Recent Research Conferences
Dr. James Eubanks

Ontario was well represented at the recent 2nd European Rett Syndrome Conference that took place from October 6-10 in Edinburgh, Scotland. This conference was attended by approximately 300 scientists, clinicians, and trainees who have specific research interests in Rett syndrome and by many parents and care-givers of children affected by Rett syndrome. Dr. Nathalie Bérubé from the University of Western Ontario presented her work showing that MeCP2 is part of an assembly in the nucleus of cells that also contains the proteins ATRX and Cohesin, and that together these factors work to program whether or not specific target genes in the developing brain will be expressed. This is the first illustration that MeCP2 functions with these other proteins, and also shows for the first time that a phenomenon called "genomic imprinting" is directly regulated by the functions of MeCP2. This work has recently been published in the prestigious scientific journal Developmental Cell. Dr. James Eubanks from the University of Toronto presented some of his work showing that the severe Rett syndrome phenotype of MeCP2-deficient mice can be reversed by functional restoration of MeCP2 in different regions of the brain. He also presented some of his results on phenotypic reversal in MeCP2-deficient mice, which extend directly from the rescue study conducted originally by Adrian Bird's group. Dr. Eubanks was able to completely reproduce the phenotypic reversal outcome seen in the Bird study, and show that in addition to general behavioral improvement, the "rescued" mice also showed improvements in their walking, rearing, and anxiety behaviors.

Dr. Eubanks also chaired a scientific session focusing on investigations of neurological impairments in Rett syndrome patients and animal models, and participated as a panel member with Drs Adrian Bird, Peter Huppke, Stuart Cobb, Laurent Villard, and Angus Clarke in the roundtable discussions that closed the scientific sessions of the meeting.

Breaking Discoveries

One of the more significant discoveries at this meeting was presented by Daniel Lioy, who is a graduate student in the renowned laboratory of Dr. Gail Mandel in Portland, Oregon. Rett syndrome has been historically viewed as a disorder of neural function and perhaps maturation, and until now most clinicians and scientists felt the deficits that cause Rett syndrome originated solely from impaired neuronal communication. Dr. Mandel's group has now shown in an elegant study that this is not the whole picture. Within the brain, neurons represent only one class of several cell types that are present throughout life. In most regions of the brain, the glial cells actually outnumber neurons, and these glial cells are generally thought to provide functional support for these neurons. Until last year, it was generally felt that MeCP2 was not expressed in these glial cells, but rather was restricted to functioning in neurons. Dr. Mandel has now shown clearly that MeCP2 is expressed in glial cells, and at this conference, Daniel presented their work showing that the reactivation of MeCP2 only in glial cells dramatically improves the behavioral deficits of MeCP2-deficient mice. This work shows that in addition to considering how MeCP2 normally functions in neurons, we must consider how MeCP2 influences glial cell activities to not only understand the mechanisms of Rett syndrome, but to also develop the most effective treatment strategies.

A second exciting presentation was given by Dr. Peter Huppke, from Göttingen, Germany, who discussed his ongoing work on testing drugs that facilitate nonsense mutation read-through.

Roughly one-third of Rett syndrome cases are caused by nonsense mutations, and recent work suggests that this particular type of mutation may be combatted by specific types of drugs. Dr. Huppke has been testing how effectively different types of aminoglycoside drugs overcome different nonsense mutations of MeCP2. He presented exciting data showing read-through of MeCP2 nonsense mutations is possible, and discussed his preliminary results showing that novel drugs being developed in Israel seem to work better than the traditional aminoglycosides. To allow the potential of these drugs to be fully tested, his group has now generated their own MeCP2 mutant mouse that expresses the R168X mutation. He presented his new data showing that this mouse develops many of the same symptoms as conventional MeCP2-null mice, and because it expresses the nonsense mutation, it allows for the effectiveness of these read-through drugs to be tested in a live mouse. Dr. Huppke indicated that these studies are now underway, but that it is too early to tell what the effects will be.

Funding Success

Two Ontario investigators have been awarded research grants by the International Rett Syndrome Foundation for their 2010 grant application cycle. Dr. Nathalie Bérubé from the University of Western Ontario received $100,000 in research funding for her grant entitled: "Epigenetic Regulation of Gene Expression By MeCP2 in the Mouse Brain", and Dr. Liang Zhang from the Toronto Western Research Institute received $50,000 in research funding for his grant entitled: "Evaluating Carbonic Anhydrase Inhibitors as Potential Treatments for Rett Syndrome".