

July 29, 2009

RECENT FUNDING AWARDS

"The process of scientific discovery is, in effect, a continual flight from wonder."

Albert Einstein

- **Dr. Kym Boycott** received a 3 year research grant through a New Investigator Research Grants Program sponsored by the SickKids Foundation and the Canadian Institute of Health Research of \$300, 966 for her work in the identification of a novel gene for Joubert Syndrome.

Abstract: The grant, entitled 'Identification of a novel gene for Joubert syndrome; a mid-hindbrain malformation' is providing funds to identify and characterize the gene for the Joubert syndrome related disorder in Hutterite children of Canada and gain insight into its role in neurodevelopment. Co-investigators include Dr. Dennis Bulman, Ottawa Hospital Research Institute, Drs. Micheil Innes and Jillian Parboosingh, University of Calgary, and Dr. Andreas Janecke, Innsbruck Medical University. The Joubert syndrome related disorders (JSRDs) are a group of inherited autosomal recessive conditions that share a unique congenital malformation of the cerebellum and midbrain, which when visualized on MRI is called the molar tooth sign. Children with a JSRD have low tone, developmental delay/cognitive impairment, and eye-movement and/or breathing abnormalities. Other findings can include additional brain differences, autism, extra fingers, blindness, and kidney and liver disease. So far seven genes have been identified to cause this group of conditions but this only represents about 35% of patients, so for many a genetic diagnosis is not possible. The gene for JSRD in the Hutterite population has been mapped to a relatively small interval and this research will use an innovative new approach to sequence the entire chromosome region - from top to bottom, referred to as 'next generation sequencing'. A cohort of over 2000 samples from children with JSRD as well as related conditions is available through international collaboration to understand the spectrum of clinical features that can be seen with mutations in this gene. The identified gene and gene-product will be studied to begin to understand its role in brain development.

- **Dr. Ashok Kumar** received a \$576,420 HIV/AIDS Research Initiative Operating Grant for his work on the regulation of IL-12 family of Th1 cytokines IL-12, IL-23 and IL-27 by HIV.

Abstract: Immune response to infection is governed by cytokines secreted by various cells of the immune system. Cytokines have been classified into T helper (Th) type 1 and type 2 cytokines. Th1 cytokines promote cell mediated immune responses (CMIR) whereas Th2 cytokines mediate antibody responses. In HIV infection, the protective CMI responses diminish as disease progresses from the asymptomatic stage to the onset of AIDS. By down-regulating protective CMIR, HIV avoids an effective immune response resulting in progressive immunodeficiency and eventually the onset of AIDS related symptoms. We hypothesize that HIV infection disrupts the Th responses causing down regulation of Th1 cytokines such as IL-12, IL-23 and IL-27 (members of the IL-12 family of cytokines) thereby resulting in the loss of immune competence. An important key to elucidating the immune unresponsiveness associated with a profound down regulation of Th1 cytokines, therefore, lies in deciphering the molecular mechanism involved in this process. The mechanism by which IL-12, IL-23 and IL-27 production is regulated following infection of monocytic and dendritic cells is not clear at present. Our preliminary results suggest that the HIV regulatory gene products vpr and nef modulate Th1 cytokines production in LPS-stimulated human monocytic cells. In this research proposal, we will investigate the mechanisms by which the HIV regulatory proteins nef, tat and vpr down regulate the production of Th1 cytokines namely IL-12, IL-23 and IL-27 in monocytic and dendritic cells. The results of these studies will provide further insights into the molecular mechanisms by which HIV induces immunodeficiency. Understanding the signaling pathways in HIV-induced dysregulation of Th1 cytokines may allow the development of effective therapeutic strategies aimed at enhancing immune responsiveness and potentially eliminating virus from the tissue reservoirs in HIV infected individuals who receive potent anti-retroviral therapy.

- **Dr. Robert A. Screaton** was awarded a \$470,312 operating grant to study the role of MARK2: TORC2: CREB signaling in beta cell regeneration.

Abstract: Increasing our understanding of beta cell survival mechanisms is critical to the improvement of treatment of type I and type II diabetes. While islet transplantation offers a promising treatment, this approach is limited by graft immune rejection and impaired function and survival of transplanted islets. The switch protein CREB is critical for the long-term survival of insulin-producing islet cells. Loss of CREB function in islet cells leads to islet cell death and to diabetes. We have identified a complex of signaling proteins - those that detect signals from outside the cell and transmit this information within the cell - that control CREB function in islet cells. This complex includes the enzyme MARK2 and a protein called TORC2 which is required to turn CREB on. We hope to establish what contribution MARK2 and TORC2 makes to the control of CREB activity in islet cells, and to determine whether or not drugs that modify TORC2 activity could be used to promote islet cell function and survival. The knowledge gained will be applied to preserve islet cell survival during islet transplantation for children with Type I diabetes, and to improve islet cell function in Type II diabetes patients who display impaired glucose control.

- **Dr. Leanne M. Ward** received a \$1,211,835 operating grant for her work on steroid-induced osteoporosis in the pediatric population.

Abstract: Children with serious chronic illnesses such as leukemia, nephrotic syndrome (a kidney disorder) and rheumatic conditions (such as arthritis, dermatomyositis and lupus) are frequently treated with a medication known as glucocorticoids. While effective in treating the underlying conditions, glucocorticoids have the potential to cause osteoporosis in children, a thinning of the bones. We have learned through a prior grant funded by CIHR, that children receiving glucocorticoids for serious illnesses have a higher than expected rate of osteoporosis, which causes painful vertebral (spine) fractures. In this next phase of our research project, known as the STeroid-induced Osteoporosis in the Pediatric Population (STOPP) study, we plan to determine the ongoing rate of spine fractures in children with chronic disease and the clinical profile of children at greatest risk for developing such fractures in the long-term. In addition, the young skeleton differs greatly from that of adults since children with osteoporosis have the potential to recover from spine fractures through bone growth. As pediatric researchers, it is important that we determine to what extent children are able to reconstruct fractured vertebrae, and the clinical profile of the child with the greatest potential to do so. The information that we gain from this study will allow us to develop national guidelines for the early identification, treatment and prevention of osteoporosis in children with serious underlying disorders.

Co-investigators: ALOS, Nathalie B; ATKINSON, Stephanie A; CABRAL, David Allan; COUCH, Robert; CUMMINGS, Elizabeth A; DIX, David B; DUBOIS, Josée; FEBER, Janusz; GABOURY, Isabelle; GRANT, Ronald M; HALTON, Jacqueline M; HAY, John A; HOUGHTON, Kristin M; HUBER, Adam M; LANG, Bianca A; MOHER, David; RAUCH, Frank; RODD, Celia J; SCUCCIMARRI, Rosie; SIMINOSKI, Kerry; STEPHURE, David K; TABACK, Shayne P.

Congratulations to all !