With the inaugural edition of the “Progress in Parkinson’s” newsletter, we are excited to share some of our recent advances in the fight against Parkinson’s disease here at the UCLA Center for the Study of Parkinson’s Disease (CSPD). The overarching mission of our research has always been to drive the development of the next generation of therapies. Over a decade of collaborative efforts among epidemiologists, clinicians and basic scientists from multiple and diverse disciplines has allowed us to focus on the root causes of the dysfunction that leads to Parkinson’s disease, rather than the symptoms. Wondering what causes Parkinson’s, we are examining the complex interactions of genetic variation and environmental factors that increase the risk of developing the disease and tracking the specific molecules and pathways involved. Better modeling allows us to find the smallest cellular and subcellular changes long before the loss of nerve cells that cause the motor symptoms in patients. The synergy among our team members means that observations in PD patients are rapidly analyzed in our scientific models, while the relevance of data obtained in laboratory experiments can be validated in patients. We hope that the newsletter will keep you informed about the progress we make towards finding treatments to transform the lives of Parkinson’s patients and their caregivers.

~Marie-Francoise

Marie-Francoise Chesselet, MD, PhD is the Director of the Center for the Study of Parkinson’s Disease at UCLA. She is the Charles E. Markham Chair and Professor in Neurology and Chair of the Department of Neurobiology.

“We continue to close in on the specific genetic and environmental risk factors for PD.”

Progress in Parkinson’s
from understanding ... to curing

Spring 2013
A key to developing targeted and effective treatments for a complex disorder such as Parkinson’s disease is understanding the causes. As with any complex human disease, the causes of Parkinson’s have been difficult to resolve/determine. With the exception of the rare inherited cases where a number of specific genes are clearly implicated, about 90% of cases are likely caused by a combination of individual genetic susceptibility (or resilience) and environmental influences ranging from toxins to nutrition and stress levels. The task of identifying how and to what extent these factors contribute to the risk of developing Parkinson’s seemed a daunting task. Relying on patient recall of a myriad of potential culprits (which could had occurred up to 30 years prior to diagnosis) would surely not yield accurate information. Furthermore, narrowing down potential risk factors from human studies would be of limited value without the ability to study the underlying cellular and molecular mechanisms by which they exert their effects. But a certain team of UCLA experts were in a unique position to take on the challenge – not only did epidemiologist Beate Ritz, MD, PhD, neurologist Jeff Bronstein, MD, PhD and research professor, Marie-Francoise Chesselet, MD, PhD, each specialize in Parkinson’s disease, they happened to live within a few hours’ drive from the California Central Valley, a 400 mile long stretch of the most fertile and productive agricultural land in the nation and probably the world. And it so happens that California, unique in so many
respects, is the only state in the nation to have been mandated by law to keep records of all pesticides applied for the past 35 years. In the largest study of its kind, these records were used in conjunction with satellite maps of the area to pinpoint every residence with respect to the radius of pesticide application, creating a detailed and accurate map of exposure for residents and workers throughout the area. With painstaking accuracy, utilizing every resource from computer modeling to door-to-door address verification, over 300 patients and 400 normal controls were enrolled into the study, and have been followed up for a period of over 10 years. Given the large number of pesticides, herbicides, fungicides, and insecticides used in combination and over long periods of time, they focused on those known from animal studies to be linked to Parkinson’s, such as benomyl, paraquat, manebe and rotenone. More significantly, this unique study had the potential to evaluate, for the first time, how certain individual genetic variations may combine with other genetic and environmental factors to increase or decrease Parkinson’s risk. The significance of the study was acknowledged by the National Institutes of Environmental Health Sciences as one of only three NIEHS funded Centers in Neurodegeneration Science in the nation, leading to more detailed analysis of the wealth of information.

With the completion of each phase of data analysis, evidence began to mount implicating exposure to certain pesticides as a serious risk factor for developing Parkinson’s, and more interestingly, the multiplied risk for certain pesticide combinations. Because of the collaboration and synergy among the group of UCLA scientists, specific parameters from the epidemiological studies were simultaneously being examined in the laboratory on cellular and animal models, pointing to specific neuronal pathways and molecules involved in disease etiology and progression. Conversely, data obtained in the lab inform and shape the direction of investigation in human patients. These studies continue to provide valuable information about how Parkinson’s may begin and how it progresses in light of various genetic and environmental influences, and clues to prevent, slow down, and cure.
Q: Your work has primarily focused on two specific genes, pink1 and parkin, has had a major impact on our understanding of Parkinson’s disease. Can you explain the significance of these genes, especially since most PD cases are not inherited?

A: For decades, Parkinson’s disease was defined as a problem of dopamine depletion, and the approach was: Dopamine is missing, so let’s replace it. Unfortunately, this strategy is very limited, because it doesn’t get to the root causes of the disease, and as far as treatment, only addresses symptoms partially. Since the mechanisms of disease are the same for whether PD is inherited or not, we can look at the underlying molecular pathways that are in common across the board. Two of the mutations found in familial PD are in the pink-1 and parkin genes. We were able to show that in the fruitfly model, the loss of PINK1 led to defects in mitochondria of several tissues, including dopamine neurons and muscles. Interestingly, parkin mutants also had defects similar to pink-1 mutants, suggesting that both molecules are involved in the same cellular pathway. More specifically, we were able to show that there is a problem in the way mitochondria renew themselves, a process known as fission and fusion. Our theory is that because of this defect, the mitochondria accumulate a lot of damage, eventually leading to the dysfunction and death of the dopaminergic neurons. This is very important, because it allows us to look for drugs.
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that target the mitochondria specifically, so we are addressing the root cause of the disease, not the result (symptoms), and that’s a huge step in the right direction.

Q: Your lab uses mainly drosophila (fruitfly) and cellular models. Can you explain how you can study a complex human disease like Parkinson’s in such simple models?

A: People may be surprised to hear that about 75% of our genes are also found in the fly, and more importantly, that the pathways and processes that these genes control are comparable. For example, when we replaced the defective pink1 and parkin genes in the drosophila with the human wildtype (normal) genes, we were able to rescue the defects in flies, both at the cellular level and behaviorally. And we can see mitochondrial defects in patients similar to those in our models. So these models give us a way to examine in detail the specific pathways and cellular events that are involved in the disease process. These simple models have allowed us to pinpoint the defect in the mitochondria, and now we are studying exactly how this happens, which should provide us with much more advanced ways of treating the disease at its core.

Q: What do you think are today’s challenges and promises facing the field today?

A: One great challenge which patients face is the different non-motor symptoms, and the progressive nature of the disease, neither of which is addressed with current regiments. This means the challenge for us, the scientists and physicians, is to be able to diagnose the disease at the earliest possible signs, before any serious symptoms are evident, and to stop the progression, and hopefully even reverse it. We have come a long way just in the last decade shifting our focus to the cause rather than the symptoms. And as we begin to understand the exact mechanisms of the disease, and find possible therapeutic targets, the challenge will be to translate what we learn in the lab into viable treatments for patients. I think it’s a very promising time to be involved in Parkinson’s research.

Ming Guo, MD, PhD, is Associate Professor of Neurology and Molecular & Medical Pharmacology/Department of Neurology at the David Geffen School of Medicine at UCLA. She is widely recognized for her groundbreaking work on the role of mitochondria in aging and neurodegenerative diseases such as Parkinson’s and Alzheimer’s. In addition to a number of active NIH grants, Dr Guo has received several private foundation awards, including the Alfred P. Sloan Foundation Award, the McKnight Foundation Brain Disease Award and the Klingenstein Fellowship. She was selected among the 10 fellows as the 12th Robert H. Ebert Clinical Scholar, outstanding physician- scientist of the year. A Board-Certified Neurologist, she serves as a National Neurology Clinical Board Examiner for the American Board of Psychiatry and Neurology, and an NIH Study Section Regular Member.
On February 25-27, Post Doctoral scholars Shilpa Narayan (laboratory of Beate Ritz, MD, PhD), Arthur Fitzmaurice (laboratory of Jeff Bronstein, MD, PhD, and Hakeem Lawal (laboratory of David Krantz, MD, PhD) from the UCLA Center for the Study of Parkinson’s participated in the 2013 PAN (Parkinson’s Action Network) conference in Washington, DC. Dr Narayan presented her work on the use of household organo-phosphorus pesticides and Parkinson’s risk; Dr Lawal discussed results of drug screenings which have yielded potential neuroprotective mechanisms, and Dr Fitzmaurice focused on the specific cellular mechanisms in response to the interaction between genes and pesticides. The meeting was attended by patients, advocates, scientists and members of NIH, including Dr Story Landis, Director of the National Institutes of Neurological Disorders and Disease, (NINDS). The young scholars also had an opportunity to join the California delegates and meet with legislative representatives to Senators Boxer and Feinstein to discuss the crucial need for continued PD research funding.

Drs Narayan, Fitzmaurice, and Lawal join members of the California delegation of PAN to meet with Senator Barbara Boxer (far right, standing) on Capitol Hill. Photo courtesy of Robin Katsaros

Congratulations....

...to Dr Kimberly McDowell and Dr Amandeep Mann, both post-doctoral scholars from the laboratory of Dr Chesselet, for their award-winning poster presentations at the annual UCLA Neurology Science Day competition. Their studies test novel treatments for Parkinson’s disease in a mouse model that expresses excess alpha-synuclein, a protein linked to both familial and non-familial forms of Parkinson’s disease. Dr McDowell received first prize for her work on the use of a pharmaceutical chaperone for glucocerebrocidase, the gene involved in Gaucher disease and a risk factor for Parkinson’s disease, while Dr Mann captured third prize for her research on the inhibition of kynurenine 3-monoxygenase, an enzyme that increases the formation of toxic molecules in brain. These compounds are among seven promising new therapeutics for PD, in pre-clinical testing in the Chesselet laboratory.