A note from the editor

Collaboration. It is the cornerstone of our research here at the CSPD. From cells to circuits to patients, each member of our research community contributes a unique expertise and perspective, and sheds light on a different aspect of this complex puzzle. But our collaborations don’t stop at the borders of UCLA, as evidenced in the many partnerships with other universities, biotech and pharmaceutical companies, and foundations. It is in the same spirit of collaboration that the UCLA CSPD hosted the first ever West Coast Symposium on Parkinson’s Disease. Born from collaboration with, and support of, the Parkinson’s Disease Foundation (PDF), the one and a half day meeting showcased the depth and breadth of ongoing PD research at UCLA and other institutions along the West Coast, from the University of British Columbia to UC San Diego and points in between. For some, it was their first chance to participate at a meeting dedicated entirely to Parkinson’s disease (since major PD conferences are routinely held on the East Coast), allowing them to share their work, discuss research priorities and find collaboration opportunities with colleagues in the field. The overarching focus of the meeting was on one of the biggest challenges facing patients and researchers alike – the question of predicting the rate of progression in PD.

But perhaps the highlight of the meeting was the enthusiastic participation of Parkinson’s patients and advocates in our scientific discussions, marking the beginning of a new collaborative chapter for the CSPD – one that involves patients, advocates, and researchers sharing and learning from each other. The spirit and determination of the participating patients were truly an inspiration to all of us, and visibly energized the research community. It was a powerful reminder that we are all working towards the same goal, to find better therapies and ultimately a cure. And it is a goal worth achieving - Together.

Kathy Shenassa, PhD
Scientific Programs Coordinator
When Kim McDowell moved to UCLA from the University of Maryland where she received her PhD, she brought with her extensive experience in recording and analyzing sleep patterns in laboratory animals. “Kim’s skills with studying sleep was a determining factor in my decision to offer her a post-doctoral position in my laboratory”, says Marie-Francoise Chesselet, Charles H. Markham Professor of Neurology and Director of the UCLA Center for the Study of Parkinson’s Disease (CSPD). Indeed, sleep disorders are present in a majority of PD patients, can start many years before the motor symptoms, are often not well treated with available “sleeping pills”, and have a major impact on the patient quality of life. The Chesselet laboratory had shown that their mouse model of PD, mice that produce an excess of alpha synuclein (the major component of Lewy bodies), showed many of the non-motor symptoms also present in patients. Unfortunately, they had never had the opportunity to study sleep in this model. With Dr. McDowell, they now had the expertise to do so but two major obstacles remained. First, the laboratory did not have the necessary equipment to record sleep in mice and second, they had no funding for the experiments. The first problem was resolved with the help of Dr Ken Roos, Director of the Physiology Core in the David Geffen School of Medicine at UCLA. Dr Roos made the specialized facilities and equipment available to Kim, but she still needed funds to purchase transducers and software, pay users fees, and other related experimental costs. Enter Dana and Richard Pachulski, long time and passionate supporters of UCLA. Thanks to Dr. Kathy Shenassa, Scientific Programs Coordinator for the CSPD, Dana and Richard had heard about the work in the Chesselet lab. “We were intrigued by the implications of this research, and we wanted to help,” noted Dana Pachulski, after a visit to the Chesslet lab. “We have one of the top research programs right in our back yard, and it makes sense to support the scientists directly, where it will have the greatest impact.” Their generous gift to the lab enabled Kim to show that these mice indeed show profound anomalies in their sleep patterns, with a decrease in “REM sleep”, the dream-phase of sleep. The immediate result? Tsumura pharmaceuticals (Japan), aware that this was the first and only model of PD-related sleep disorders, has awarded a major grant to support the testing of a natural compound, already used in Japan but not available in the US, by the Chesselet lab. If successful, the study will provide critical information to pave the way to effectively treat sleep disorders in PD patients.

Gift from Dana and Richard Pachulski leads to novel model to assess treatments for sleep disorders in PD

Dr McDowell received the Brain Research Institute’s Travel Award to present her findings at the annual Society for Neuroscience meeting in San Diego.
It is called paradoxical movement in Parkinson’s disease. Memorably portrayed in the movie “Awakenings”, starring Robin Williams and Robert De Niro, patients who have difficulty reaching or grabbing an object, can catch a ball thrown at them or quickly react to grasp a falling pair of glasses. The short, shuffling walk characteristic of Parkinson’s disease, can suddenly be transformed when the patient encounters a high contrast series of lines on the floor spaced as one’s normal steps would be.

Cognitive Neuroscientist, Michele A. Basso, Ph.D., has always been interested in the relationship between vision and action. “The main focus of my research is to understand how the brain translates sensory information into an action. We are particularly interested in the neuronal events that occur between visual perception and resulting actions such as learning, memory and decision-making. Understanding the neuronal circuits that underlie these mental processes and how they go awry, will teach us a lot about diseases such as Parkinson’s disease, HD and dystonia.”

How does perception and decision-making relate to Parkinson’s disease?

Although Parkinson’s disease is considered a movement disorder, Basso believes many of the manifest motor symptoms can be explained by malfunctions in circuits that underlie cognitive processes. Motor symptoms are caused by the loss of dopamine, the main neurotransmitter of the substantia nigra, part of a midbrain region known as the Basal Ganglia. Studies have shown that this area of the brain, together with the superior colliculus, is involved in the execution of voluntary movements, through a complex “loop” of excitatory and inhibitory impulses that project to, and away from, the cerebral cortex. The Superior Colliculus is a structure deep in the midbrain that serves as a convergence point for inputs from visual fields,
The direction of eye movements as subjects scan the visual stimulus is recorded. In the top panel, the small dots on the screen clearly point to the right, and the subject looks at the circle to the right. However, as the orientation of the dots becomes more ambiguous (they don’t seem to point in any particular direction), subjects will have to “guess”. To reveal underlying differences in circuitry, the visual stimulus is manipulated so that the dots point to the left 80% of the time, and to the right 20% of the time. As subjects learn this bias, they choose to look to the left circle more frequently. Since this task relies on remembering information learned from experience, those with impairment to this circuit (such as PD patients) will not be able to adapt their responses.

as well as other sensory and motor fields, and plays an important role in the control of eye movements. The superior colliculus also receives information from the basal ganglia, making the basal ganglia - superior colliculus circuit is the hot-spot for eye movement based decision-making. Rapid movement of the eyes, called saccades, are used by Basso and her colleagues as a way to learn about the circuitry linking visual input to decisions. Tracking saccades as a subject scans a picture or shifts their gaze towards a target, sheds light onto the complex cognitive processes governing decision-making. The complex pathway connecting the cerebral cortex, superior colliculus (visual), substantia nigra (motor) and corresponding cortical projections, has been implicated in a number of disorders, such as ADHD, addiction, obsessive- compulsive disorder, schizophrenia, and of course, Parkinson’s disease. “So it would make sense that this region of the brain (cortico-nigro-collicular pathway) plays a key role in either storing or retrieving relevant information about past experiences, which the brain draws upon when considering a course of action”. In other words, the ability to move is not impaired, rather, information needed to execute movements is not accessible.

In order to tease out how the basal ganglia contribute to decision-making, Basso and her team study how both human and non-human primates make decisions in the presence of sensory (visual) uncertainty, either with or without the availability of memory information to direct the decisions. For example, the subject is presented with a screen projection of “snow”, (the static noise seen on analog televisions in the absence of a signal). Specific visual stimuli, such as a series of bars on the left or the right hands side, are embedded in the noise. The visibility of the visual stimuli can be manipulated so that they can go from being very clear to being extremely difficult to detect. As you would expect, accuracy of the responses follow a simple relationship: when the signals are clearly visible, subjects can accurately predict the direction of the display. However, as the signal gets more and more difficult to detect, the rate of accuracy decreases until it is about 50%, or equivalent to random guesses. Now, the researcher can introduce a bias in the rate of appearance of a signal, for example, the signal to the left will appear 80% of the time. Subjects learn to adapt to this bias, so that when the bars are not clearly visible, they will favor “left” over “right” because they have learned from their experience. Interestingly, Parkinson’s patients are not able to adapt their response, suggesting that the part of their brain circuitry which controls decision-making based on memory, is impaired. This simple concept has many implications for how we try to improve the
The Superior Colliculus and Basal Ganglia communicate with each other and the cerebral cortex via complex inhibitory and excitatory circuits, (left). Using in vitro modeling and a variety of patch clamp and imaging techniques, these circuits are studied at the level of single neurons (middle) and neuronal networks (right).

quality of life for Parkinson’s patients. For example, “recording from the monkey brain during this type of task is revealing the circuitry behind action memories, which will open up new drug targets, improvements to DBS, and even as a biomarker or predictive tool,” says Dr Basso.

The cognitive studies are further complemented by Basso’s in vitro work on the Basal Ganglia-Superior Colliculus circuit in the rodent. “This allows us to look at cellular neurophysiology, molecular mechanisms, and pharmacology of the area we are studying in patients and non-human primates, so we have a complete understanding of the role of this circuit in health and disease. It will have implications for many disorders that affect decision-making.”

The future is filled with possibilities. In collaboration with Dr Nader Pouratian, Assistant Professor of Neurosurgery and Director of the Neurosurgical Movement Disorders Program (an expert on Deep Brain Stimulation), she will be studying patients who undergo DBS surgery, and evaluate if and how the stimulation interacts with this circuit. Here again, measuring saccades can provide critical information for evaluating the effects of DBS on the general circuitry. Ultimately, the goal is to use this technology to develop smarter stimulators, which not only send signals, but can also read incoming signals and regulate their on/off cycles to enhance the functionality of the existing neurons within the circuit. Other collaborators include Dr Allan Wu, Director of the UCLA laboratory for Motor Behavior and Neurorehabilitation, and Dr Carlos Portera-Cailliau, Associate Professor in Neurology, on developing more sensitive psychometric and imaging tests that could be used as a way of early diagnosis, predicting disease onset before other motor symptoms are apparent, or to identify subsets of patients who exhibit different levels or rates of cognitive decline.

The road to discovery seems challenging, but Basso is excited by the possibilities. “Every small result brings us a little closer to understanding how the brain works in health and disease. And this will help us develop better solutions to neurological disorders.”

PD patient:

PD patient with Deep Brain Stimulation:

Measuring the stability of saccadic eye movements can be an informative tool in understanding the circuitry of movement impairment in PD. In this example, unstable eye fixations (top) are stabilized with DBS (bottom).

For information on participating in similar research studies, click HERE.
One of the critical issues facing Parkinson’s researchers and patients alike is the unpredictable rate of disease progression. Last October, the UCLA CSPD hosted the first ever West Coast symposium, sponsored by the Parkinson’s Disease Foundation (PDF) to explore topics relevant to the question of progression. Co-chaired by Dr Marie-Francoise Chesselet, Charles Markham Chair of Neurology and Director of the UCLA CSPD, and Dr Steve Finkbeiner, Professor of Neurology at UCSF and Associate Director of Gladstone Institute of Neurological Disease, the symposium began on the afternoon of October 7 with a poster session featuring 24 presentations from a number of west coast based institutions, representing a wide range of backgrounds and expertise. Presenters reported their ongoing progress in a number of “hot topics”, from the role of mitochondria, to environmental toxins and preliminary testing of potential new treatments for Parkinson’s. In addition to scientists and trainees, several patients, advocates and caregivers attended the meeting, creating an unique forum for scientists to exchange ideas with colleagues and for patients to learn about the latest advances in PD research. The lively discussions continued over a buffet dinner, allowing participants to get better acquainted. The symposium continued the following day, with featured UCLA speakers Carla Koehler, Nigel Maidment, Beate Ritz, as well as Steve Finkbeiner and Ken Nakamura (UCSF), Paula Desplats (UCSD), and Vesna Sossi (University of British Columbia). During a special roundtable lunch, an invited group of patients and PDF research advocates were able to have in-depth discussions regarding the latest trends in basic and translational research and their impact on patients’ lives, while the scientists were treated to some thoughtful and provocative questions from the perspective of patients. The final segment of the symposium was a discussion session among Primary Investigators from UCLA, UCSF, UCSD, UCI, UCSC, Cal Tech, and University of British Columbia, to discuss potential collaborations and identify areas of research priority pertaining to the question of progression in PD. The success of the West Coast Symposium created an opening for researchers and patients to further their collaborative efforts towards improving the quality of life for Parkinson’s patients.

Researchers presented the preliminary results of their work at a poster session, attended by faculty, students, and patients.
**Serum Metabolomics of Slow vs Rapid Motor Progression Parkinson’s Disease: a Pilot Study**
*(PLOS ONE published 22 Oct 2013)*

Dr Beate Ritz and colleagues from Emory University analyzed and compared the serum metabolite profiles of early-stage PD patients, whose progression was monitored for 5-10 years. After exhaustive analysis, a biomarker called N8-acetyl spermidine, was found to be elevated in the serum of fast progressors, but not in those whose symptoms progress at a slow rate, or in healthy subjects. The study provides an encouraging first step towards developing reliable biomarkers to predict the rate of progression, which could lead to improved disease management strategies and more efficient clinical trials.

*(Read the full Press Release HERE)*

**Aldehyde dehydrogenase variation enhances effect of pesticides associated with Parkinson disease.**
*(Neurology. Published Feb 4, 2014)*

Following up on their previous studies which showed certain pesticides can increase the risk of developing Parkinson’s disease by two- to six-fold, Dr Jeff Bronstein, and his research team have shown that an individual's genetic makeup can determine the extent of their vulnerability to pesticides. Specifically, the UCLA team had discovered that the fungicide Benomyl (banned by the EPA) prevented the enzyme Aldehyde Dehydrogenase (ALDH) from detoxifying DOPAL, a naturally occurring byproduct in the brain. This leads to an accumulation of the toxin in the brain, and neuronal damage and disease over time. The study identified 11 additional pesticides used commonly and at lower concentrations for pest control in homes and offices, and in the food supply, which “significantly broadens the number of people at risk”.

Demonstrating the significance of gene-environment interactions, the researchers found that people with a common variant of the ALDH2 gene are significantly more vulnerable to developing Parkinson’s with pesticide exposure, although having the gene variant by itself does not seem to increase the risk of PD, notes Bronstein, Professor of Neurology and Director of the UCLA Movement Disorders Clinic.

Understanding the role of ALDH in the underlying pathology of PD could lead to development of therapies specifically targeting this pathway. In addition, regulation of harmful pesticides should reduce the risk of Parkinson’s.

*(Read the full Press Release HERE)*

**Pesticides and Parkinson's: Gene-Environment Interactions**

Click on the link above to view an educational webinar (originally aired in November 2013), where Beate Ritz, MD, PhD Professor and Chair, Epidemiology and Professor of Neurology, explains her research on the interaction of genes and environmental factors in Parkinson's disease.
Congratulations....

• Dr Ming Guo, Associate Professor in Neurology, has been awarded one of seven APDA research grants to continue her work identifying and characterizing the PINK1/Parkin pathway in drosophila and mammalian cells. Dr Guo has also received the prestigious EUREKA (Exceptional Unconventional Research Enabling Knowledge Acceleration) grant from the National Institutes of Neurological Disease and Stroke (NINDS), to continue her important work on the role of mitochondria in health and disease. Awarded only to a handful of investigators, this grant provides “support for innovative, high-risk biomedical research initiatives with the potential for achieving significant health impact.”

• Dr Hakeem Lawal, former post-doctoral fellow in the laboratory of Dr David Krantz, has joined the faculty of Delaware State University as an Assistant Professor in the Department of Biology, where he will continue to work on the cellular and molecular basis of neuro-degenerative diseases using drosophila models.

• Dr Arthur Fitzmaurice has joined the National Science Foundation as an AAAS Science and Technology Policy Fellow, following his doctoral and post-doctoral training with Dr Jeff Bronstein, which focused on the molecular mechanisms of how pesticides lead to Parkinson’s disease.

2013 World Parkinson Congress in Montreal

Drs. Ritz and Chesselet presented their work on Parkinson's disease at the World Parkinson Congress in Montreal, CA in October. The Congress is an unique venue in that it includes scientists, physicians, other health professionals, patients, and caretakers. The next meeting will be in Portland, Oregon, from September 20 to 23, 2016, with Dr Chesselet as Program Chair. Mark your calendars!

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