IRSF Investigator Spotlight: Lisa Monteggia, PhD, University of Texas Southwestern Medical Center

By Jim Keller

As 2011 steps into full swing, Chief Scientific Officer, Dr. Antony Horton and I have been working closely with our Co-Chairs for IRSF's 12th Annual Rett Syndrome Symposium to take place June 26th through 28th at the Lansdowne Resort and Spa in Leesburg, Virginia. This year the symposium will be chaired by Yi Eve Sun, PhD (University of California – Los Angeles) and James H. Eubanks, PhD (University Health Network, Toronto Western Research Institute). Together we identified Session Chairs to help set the agenda and to further the scope and overall impact of our annual meeting. One of our Co-Chairs this year is Dr. Lisa Monteggia from the University of Texas Southwestern Medical Center in Dallas, TX. Dr. Monteggia, an Associate Professor in Psychiatry, is also one of the latest recipients of an IRSF Regular Research Grant as announced last fall. Her project titled "Elucidation of Epigenetic Mechanisms in Rett Syndrome" involves studying changes that occur in neurons as a result of mutations in MeCP2.

Neurodevelopmental disorders such as Rett syndrome (RTT), are thought to be the result of a communication breakdown between neurons. Recent work has shown that a biochemical process called "methylation" provides a way of modifying DNA in order to regulate gene activity and is an important mechanism for fine-tuning how nerve synapses function. If this process is interfered with in any way, it may result in communication breakdown between neurons. This can be best pictured as a broken switchboard where all of the telephone lines are working but not connected properly.

The key enzymes that methylate DNA are called DNA methyltransferases and these form a family of proteins which include the enzymes DNMT1 and DNMT3a. Dr. Monteggia uses a carefully designed strategy that integrates a variety of genetic, behavioral, electrophysiological and optical imaging techniques to examine alterations in DNA methylation via these enzymes. Ultimately she hopes to correct any irregularities in communication breakdown by modifying them with drugs that subtly alter their function thereby fixing the 'switchboard' and restoring communication.

Dr. Monteggia's first research experience was as an undergraduate at the University of Illinois at Urbana. She was initially interested in microbiology, which helped her gain insight into molecular biology techniques. Dr. Monteggia's research interests shifted toward neuroscience, initially while she was employed at Abbott laboratories and later in graduate school. She took advantage of her molecular biology background to examine nerve cell signaling in the central nervous system (CNS). As a postdoctoral fellow, Dr. Monteggia shifted her focus to study the role of the neurotrophin family of proteins, which are important in development and the regulation of mood and antidepressant responses. Her lab's research into Rett syndrome began as she was setting up her lab as an assistant professor and she came across publications from Dr. Huda Zoghbi's laboratory on the identification of the MeCP2 gene with RTT. Neurotrophins are regulated by MeCP2 and Dr. Monteggia thought, here was a devastating disease with clear neuropsychiatric characteristics associated with a single gene. The study of MeCP2 then, represented unchartered territory that could yield novel insight into

how gene regulation impacts behavior, and that could possibly be linked to her neurotrophin work. This, she thought, would provide valuable information relevant to the disease process and hopefully a treatment.

What is the single most rewarding aspect of conducting Rett syndrome research?
Working on RTT provides strong motivation that our basic discoveries may find applicability in alleviating suffering induced by this devastating disease.

What is a potential positive outcome of the research you're conducting that is specific to your IRSF Award?
This proposal addresses a fundamental question of how DNA methylation/regulation in mature neurons may impact behavior and neuronal function.

If you could pick any one symptom of Rett syndrome to prevent or to provide relief for, what would it be?
Our goal is to define and understand precise synaptic transmission deficits associated with RTT. Our hope is that this endeavor will help alleviate neurological symptoms associated with this disease.

What other diseases does your research focus on?
We are also interested in depression. We are intensively working in identifying novel neuronal signaling pathways that may constitute the basis for better and more effective antidepressants.

What else would you like the RTT community to know about you?
In addition to conducting research, I am also a member of the Molecular Neuropharmacology and Signaling Study Section (MNPS) and IRSF's Scientific Review Board. I also sit on the Editorial Board of Biological Psychiatry and am the Deputy Editor for Neuropsychopharmacology.