this fight.

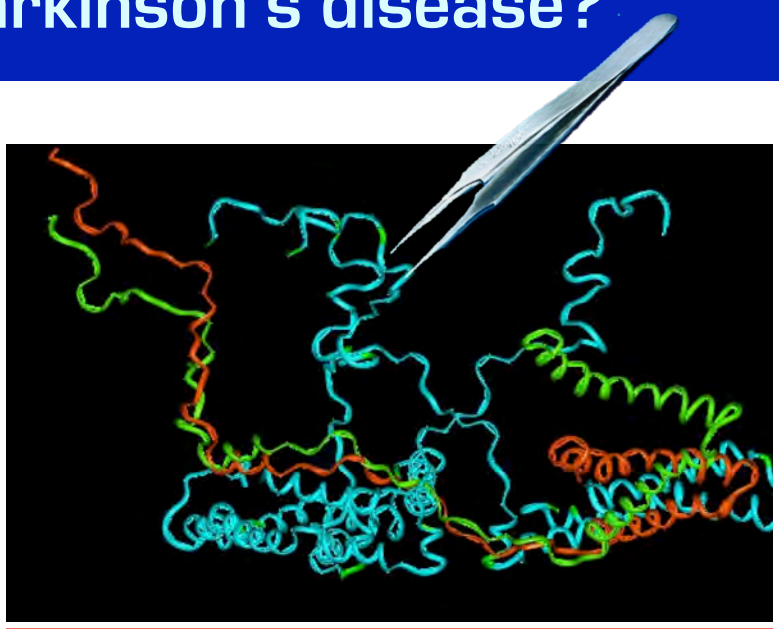
Call to Action: The California Parkinson's Registry

will gather basic information from diagnosed Parkinson's patients and enable researchers to identify the causes of the disease and its progression, and lead to PREVENTION and a CURE. The data gathered will help us understand the links between genetics, environment, and how symptoms begin and progress, saving us precious TIME and RESEARCH DOLLARS in our efforts on behalf of patients and their families.

PLEASE TAKE A MOMENT TO CONTACT THE LEGISLATURE AND VOICE YOUR SUPPORT FOR THE FUNDING OF THE REGISTRY:

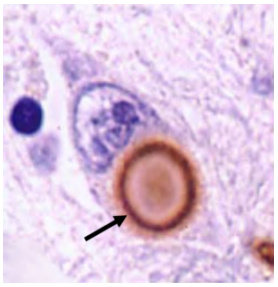
http://www.cspd.ucla.edu/california-parkinsons-registry

Could "Molecular Tweezers" open up new possibilities for the treatment of Parkinson's disease?



alpha-synuclein is normally present in healthy cells, but in the Parkinson's brain, begins to stick to each other, forming toxic clumps. Preventing these aggregates could prevent the resulting cellular dysfunction and death.

One of the distinctive hallmarks of Parkinson's disease is the presence of small "spots" inside nerve cells called Lewy Bodies, named after neurologist Friedrich Heinrich Lewy who discovered them in 1912. It took scientists 85 years to determine that the main component of Lewy bodies is a protein called alpha-synuclein – a relatively small protein; whose exact function is still not very well understood. What we do know is that in Parkinson's disease, alpha-synuclein molecules "stick" together to form Lewy bodies. (It is important to note that a similar process of protein clumping occurs in diseases such as Alzheimer's and Huntington's, and therefore seems to be relevant to many disorders.) This process likely begins many years before the onset of symptoms, with alpha-synuclein molecules progressively accumulating and sticking together until the final aggregates associated with disease pathology are formed within cells. If the clumping of alpha-synuclein into Lewy bodies is what causes the disease, then blocking the clumping process may be the key to therapy for Parkinson's – one that will not only treat the symptoms, but also the cause of the disease and its progression. This is exactly the strategy that Dr Gal Bitan, Associate Professor of neurology at the David Geffen School of Medicine at UCLA has developed in his search for a potential drug.



We asked Dr Bitan to explain how he developed this approach:

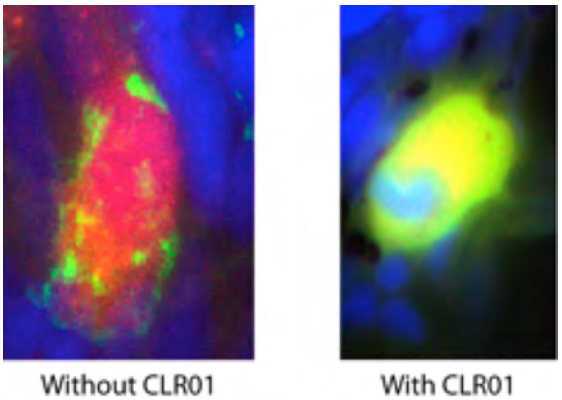
Over the last two decades of research, multiple lines of evidence have emerged that support the idea that alpha-synuclein clumping can cause Parkinson's. For example, we know from genetic studies that mutations in the alpha-synuclein gene cause familial Parkinson's. Even without a mutation, just an increase in the amount of this protein due to abnormal duplication or triplication of the alpha-synuclein gene causes familial Parkinson's. In addition, many experiments have shown that alpha-synuclein on its own is not toxic to nerve cells, but when its molecules aggregate together, the clumps become toxic. Interestingly, increasing evidence indicates that the final clumps, those that are found in Lewy bodies and contain thousands of molecules or even more, probably are not what causes Parkinson's disease. Rather, the most toxic structures to the cells are probably the small, elusive aggregates called "oligomers" that contain only a few molecules. We now believe it is actually the oligomers that shut down nerve cells, including those that produce dopamine, and eventually kill them.

"If that is true," Dr. Bitan hypothesizes, "a successful strategy should be changed from trying to prevent formation of the final clumps in the Lewy bodies, to preventing formation of the *oligomers*. Or simply put, the strategy should be defined as anything that blocks the toxicity of alpha-synuclein."

So how do you go about finding the right compounds to prevent these oligomers from forming?

We used a systematic approach – we looked at the structure of these proteins and how they interact with each other and other proteins in the cell, and based on that, analyzed different compounds based on their potential to interact with alpha-synuclein. We discovered compounds called "molecular tweezers," which were prepared by our collaborators, Drs. Thomas Schrader and Frank-Gerrit Klärner, at the University of Duisburg-Essen in Germany, that seemed to have the necessary properties. Once we tested these compounds, we confirmed that they could block the formation of toxic alpha-synuclein clumps. It was even more intriguing to see that these molecular tweezers have the same effect on other proteins that cause related diseases, such as Alzheimer's, Huntington's, ALS (Lou Gehrig's disease) and other diseases. How could one single compound work on different diseases?

This is because the molecular tweezers block not a particular protein, but the process of formation of the toxic clumps, which is common to all of these diseases. They do that by preventing the molecular interaction that lead to formation of the toxic oligomers, taking advantage of the fact that the oligomers are very unstable molecules. Unlike normal proteins that have a stable structure held by strong forces, optimized through millions of years of evolution, oligomers are held together by weak forces that can easily be broken. This means that using the molecular tweezers should not interfere with normal protein function, and therefore, not expected to have side effects.



Neurons with accumulated alpha-synuclein (left panel) are cleared of the aggregation with CLR01

We understand that you have developed a lead molecule called CLR01. Could this molecule work on preventing alpha-synuclein aggregation?

First, we tested CLR01 against alpha-synuclein in the test tube and then in cell culture. The next step was to put this molecule to more sophisticated tests, in collaboration with several research groups at UCLA, including Dr. Jeff Bronstein and Dr. Marie-Françoise Chesselet, and with chemists and physicists including Dr. Joe Loo at UCLA and Dr. Lisa Lapidus at Michigan State University.

Simple test-tube experiments showed that CLR01, not only stopped the formation of alpha-synuclein clumps, but also dissociated pre-existing clumps. Next, we tested whether CLR01 could prevent the toxicity of alpha-synuclein oligomers in cell culture experiments and found that indeed the compound was effective as a toxicity inhibitor.

In collaboration with Dr. Bronstein, we then examined the effect of CLR01 in a zebrafish embryo model that expresses the human form of alpha-synuclein. CLR01 prevented formation of toxic oligomers and clumps, allowed the fish, which otherwise would suffer deformation, to develop normally, and extended their lives significantly. Importantly, there were no observable side effects to the treatment.

These promising results allowed us to look at the effects of CLR01 from a different angle. One of Dr. Bronstein's main interests is the effect of pesticides as risk factors for developing Parkinson's. He has examined many pesticides used by farmers and household plant growers and found that most of them increased the risk for Parkinson's. Among these pesticides, ziram is one causing a higher risk of developing Parkinson's. But why ziram is toxic and confers a higher risk for Parkinson's is not known. Could it be because it induces alpha-synuclein to form toxic oligomers and clumps? If so, CLR01 could prevent the toxicity of ziram and protect against the increased risk of Parkinson's. Using a zebrafish embryo again, this is exactly what was found. CLR01 prevented the toxicity of ziram because it did not allow the zebrafish synuclein (which is an analog of the human alpha-synuclein) to form toxic oligomers and clumps.

In a parallel set of experiments, Dr. Chesselet examined the effect of CLR01 in a mouse model that has the human form of alpha-synuclein in its brain. As a result, the mice show motor deficits already at 2-3 months of age and later develop a loss of dopamine. The mice were given CLR01 by a special injection device that maintains a constant slow release of the compound into the blood stream or directly into the brain. The treatment lasted for a month and the mice receiving the compound performed significantly better than those receiving placebo in tests of motor deficits. Again, the mice showed no side effects. In fact, when we give normal mice high doses of the CLR01 (much higher than the therapeutic doses used with the alpha-synuclein mice), there are no adverse effects which gives our compound a high safety window and makes it a candidate for further testing and eventually clinical trials.

Dr Bitan's team is currently working to raise the funds needed to perform the tests required by the FDA before clinical trials can begin.

For status updates or to support Dr Bitan's work, please visit:

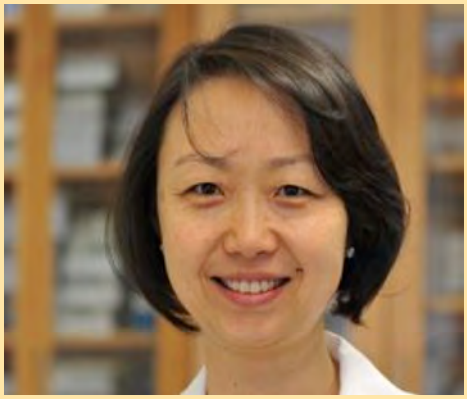
www.btdd.org

Dr. Gal Bitan, Associate Professor of Neurology at the David Geffen School of Medicine, has been focused on how to stop this toxic accumulation of toxic proteins such as alpha-synuclein as a way of treating and even preventing Parkinson's disease. Even more significant, is that this therapy could also be applied to other diseases which have a protein aggregation problem. Dr. Bitan's research is supported in part by The UCLA Jim Easton Consortium for Alzheimer's Drug Discovery and Biomarker Development, RJG Foundation, Cure Alzheimer's Fund, Team Parkinson/Parkinson Alliance, Judith & Jean Pape Adams Charitable Foundation, RGK Foundation, Michael J. Fox Foundation, and the CurePSP Foundation.

New Gene Discovery Could Provide Important Clues for Future Therapies:

UCLA scientists identify novel gene involved in Parkinson's disease

Over the past 15 years, scientists have found that about 10% of Parkinson's disease cases are due to heritable mutations in single genes.



Ming Guo, MD, PhD, is a practicing neurologist, Professor of Neurology & Pharmacology, and among many other distinctions, Chairs the Board of Scientific Counselor at the National Institute of Neurological Disorders and Stroke (NIH/NINDS). She also serves on the Scientific Program committee at the American Neurological Association, the Society of Neuroscience, on the editorial board for Aging Cell and PLoS ONE, and is a member of the Scientific Advisory Board of the Giannini Medical Foundation.

By studying the function of these PD genes in health and disease, researchers have gained invaluable insight about the underlying pathology and progression in Parkinson's. One such pivotal study, published in the journal Nature in 2006 by Dr. Ming Guo, UCLA professor of neurology and pharmacology, and a practicing Neurologist, showed that PINK1 and parkin, two genes causing young-onset PD, work together to maintain the integrity of mitochondria – the energy factories of cells. One of two groups worldwide to first report this discovery, Guo has continued to study mitochondrial function and their role in PD pathogenesis. "The key roles of the PINK1/Parkin pathway on mitochondrial integrity and quality control has great impact not only on the PD research field, but also has been shown as crucially important for aging and other aging-related diseases such as Alzheimer's disease, heart diseases, diabetes and cancer."

In her latest groundbreaking five year study, published in the open-access journal eLife in June, Guo and her team found that a new gene, MUL1 (also known as MULAN or MAPL), plays an important role in mediating the pathology of PINK1/parkin. Using the powerful genetics of fruitfly (*Drosophila)* and mouse models of PD, Guo and her team showed that increasing the levels of MUL1 prevents mitochondrial damage, while removing MUL1 actually made the illness worse, with corresponding increase in mitochondrial and tissue damage.

As Dr. Guo's team aims to understand more about PD pathogenesis and developing new treatments, patients with early-onset PD or those with suspected familial /inherited Parkinson's are particularly welcome to contact her for further genetic evaluations and studies (mingfly@ucla.edu)

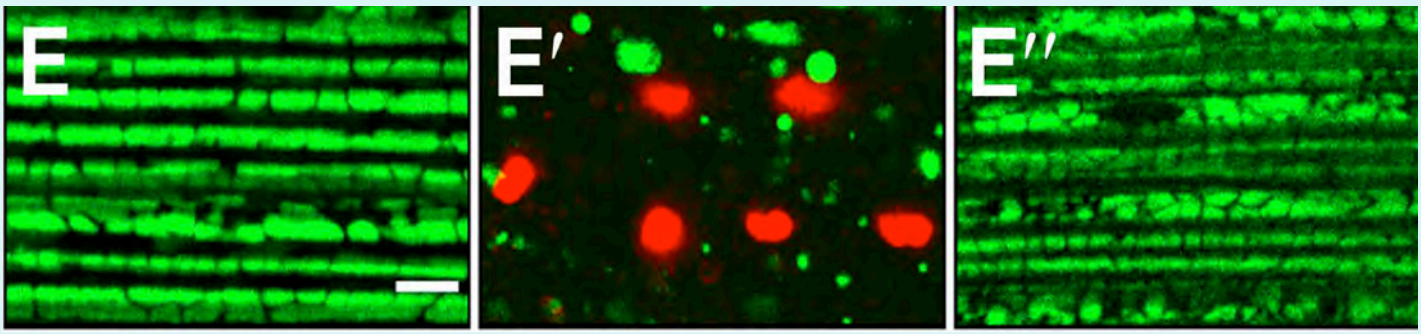


Figure E shows the normally structured mitochondria (labeled with green) along muscle fibers in a wildtype fly. In the parkin mutant (E'), mitochondria (green) lose their shape and structure, and degenerate. In addition, cells die as indicated by the red label. However, overexpressing MUL1 in the parkin mutant rescues the mitochondria almost back to normal and prevents cell death and degeneration (E").

"These studies suggest that optimizing the levels of MUL1 could certainly be a new therapeutic target. We can develop drugs that increase the levels of MUL1 to help keep mitochondrial integrity, or avoid anything that causes a decrease in its levels," says Guo.

The powerhouses of the cell, mitochondria are small, dynamic organelles with their own genetic materials, responsible for providing the cell with abundant energy by breaking down sugar (a process known as cellular respiration). Depending on its metabolic requirements, each cell can have anywhere from a few to thousands of mitochondria. Healthy mitochondria not only supply the high cellular energy demands, but are also involved in many other key processes including cell death, synthesis of lipids, to maintain health of tissues including brain, heart and muscles. In fact, mitochondrial health plays a significant role in the aging process, so perhaps it is no coincidence that age is the biggest risk factor for developing PD. PINK1 and Parkin were previously shown by Guo to play central roles in maintaining mitochondrial health: they help maintain the regular shape of mitochondria and promote elimination of damaged mitochondria. The discovery of MUL1 has significantly advanced our understanding of this pathogenesis process and is a very promising therapeutic target.

How do PINK1/Parkin and MUL1 work together to keep the mitochondria healthy? The normal shape of mitochondria is precisely maintained by a dynamic balance between mitochondrial fission (where a larger mitochondrion divides into two smaller ones) and fusion (two small mitochondria join and fuse into a larger one). The gene mediating mitochondrial fusion is called Mitofusin. PINK1 and Parkin control the intracellular levels of Mitofusin, and can promote the degradation of Mitofusin when necessary, since too much mitochondrial fusion usually results in mitochondrial abnormalities and compromised quality. The Guo lab has found that MUL1 encodes a protein that also promotes degradation of Mitofusin. In addition, when PINK1, Parkin, or MUL1 are each individually mutated, there is an increase in the levels of Mitofusin, unhealthy mitochondria, and increased symptoms of PD in PINK1/parkin mutations.

"Our approach of treating the underlying cause of degeneration, if successful, will focus on maintaining the overall health of these neurons and preventing their loss in the first place, stopping the progression of PD at a much earlier, pre-symptomatic stage. I believe that this makes MUL1 a very promising drug target to prevent and even cure PD."

CSPD *in the* NEWS

Re-Thinking the Association between Smoking and Parkinson's Disease

For the past several years, the subject of smoking has been a great topic of interest in Parkinson's research. After all, several studies have shown a surprising but undeniable trend: There seem to be fewer smokers among Parkinson's patients, and by the same token, a greater number of non-smokers had Parkinson's. According to one study, smokers were 44 percent less likely to develop Parkinson's disease than people who had never smoked. Interestingly, people who had smoked in the past and subsequently quit, were 22 percent less likely to develop Parkinson's than people who had never smoked. These intriguing findings seemed to suggest that smoking may play a protective role in Parkinson's, and prompted a flurry of research into the possible role of nicotine as a therapeutic measure.

However, Dr Beate Ritz, Professor of Epidemiology and Neurology at UCLA, wondered whether there was an alternative, not so obvious, explanation for the observed correlation. After all, the myriad of previous research on smoking and nicotine had never before suggested any beneficial mechanisms or neuronal pathways consistent with these observations. Instead, Dr Ritz decided to delve deeper into subjects' smoking habits – whether they had ever smoked and how easy it was for them to quit smoking. The results were illuminating: the observation that there were fewer smokers among the PD patients correlated directly with the fact that *it was easier for PD patients to quit smoking*. In other words, the higher number of smokers among the non-PD population was because they had a much harder time quitting smoking when they had attempted to do so.

"These observations suggest that a mechanism associated with Parkinson's disease risk may influence smoking behavior or that less reward from nicotinic stimulation might be an event prodromal to Parkinson's disease," Dr Ritz hypothesized. In other words, early changes in the brain of Parkinson's patients make them less likely to find nicotine as rewarding, and could be another aspect of premanifest Parkinson's, such as REM disorder, olfactory dysfunction or constipation.

Parkinson disease and smoking revisited: ease of quitting is an early sign of the disease. Ritz B, Lee PD, Lassen CF, Arah OA. Neurology. 2014 Oct 14;83(16):1396-402.

CSPD *in the* NEWS

Drug developed for Gaucher Disease shows promise in slowing down PD in pre-clinical studies

In a recent UCLA CSPD study, a drug developed for Gaucher's disease was shown to slow down symptoms of Parkinson's progression in a mouse model, improving motor function, stopping inflammation of the brain, and reducing the levels of the toxic form of alpha-synuclein, which has a critical role in Parkinson's disease. Perhaps more importantly, it targets the underlying cellular defects, rather than the symptoms.

The drug, AT2101, was originally created by Amicus Therapeutics to treat Gaucher, a rare genetic disease caused by a deficit in the production of the enzyme beta-glucocerbrosidase, or GCase. Interestingly, mutations the in GCase gene are one of the most common risk factors for PD, and lead to the accumulation of alpha-synuclein in the brain. The mice used in the study, like most PD patients, do not have the GCase mutation, but overexpress alpha-synuclein and develop deficits similar to PD patients, which means that it could be beneficial regardless of whether there is a GCase mutation or not.

Dr Marie-Francoise Chesselet, Charles H. Markham Professor and Interim Chair of Neurology, Director of CSPD, and senior author of the study, noted that this was the first time a compound targeting Gaucher has been tested in a mouse model of PD and shown to be effective. "The promising findings in this study suggest that further investigation of this compound in Parkinson's is warranted."

The study confirms the idea that GCase activity has something to do with Parkinson's disease, and that increasing its stability and activity by using a pharmaceutical "chaperone" - a drug that binds misfolded proteins and escorts them to the correct cellular location for processing - is beneficial in reducing a number of the progressive and behavioral deficits and pathology observed in the mouse model. Further studies are needed to evaluate its therapeutic potential in humans.

A GCase Chaperone Improves Motor Function in a Mouse Model of Synucleinopathy. Richter F, Fleming SM, Watson M, Lemesre V, Pellegrino L, Ranes B, Zhu C, Mortazavi F, Mulligan CK, Sioshansi PC, Hean S, De La Rosa K, Khanna R,Flanagan J, Lockhart DJ, Wustman BA, Clark SW, Chesselet MF. Neurotherapeutics. 2014 Jul 20.

Walking the walk

UCLA Researchers joined the Parkinson's Association Walk in Los Angeles, "Fighting Parkinson's Step by Step" in September. Above: Dr Michele Basso, undergraduate researchers Tatiana Nemanim, Stephanie Melchor, at the halfway mark. The UCLA team also participated in the "research tent" to answer questions. Pictured below from Left: Dr Gal Bitan, Dr Marie-Francoise Chesselet, Tatiana Nemanim, Stephanie Melchor, Dr Jeff Bronstein, Dr Kathy Shenassa.

CSPD *and the* COMMUNITY

In 2014, representative from the Parkinson's Disease Foundation (PDF), Parkinson's Action Network (PAN), Parkinson's Association, and the American Parkinson's Disease Association (APDA) attended a research roundtable at UCLA to discuss current research projects, and how to help scientists achieve their goals. The CALIFORNIA PARKINSON'S REGISTRY was identified as a priority project, which due to collaborative efforts of scientists and advocates, is currently under funding review by the CA Legislature.

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