Background Information on Research Projects on Adverse Drug Reactions

Genotype-specific Approaches to Therapy in Childhood: The Canadian Pharmacogenomics Network for Drug Safety (CPNDS)

Project Summary
Adverse drug reactions (ADRs) are in the fifth most frequent cause of death in North America. Half of these reactions are likely caused by inherited genetic differences and are currently considered ‘unavoidable’. This project aims to understand why certain drugs are safe for use in some children but not in others and then to create easy to administer diagnostic tests that will predict and therefore prevent specific ADRs in children. To meet their goals, CPNDS is collecting data through a Canada-wide surveillance network that operates within nine of Canada’s largest children’s hospitals. They then perform large-scale genomic and proteomic studies to define genes critical for ADRs. These results are being used to help develop diagnostic tests to recognize a child’s genetic fingerprint and allow personalized dosing recommendations to be implemented for commonly used drugs.

More on the Science
The goal of the CPNDS program is to prevent adverse drug reactions (ADRs) in children by identifying predictive genomic markers for these reactions. This project aims to create personalized dosing recommendations for common drugs based on a child’s genetic profile.

CPNDS identifies ADR predictive markers by comparing clinical drug experience information as well as DNA from patients who suffered ADRs with patients of the same age who had no reaction after the same medication. CPNDS obtains its clinical material from a unique Canada-wide surveillance network that operates within nine of Canada’s major children’s hospitals.

Using these valuable clinical resources plus existing strengths and expertise in clinical genomics and genetics, the CPNDS program will apply innovative large-scale genomic and proteomic strategies to define the genes that cause, or are predictive of, childhood ADRs.

First of all, CPNDS is examining known functional single nucleotide polymorphisms (SNPs) in candidate genes to find predictive markers. Base pair changes that alter drug metabolism, drug transport or other physiological pathways of ADRs may be causative and therefore helpful in predicting ADRs. They will also identify novel ADR-predictive SNPs by sequencing candidate genes in the patients.

Pharmacokinetic studies will be done to validate the novel ADR predictive SNPs and mutations. Pharmacokinetic analysis will also be used to characterize ADR mechanisms by determining drug concentrations in affected patients.

The post-genomic era represents an unprecedented opportunity to prevent ‘unavoidable ADRs’ by translating our increasing genomic and proteomic knowledge.
into tools that impact the care and treatment of children. Armed with new predictive knowledge of a child’s genomic ADR risk profile, CPNDS will provide a cost-effective prevention strategy to reduce the incidence of childhood ADRs. The outcomes of the project could influence paediatric medical practices around the world.

Biographies (Project Leaders)

Dr. Michael Hayden
Director, UBC Centre for Molecular Medicine and Therapeutics and Killam Professor in the faculty of Medicine at UBC.

Michael Hayden is a full Professor of Medical Genetics at the University of British Columbia and the Director of the Center for Molecular Medicine and Therapeutics in Vancouver. Dr. Hayden has served as Chief Scientific Officer for Xenon Pharmaceuticals Inc. since March 1999 and been a member of the Board since November 1996.

Author of over 400 peer-reviewed publications and 150 invited submissions; Dr. Hayden focuses his research primarily on genetic diseases. Dr. Hayden played a key role in the development of predictive testing for Huntington's disease (HD) and his research group was instrumental in the demonstration of proteolytic cleavage of Huntington, contributing to the understanding of HD pathogenesis. Dr. Hayden is currently conducting research into the genetic factors that determine differences in drug reactions between individual patients.

The recipient of numerous prestigious honors and awards, Dr. Hayden was elected to the American Society of Clinical Investigation in 1992, the Board of the American Society of Human Genetics in 1994 and the Royal Society of Canada in 1995. In 2007 he was awarded the Prix Galien one of the highest honours in the field of biopharmaceuticals in Canada. He is currently nominated as one of the five finalists for the Globe and Mail’s Nation Builder 2008. Other distinctions held by Dr. Hayden are the 2003 Henry Friesen Award of the Royal College of Physicians and Surgeons of Canada, the 2001 Award of Excellence of the Genetics Society of Canada and the Ottawa Life Sciences Award of Merit. He also received the 1998 Distinguished Scientist Award of the Canadian Society of Clinical Investigation and the 2000 BC Biotechnology Alliance Award for Vision and Leadership.

Dr. Hayden received his medical training (1975) and his PhD in Genetics (1979) from the University of Cape Town, South Africa. He completed a post-doctoral fellowship and further training in Internal Medicine at Harvard Medical School.

Dr. Bruce C. Carleton
Professor of Paediatrics and Pharmaceutical Sciences, UBC
Director, Pharmaceutical Outcomes Program, Children's and Women's Health Centre of British Columbia
Senior Clinician Scientist, Child & Family Research Institute

Dr. Carleton earned his Bachelor degree in pharmaceutical sciences in 1986 from Washington State University. He continued at the University of Utah, earning a Doctor of Pharmacy degree in 1989. After completing a residency in clinical therapeutics at
the University of Utah and Primary Children’s Medical Centers in Salt Lake City, as well as post-doctoral research fellowships in experimental therapeutics and immunopharmacology at the University of Minnesota, he joined the faculty at the University of British Columbia in 1991.

Dr. Carleton is also cross-appointed to the Children’s and Women’s Health Centre of British Columbia where he has served as Director of the Pharmaceutical Outcomes Program since 1994. He also holds an appointment at UBC in the Centre for Health Services and Policy Research. He is also an adjunct Professor at the School of Health Information Science at University of Victoria.

The central theme of Dr. Carleton’s research program is the study of drug therapy with the goal of improving human health and quality of life. He is particularly interested in the development of models for the evaluation of the effectiveness of drugs on health outcomes, medication use models designed to improve patient health, and the development of effective and pragmatic surveillance systems to improve the safe use of medication.

Dr. Carleton has a clinical interest in asthma and the clinical use of drugs in children. Another key area of interest is in the epidemiology and clinical management of adverse drug events. His current collaborations include those with Dr. Michael Hayden in the investigation of genetic factors that contribute to adverse drug reactions in pediatric patients.

Additional Information:

Involved Institutions: UBC Centre for Molecular Medicine and Therapeutics, Child & Family Research Institute, BC Children’s Hospital and BC Women’s Hospital & Health Centre, Centre for Healthcare Innovation and Improvement, University of British Columbia

Approved Project Budget: $3.9 million

Technology Applications: Pharmacogenomics; Diagnostic tests; Personalized medicine

Project Co-Applicants
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Dr. Gideon Koren, The Hospital for Sick Children
Dr. Adrian Levy, UBC
Dr. Stuart MacLeod, Child & Family Research Institute
Dr. Craig Mitton, UBC
Dr. Michael S. Phillips, Genome Quebec
Dr. Michael Rieder, University of Western Ontario
Dr. Wyeth W. Wasserman, Centre for Molecular Medicine and Therapeutics

Project Co-Funders
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