CANADIAN GENETIC DISEASES NETWORK

ANNUAL REPORT 2000

Their genes.

Our Piece of the Puzzle

Table of Contents

Healthy genes and our environment are key pieces of the puzzle in preventing disease.

At the Canadian Genetic Diseases Network, our research focuses on genes and finding the genetic basis of human disease. Our partnerships help find the cures for disease.

About the Canadian Genetic Diseases Network (CGDN): Profile

CGDN's mission is to be the primary catalyst in advancing Canada's scientific and commercial competitiveness in genetic research and the application of genetic discoveries to the prevention, diagnosis and treatment of human disease.

CGDN is a not-for-profit corporation that conducts collaborative research in human genetic disease, trains scientists, establishes frameworks and partnerships for the commercialization of research, and ensures that the benefits and risks of research in human genetic disease are publically recognized.

Our projects and core technology facilities focus on the molecular and cellular causes of common diseases such as cancer, heart disease, and Alzheimer's.

Our scientists and their teams are based in universities, hospitals, and research centres across Canada, forming the basis of the CGDN nation-wide network which includes stakeholders in academic institutions, biotechnology, pharmaceutics and diagnostics. CGDN corporate headquarters in Vancouver manages training, partnerships and commercial development of intellectual property.

At CGDN we aim to help solve the puzzle of how our genes and our environment contribute to genetic disease.

Year 2000 – the emergence of gene based medicine.

CGDN is on the cutting edge of R&D.

The leading news of 1999/2000 in human genetics research is the completion of the first working draft of the human genome. Called the 'Human Genome Project', this information determines the sequence of the three billion DNA subunits which comprise all human chromosomes. With this tool, scientists worldwide have access to the most extensive public data ever assembled which will eventually led to the location of an estimated 100,000 genes in our human DNA.

CGDN's role in the Human Genome Project

CGDN members are among Canada's leading R&D specialists in genetic disease. Credited with over 600 scientific publications annually, major technological advances, and discoveries in many common genetic disorders (see 'Discovery' below), our researchers and their teams have made significant contributions to the international effort to sequence and map the entire human genome. In particular, principal investigator Dr. Norman Dovichi of the University of Alberta, launched the DNA sequencing machine prototype which is a major underpinning of the Human Genome Project. Our Associate Scientific Director, Dr. Charles Scriver of McGill University, is the co-director of the Human Genome Organization's (HUGO) Mutation Database Initiative which provides access to up-to-date lists of mutations in genes. Dr. Stephen Scherer of Toronto's Hospital for Sick Children is Chair of the HUGO Genome Mapping Committee. The Human Genome Meeting (HGM) 2000 was hosted in Vancouver by the Canadian scientific community while CGDN investigators played a leading role as organizers and presenters. Dr. Michael Hayden served as Chair of the HGM2000 Local Organizing Committee; Dr. Lap-Chee Tsui (Chair of the CGDN Scientific Advisory Board) served as Chair of the HGM2000 International Scientific Committee. Dr. Tsui is current President of HUGO.

Leadership in promoting genome technology and genetic research in Canada

During the year, CGDN played a significant role in the successful proposal to create Genome Canada, the $160 million five-year federal funding initiative in genome research and integrated technologies which was announced in February 2000. As part of this initiative, five regional centers will be funded to implement new projects in genetics. CGDN has played an active role in the development of Genome BC and Genome Quebec. Additionally, CGDN lead the development of a new Canadian Institute for Genetic Research (CIGR) which is one of 13 institutes funded by the federal Canadian Institutes for Health Research. Dr. Roderick McInnes, a CGDN principal investigator, has been appointed Scientific Director of CIGR.

Realizing our mission in 2000

Discovery

In 1999/2000 CGDN researchers published a number of significant findings in diabetes, cardiovascular disease, tuberculosis, Alzheimer's disease, muscle disease, cell death, and eye disease among others. These discoveries are described here in the 'Science Report'. CGDN papers appeared in leading scientific journals such as *Nature*, *Cell*, *Science*, *Nature Genetics*, *American Journal of Human Genetics*, etc. More than half of this research is based on collaborations among CGDN members. We are also proud that, in 1999/2000, our investigators and their teams were recognized with over 60 Canadian and international awards for excellence in science.

Training

CGDN scholarships, studentships and fellowships together with an inter-laboratory 'visiting scientist' program continue to play a pivotal part in the CGDN training strategy to match new and senior investigators in a learning environment. The annual CGDN scientific meeting in Vancouver, held in conjunction with the HGM2000 conference, provided an opportunity for 150 CGDN principal investigators and students to network and access the latest developments in genetic research both at home and abroad. Additionally, CGDN's partnerships with spin-off companies such as Xenon Genetics Inc., NeuroVir Therapeutics Inc., SignalGene Inc. and others provide an opportunity for young scientists to develop entrepreneurial

The Rt. Hon.
Don Mazankowski, PC, OC

Dr. Michael Hayden
Scientific Director

Dr. Ron Woznow
Chief Executive Officer

skills – valuable assets in helping build and maintain Canada's biotechnology infrastructure. Our laboratory based bioinformatics workshops have been an unqualified success since inception in 1999. In partnership with the Biotechnology Human Resource Council and Human Resources Development Canada, CGDN has run four certificate-based courses which train highly qualified personnel in the development and use of computational tools for the study of biology.

Translating research

In 1999/2000 the CGDN 'strategic fund', an initiative which bridges the gap between core funding of basic research and seed funding for start-up companies, provided total funding of $357,500 to projects in research and management of disease, therapy for eye disease, Down's syndrome, genetic susceptibility to disease, heart disease, and an economically efficient method of production of antibodies *in vitro*. The success of this program, lead CGDN to increase the strategic fund by almost 20% to $425,000 in fiscal year 2001.

This year two new spin-off companies, Genexyn Pharmaceuticals Inc. and Ecogenix were formed based on technologies developed by the strategic fund in the labs of Dr. Frank Jirik in Vancouver and Dr. Daniel Sinnett in Montreal, respectively. Since 1995, a total of six spin-off companies have been launched. In 1999/2000 three licences for intellectual property were granted to industry, four patent applications filed, and two patents issued (see 'Commercial Report').

Our commitment to gene based medicine

The Canadian Gene Cure Foundation, with financial and management support from CGDN, was incorporated as a charity to raise funds for genetic research in Canada. In 1999 the Foundation hired an Executive Director and launched operations in Toronto. In 2000, The Right Honourable Raymon Hnatyshyn accepted the position of honorary patron. The Foundation's annual *Jeans for Genes* fundraiser, based on a successful pilot campaign in 1999, will run again in November 2000 in Toronto, Montreal, and Vancouver in partnership with R_X&D, an organization of Canada's research based pharmaceutical companies. The co-chairs of the campaign this year are André Marcheterre, President of Merck Frosst Canada Inc., and Murray Elston, President of R_X&D.

CGDN'S history of strong leadership

In April 2000 Mr. Graham Strachan retired after nine years as a director of CGDN and five years as Board Chair, from 1995 to 2000. The Board, management, and members of CGDN would like to acknowledge Mr. Strachan's outstanding leadership during these important years of growth and renewal. He leaves us with a strong organization. The Board of CGDN elected and welcomed The Right Honourable Don Mazankowski, PC, OC as Board Chair at the April 2000 annual general meeting.

We expect that 2001 will be another successful year, with CGDN well positioned to enter the new era in gene based medicine.

Don Mazankowski, PC, OC
Chairman

Michael Hayden, MB ChB PhD FRCP(C) FRSC
Scientific Director

Ron Woznow, PhD
Chief Executive Officer

"From Genes to Therapies"

Gene Identification

Researchers

L. Field (Calgary); D. Cox, M. Walter (Edmonton); G. Ebers, R. Hegele (London); B. Triggs-Raine (Manitoba); P. Gros, T. Hudson, K. Morgan, G. Rouleau, E. Skamene, E. Schurr (Montreal); F. Rousseau (Quebec); R. McInnes, J. Rommens, S. Scherer, K. Siminovitch, P. St George-Hyslop, L-C. Tsui (Toronto); M. Hayden (Vancouver)

Projects

Craniofacial diseases	Nonsyndromic cleft lip with or without cleft palate
Gastrointestinal diseases	Cystic fibrosis, inflammatory bowel disease, liver disease
Diabetes	IDDM, NIDDM
Cardiovascular diseases	HDL deficiency, intracranial aneurysm
Neurological disorders	Dyslexia, familial dementia, multiple sclerosis, William's syndrome, Tourette syndrome
Bone & joint disorders	Rheumatoid arthritis
Modifier genes	Cystic fibrosis, triplet expansion diseases
Susceptibility to infection	Legionnaires' disease, CMV, malaria, salmonella, tuberculosis
Ocular diseases	Glaucoma, retinitis pigmentosa, developmental eye defects

Pathogenesis & Functional Genomics

Researchers

N. Dovichi (Edmonton); R. Gravel (Calgary), T. Hudson, G. Mitchell, K. Morgan, G. Rouleau, R. Rozen (Montreal); A. MacKenzie, R. Korneluk (Ottawa); F. Rousseau (Quebec); B. Gallie, D. MacLennan, B. Robinson, P. St George-Hyslop (Toronto); M. Hayden, P. Hieter (Vancouver)

Projects

Cancer	Retinoblastoma, folate metabolism and tumours
Neurological disorders	Apoptosis, Alzheimer's disease, Huntington disease, fragile X syndrome
Metabolic disorders	Tay-Sachs and Sandhoff diseases, respiratory chain defects, obesity
Neuromuscular disorders	Calcium regulation and muscle disease, myotonic dystrophy
Functional genomics	SAGE analysis, DNA chips, methylation patterns in genomic DNA

Genetic Therapies

Researchers

C. Scriver (Montreal); R. Worton (Ottawa); J. Dick, R. McInnes, C. Roifman, L-C. Tsui (Toronto); L. Clarke, P. Cullis, M. Hayden, F. Jirik, F. Tufaro (Vancouver)

Projects

Technology development	Viral vectors: HSV, liposomes, stem cells
Applications	Murine tumour models, LPL deficiency, murine Hurler's syndrome, cystic fibrosis, Duchenne muscular dystrophy, human immunodeficiency diseases, retinal degeneration, enzyme substitution for phenylketonuria

Genetics & Health Care

Researchers

N. Dovichi (Edmonton); C. Scriver (Montreal); B. Gallie, D. MacLennan, S. Narod, L-C Tsui (Toronto)

Projects

Technology development	DNA diagnostics
Mutations	Detection, databases
Impact/Evaluation	Meta-analysis of treatment of hereditary diseases, retinoblastoma, malignant hyperthermia, breast and ovarian cancer

Core Technologies

Facilities & Directors

Genotyping	T. Hudson, K. Morgan (Montreal)
DNA sequence analysis	M. Hayden (Vancouver), B. Koop (Victoria), S. Scherer (Toronto)
Bioinformatics	F. Ouellette (Vancouver)
Transcribed sequence detection	J. Rommens (Toronto)
Genome alteration in mice	F. Jirik (Vancouver), A. Nagy, J. Rossant (Toronto)
Genome alterations in *C. elegans*	J. Culotti (Toronto)
In vivo DNA analysis	R. Drouin (Quebec)
Protein-protein interactions	J. Friesen, J. Greenblatt, A. Pawson (Toronto)
Immunoprobes	J. Wilkins (Winnipeg)

Science Report

This has been another outstanding year for discoveries in our network, some of which are already being translated into new commercial opportunities.

This report covers year 2 (1999-2000) of CGDN's Phase III research program. A major objective of CGDN's program is to identify genes involved in common diseases and to study the resulting disease mechanisms and develop new therapeutic approaches.

Diseases such as cardiovascular disease, diabetes, Alzheimer's, cancer and other chronic disorders are caused by a complex interplay of genetic and environmental factors. To discover genetic factors underlying these diseases, CGDN investigators work with patients and their families to dissect the natural history of the disease and obtain clinical material for molecular analysis. A variety of techniques are then used to identify genes contributing to the disease – from DNA sequencing and genotyping, to computer-based linkage analysis and interrogation of the international genomic databases. Once genes have been identified, CGDN investigators apply cutting edge techniques such as the analysis of gene expression using microarrays, and develop animal models to probe the molecular basis of disease. These animal models become essential for later studies of novel therapeutic approaches.

In 1999/2000 CGDN investigators made a number of important advances, including the following:

Disease gene identification

- **Diabetes: discovery of a mutation in a gene found in Canadian aboriginal population affected by early-onset type 2 diabetes (R. Hegele, John P. Robarts Research Institute, London)**

  Diabetic patients either cannot produce insulin or use insulin ineffectively, leading to an unhealthy build up of blood glucose. Diabetes has become a common disease among over 16 million people in North America and is known to have a significant genetic component. Dr. Hegele and his colleagues have found a new variant of the hepatic nuclear factor 1α gene in members of the Oji-Cree which predisposes them to diabetes. The Oji-Cree from Northern Ontario and Manitoba are five times more likely to suffer from type 2 diabetes than the Canadian population at large. This discovery makes the development of a diagnostic procedure possible that will promote intervention strategies to prevent or delay the onset of type 2 diabetes in the Oji-Cree. *(Journal of Clinical Endocrinology and Metabolism, April 1999)*

- **Cardiovascular disease: discovery of a gene responsible for two genetic diseases that result in low levels of 'good' cholesterol and a highly elevated risk of cardiovascular disease (M. Hayden, Centre for Molecular Medicine and Therapeutics, Vancouver)**

  LDL or 'bad cholesterol' is the most common lipoprotein abnormality found in patients with atherosclerosis and premature cardiovascular disease. Dr. Hayden led an international consortium involving CGDN spin-off company, Xenon Genetics Inc., to discover the ABC1 gene – the major gene regulating HDL (good cholesterol) levels in humans. The gene provides a target for novel therapeutics against cardiovascular disease. Says Dr. Hayden, "Although medical science has developed effective methods to lower LDL or 'bad' cholesterol, until now we have not understood crucial mechanisms which elevate levels of HDL or 'good' cholesterol." *(Nature Genetics, August 1999)*

- **Spastic Ataxia: discovery of Spastic Ataxia (ARSACS) gene (A. Richter, Hôpital Ste-Justine & T. Hudson and K. Morgan, McGill University Health Centre, Montreal)**

  Specific to the population in northeastern Quebec, ARSACS is a debilitating disease that causes muscle wasting and disturbances in gait. Clinical symptoms include spasticity and aberrations in control of the eye such as nystagmus. Using genetic studies in Quebec, the group reports the cloning of the gene that causes this early-onset disease. *(Nature Genetics, February 2000)*

- **Tuberculosis: discovery of a gene locus for susceptibility to clinical tuberculosis (E. Schurr and K. Morgan, McGill University Health Centre, Montreal)**

  Tuberculosis (TB) affects more than one third of the world's population and causes more deaths than any other bacterial infection worldwide. Genetic factors have been known to influence susceptibility. Analysis of a large Canadian aboriginal pedigree after an epidemic of TB has provided convincing evidence of the existence of the major genetic locus of susceptibility to clinical tuberculosis. This discovery provides hope that researchers will soon discover a mechanism to understand susceptibility to TB. Key to this discovery was the ability to specify risk categories based on

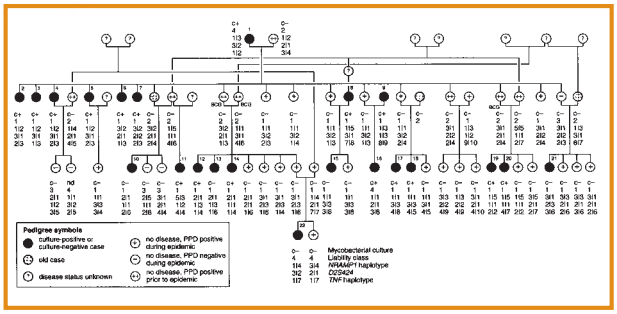


Figure 1: Partial pedigree of the extended TB kindred (Reprinted by permission of the American Journal of Human Genetics)

clinical and epidemiological information and, thus, model gene-environment interaction. Researchers believe this approach can be used for the analysis of susceptibility to other complex diseases. See Figure 1. *(American Journal of Human Genetics, August 2000)*

Pathogenesis and Functional Genomics: how mutated genes cause disease

- **Alzheimer's:**

  discovery of new molecular complexes associated with pathogenesis of Alzheimer's disease (P. St George-Hyslop, University of Toronto)

  Alzheimer's disease is the most common form of dementia among the elderly. Almost half the cases of Alzheimer's disease have a genetic contribution. Dr. St George-Hyslop's group discovered mutations in presenilin genes (previously identified as genetic determinants of familial Alzheimer's disease) that alter the trafficking of β-catenin, which forms a high-molecular weight membrane-bound complex with the presenilins. The results of these experiments indicate that mistrafficking of selected presenilin ligands is a possible mechanism for the development of Alzheimer's disease. *(Nature Medicine, February 1999)*

  discovery of a novel interacting protein involved in familial Alzheimer's disease (P. St George-Hyslop, University of Toronto)

  In continuing studies of Alzheimer's disease, Dr. St George-Hyslop's group has identified a novel component of the presenilin complex, nicastrin, that can be manipulated either to produce more toxic isoforms of the Aβ peptide or can cause significant reductions in Aβ peptide production. These new insights suggest new strategies for the development of new therapeutic approaches to Alzheimer's disease. *(Nature, September 2000)*

- **Autoimmune and neurodegenerative disorders: discovery of molecular motif that modulates production of protein that inhibits apoptosis or programmed cell death (R. Korneluk, Children's Hospital of Eastern Ontario)**

  Apoptosis plays a critical role in regulating cell survival and death. The clinical phenotypes of cancer, autoimmune and neurodegenerative disorders often include faulty apoptosis. Dr. Korneluk's group discovered a new internal-ribosome-entry-site (IRES) motif on XIAP, a protein that inhibits apoptosis and established the role of IRES in controlling production of XIAP. This new knowledge will help us develop ways to regulate XIAP and consequently, susceptibility to cell death. *(Nature Cell Biology, July 1999).*

- **One-hit model of cell death for inherited neuronal degeneration (R. McInnes, Hospital for Sick Children and M. Hayden, Centre for Molecular Medicine & Therapeutics)**

  Alzheimer's, Parkinson's and a host of other diseases are caused by progressive deterioration of parts of the nervous system. The actual mechanism of cell death in many of these neurodegenerative diseases is supported by studies of a 'one-hit' biochemical model triggering neuron death. In this model the disease-causing mutation imposes a mutant steady vulnerable state on the neuron and a single event randomly initiates cell death. The finding has implications for therapeutic strategies for many neurodegenerative diseases. *(Nature, July 2000)*

Genetic Therapies & Genetics and Health Care

- **Phenylketonuria (PKU): a novel approach to treat PKU by administration of phenylalanine lyase (PAL) to degrade phenylalanine (C. Scriver, McGill University)**

  The only treatment currently available for sufferers of the inherited metabolic disorder, PKU, is a lifelong low protein diet and regular checks for levels of phenylalanine. Dr. Scriver's group collaborated with IBEX Technologies Inc. to provide proof of principle that PAL reduces hyperphenylalaninemia in a mouse model. This work will lead to alter-

native and less onerous treatment for PKU. *(Proceedings of the National Academy of Sciences, USA, March 1999).*

- **Gene therapy: discovery of a novel molecule that regulates development of human blood stem cells has promise for blood gene therapy (J. Dick, Hospital for Sick Children, Toronto)**

  Special cells, called stem cells, which are able to grow and differentiate into other tissues, show much promise as potential replacements for damaged or diseased cells. However, current technology to genetically manipulate and culture stem cells such as those found in bone marrow for use in gene therapy is limited. Discovery of bone morphogenic proteins by Dr. Dick's team is found to allow stem cells used in ex vivo gene therapy experiments to live in culture for an extra two days. *(Journal of Experimental Medicine, April 1999)*

- **Eye diseases: discovery of self-renewing stem cells in the adult mammalian eye (R. McInnes and D. van der Kooy, Hospital for Sick Children and University of Toronto)**

  This breakthrough opens the possibility that the retina of the eye can regenerate. Stem cells found in the mature eye may be used in therapeutic approaches to treat eye diseases of the elderly such as macular degeneration. Dr. McInnes' group isolated retinal stem cells from the ciliary margin of the mouse eye. Researchers grew the stems cells in special agar dishes and have postulated the existence of an inhibitory element that stops these cells from differentiating in the live eye. *(Science, March 2000)*

- **DNA sequencing: development of a small scale DNA sequencing and analysis system (N. Dovichi, University of Alberta)**

  Technology improvements to miniaturize the equipment and chemistry required to sequence DNA have provided much of the momentum for the Human Genome Project. Large-scale DNA sequencing projects require instruments that generate high throughput and high sequencing accuracy at low cost. Dr. Dovichi's group developed a number of low-cost capillary electrophoresis instruments, including a 5 capillary system capable of sequencing 650 bases in 100 minutes at 98.8% accuracy. This instrument will be useful in analyzing small amounts of fluorescently-labeled DNA. See Figure 2. *(Nucleic Acids Research, December 1999)*

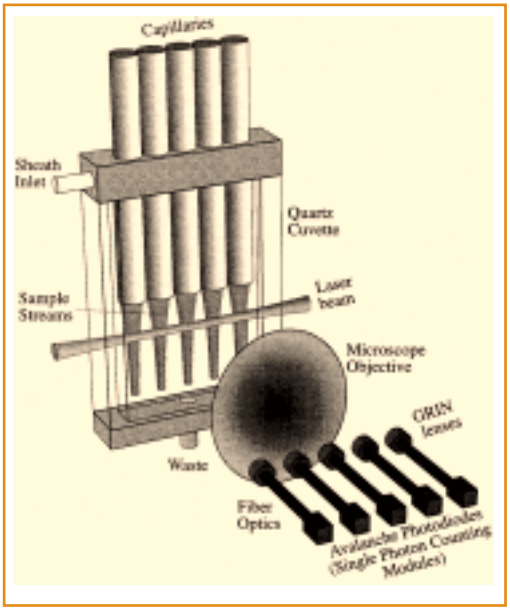


Figure 2: Sheath flow cuvette fluorescence detection chamber

- **Gene therapy: improvements in liposomes for gene therapy (P. Cullis, University of British Columbia and INEX Pharmaceuticals)**

  One of the major technological challenges of gene therapy is to find an effective way to deliver genetic material to the cell. One such method is to encapsulate genetic material in a synthetic particle called a liposome. Dr. Cullis' group improved the potency of transfection of liposomes for use in gene therapy. Using stabilized plasmid-lipid particles, the group increased the charged or cationic lipid content leading to increased transfection potency. *(Journal of Drug Targeting, March 2000)*

CGDN supports a networking environment that encourages the sharing of ideas and technologies. The success of this approach is measured by the numbers of peer-reviewed scientific papers authored by multiple-research groups versus single-research groups. For the first time, over the past year, there were more papers (277) authored by multiple-research groups than papers (265) written by a single-research group.

In 1999/2000 CGDN scientists and their students received some of the top Canadian and international awards for excellence in science.

Awards received by senior researchers

Alberta Heritage Foundation for Medical Research: Senior Scientist Award
Leigh Field, Uni. of Calgary

Alberta Women's Science Network: Mentor of the Month
Diane Cox, Uni. of Alberta

American Society of Human Genetics: President
Ronald Worton, OGHRI

Canadian Institute for Genetic Research: Scientific Director
Roderick McInnes, HSC

Canadian Lipoprotein Conference: Distinguished Scientist Award
Micheal Hayden, CMMT

Canadian Society for Clinical Investigation: Distinguished Scientist Award
Peter St. George-Hyslop, U. Toronto

G. Mendel Award: Achievement in life sciences
Emil Skamene, MGHRI

Globe and Mail: Canada Top 40 Under 40
Tom Hudson, MGHRI

Hamilton Community Foundation Award:
Brenda Gallie, OCI

Hospital for Sick Children: Citizen of the Year
Johanna Rommens, HSC

International Human Genome Organization (HUGO)
President:
Lap-Chee Tsui, HSC
Chair, Genome Mapping Committee:
Stephen Scherer, HSC
Co-director, Mutation Database Committee:
Charles Scriver, MCHRI
Chair, HGM2000 International Scientific Committee:
Lap-Chee Tsui, HSC
Chair, HGM2000 Local Organizing Committee:
Michael Hayden, CMMT

Manning Innovation Awards Foundation: 1999 Award of Distinction
Norman Dovichi, Uni. of Alberta

Medical Research Council/CIHR:
Member of Governing Council CIHR:
Philip Gros, McGill U.
MRC Scientist:
Erwin Schurr, MGHRI
Peter St. George-Hyslop, U. of Toronto
Michael Walter, U. of Alberta
Director, MRC Group in Medical Genetics:
Rima Rozen, MCHRI

Merck Frosst Canada: Excellence in Research Award
Emil Skamene, MGHRI

Milestone Medica Corporation Award:
Philippe Gros, McGill U.

Muscular Dystrophy Association of Canada: Scientist of the Year
Alex Mackenzie, CHEO

National Cancer Institute of Canada: Robert L Nobel Award of Excellence
John Dick, HSC

Premier's Research Excellence Award:
Stephen Scherer, HSC

Research in Infantile Diseases Foundation: Prix d'Excellence (Pediatric Research)
Daniel Sinnett, Hôpital Ste Justine

Revenue Commerce and Radio-Canada: Un des 50 jeunes Quebecois de l'avenir
Tom Hudson, MGHRI

Royal Society of London Glaxo Wellcome Prize and Gold Medal for Research in Medicinal and Veterinary Sciences 2000
David MacLennan, Banting & Best

University of Manitoba: Honorary Degree (DSc)
Ronald worton, OGHRI

University of Ottawa: Faculty of Medicine Award of Excellence
Ronald Worton, OGHRI

University of Toronto: Donald and Audrey Campbell Chair of Immunology
Chaim Roifman, HSC

Awards received by research team members

Alberta Heritage Foundation for Medical Research
Fellowship:
Lara Cullen, Uni. of Alberta
R. Hsiung, Uni. of Calgary
Graduate Studentship:
Deepak Kamnasaran, Uni. of Alberta

American Society of Gene Therapy: Travel Scholarship
Guillermo Guenechea, HSC

American Society of Hematology: Travel Scholarship
Guillermo Guenechea, HSC

Canadian Association of Gastroenterology: Postdoctoral Fellowship
Mark Silverberg, MSHRI

Canadian Gene Cure Foundation: Summer Studentship
Cyndey Nelson, CMMT

Canadian Genetic Diseases Network: Summer Studentships
Vincent Biron, Veronica Coronodo – U. of Alberta; Susan Bustos, Robert Edge, Vidhya Thayalan, Orem Shemtov – HSC; Michael Fraser, Jed Lipes, Jacques Moisan, Scott Owen, Dominique Veerlan – MGHRI; Mark Gillespie – OGHRI; Zylna Hybad – CHEO; Cynthia Jung, Liam Brunham, Dean Elterman – UBC; Lee Cheong – OCI; William Makis – MSHRI; Emily Meadows, Alex Greenberg – ERI;

Le Fonds pour la Formation de Chercheurs et l'Aide à la Recherche:
Pamela Tran, MCHRI

Hospital for Sick Children: Research Training Center Studentship
Maja Popvic, Graeme Boocock – HSC

Manitoba Health Research Council: Graduate Fellowship
Sherrie Kelly, Tammy Shuttleworth – Uni. of Manitoba

Manning Innovation Awards Foundation: 1999 Award of Distinction
Jianzhong Zhang, Uni. of Alberta

McGill University:
Faculty of Medicine Studentship
Sahar Sabani

Montreal Children's Hospital Research Institute
Fellowship:
Bernd Shwahn, Jaspreet Sekhon – MCHRI
Best Basic Research Presentation:
Ilan Weisberg, MCHRI
Multiple Sclerosis Studentship:
David Dyment, LHSC

National Cancer Institute of Canada: O. Harold Warwick Prize
David DiCiommo, HSC

Ontario Graduate Studentship:
Mark Van Oene, Maja Popvic – HSC

Overseas Research Scholarship:
David Dyment, James Steckley – LHSC

Society for the Study of Inborn Errors of Metabolism: Annual Award for Best Paper
Paula Waters et al., MCHRI

University of Manitoba: Graduate Studentship
Tammy Shuttleworth, Uni.of Manitoba

University of Toronto: Open Studentship
Graeme Boocock, Ray Oh, HSC

Commercialization of CGDN discoveries

An important mandate of CGDN is to help translate discoveries into economic benefit for Canada. To do this, CGDN management works closely with its scientists and their institutes to identify and protect patentable discoveries.

In 1999/2000 CGDN led the filing of four patent applications and saw two patents issued (see Table 1).

Table 1:

Patent applications filed

Investigator:	Title:
Dr. Grant Mitchell Hôpital Ste Justine	Hormone sensitive lipase mediated male fertility
Dr. Jeremy Squire University of Toronto	Nucleic acid analysis by comparative particle hybridization
Dr. Daniel Sinnett Hôpital Ste Justine	Detection of CYP1A1, CYP3A4, CYP2D6 & NAT2 variants & therapeutic use thereof.
Dr. Michael Walter University of Alberta	Novel mutation in the FREAC3 gene for diagnosis and prognosis of glaucoma and anterior dysgenesis

Patents issued

Investigator:	Title:
Dr. François Rousseau Centre Hospitalier Universitaire de Québec	Marker at the estrogen receptor gene for determination of osteoporosis predisposition (US)
Dr. Steven Narod University of Toronto	Method and kit for evaluating risk of ovarian cancer in carriers of BRCA1 mutation (US)

Strategic investment funding:

In the process of protecting discoveries (patenting), additional work is often required to satisfy the requirements of the patent office. Funding for this work has traditionally been difficult to obtain. The work is often deemed not novel enough for discovery research grants but too risky for early stage commercialization funds. To bridge this gap, CGDN made six 'strategic grants' in the last year to a total value of $357,500 (see Table 2).

Table 2

Researcher	Project area	Strategic funding
Dr. Michael Hayden Centre for Molecular Medicine & Therapeutics	Identification of novel genes & therapeutic targets for low HDL cholesterol	$ 75,000
Dr. John Wilkins University of Manitoba	Production of antibodies *in vitro*	$ 63,360
Dr. Robert Korneluk University of Ottawa	Therapy for retinis pigmentosa (eye disease)	$ 62,000
Dr. Daniel Sinnett Hôpital Ste Justine	Gene susceptibility to disease	$ 60,275
Dr. Régen Drouin Centre Hospitalier Universitaire de Québec	Prenatal diagnosis Tri-21 (Down's syndrome)	$ 50,000
Dr. Jeremy Squire University of Toronto	Gene expression analysis (research & management of disease)	$ 46,865
TOTAL		**$ 357,500**

Return on investment:

To date, CGDN has awarded over $1.2 million in strategic grants. This funding has resulted in the following:

- Twelve patents licensed to new spin-off companies.
- Two patents licensed to pharmaceutical companies.
- Over $120 million investment funding from third parties to spin-off companies.
- Over 100 jobs in spin-off companies

The financial return on this investment has been impressive – over $6 million in cash and equities. These assets form part of an endowment to fund future human genetic research in Canada.

In 1999/2000, three new CGDN spin-off companies were formed to exploit patents and technologies funded in whole or part by the Network. In addition to core and strategic funding, CGDN provides management support to these entities. They are:

- *Ecogenix Inc. of Montreal*
  Founding scientist – Dr. Daniel Sinnett
- *Genexyn Pharmaceuticals Inc., of Vancouver*
  Founding scientist – Dr. Chris Ong
- *Solutions by Sequence Inc. of Toronto*
  Founding scientist – Dr. Brenda Gallie

Training Programs

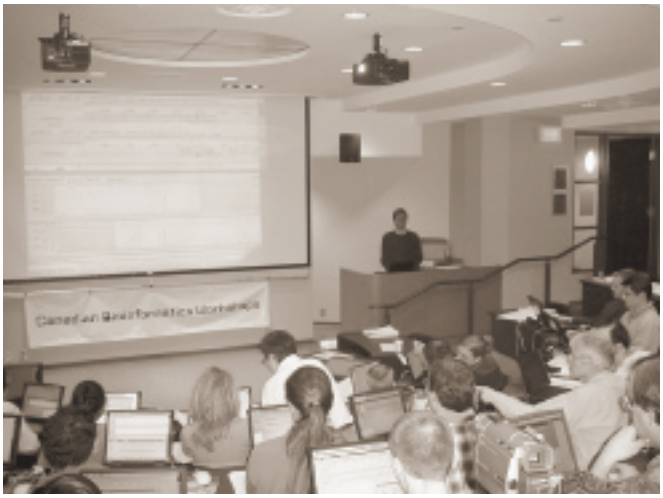
CGDN works with academic partners to provide a unique training environment that promotes research excellence. Our objective is a broad learning base with access to training in the best laboratories. CGDN sponsors training initiatives such as the Annual Scientific Meeting to encourage one-on-one interactions between trainees and the senior scientists/mentors within CGDN. In April 2000, CGDN held its Annual Scientific Meeting back-to-back with the international Human Genome Meeting 2000 in Vancouver, and provided support for principal investigators and students to attend. The result was significantly increased participation in the meeting by CGDN scientists and a higher profile for the Network on the international stage.

CGDN also leverages funds through its cost-shared fellowship and studentship programs with research institutions and disease foundations including, for the first time this year, an award made by the Canadian Gene Cure Foundation. The Foundation is a federal charity incorporated by CGDN to raise funds for the benefit of human genetic disease research in Canada. CGDN also ran another successful summer studentship program which provided support for 20 undergraduates to work in Network labs for three months.

Canadian Bioinformatics Workshops – A New National Training Program

In the past year CGDN pioneered a new national training program in bioinformatics. Taking full advantage of the small number of bioinformaticians across the country, CGDN created the Canadian Bioinformatics Workshops. The objective of the workshop series is to provide practical hands-on introduction to the methodology and algorithms underlying successful development and use of bioinformatics software. Led by Francis Ouellette, Director of CGDN's core facility in bioinformatics and organized by Stephen Herst, the series is an integrated series of four one- and two-week workshops: *Bioinformatics, Genomics, Proteomics* and *Developing the tools*. Students who successfully complete three workshops receive a certificate in bioinformatics, accredited by the universities of British Columbia, New Brunswick and Toronto and the Biotechnology Human Resource Council.

The workshops have proved to be so popular that CGDN has had to double the number of places available. Participants have included graduate students, post-doctoral fellows and professors as well as computer scientists, industry researchers and managers and scientists from federal laboratories. Over 160 have participated in the first year and 25 completed the new certificate in bioinformatics. The workshops have received pilot funding from the Sectoral Partnerships Program of Human Resources Development Canada, Burroughs Wellcome Fund, Merck Genome Research Institute, Alberta Heritage Foundation for Medical Research and substantive in-kind support from the National Research Council of Canada, SUN Microsystems Inc. and SGI Canada Inc.



Genomics workshop at SFU Harbour Centre, January 2000

The workshop series will run again in 2001 on the following dates:

Bioinformatics	Calgary	May 14 – 26, 2001
Mass spectrometry applications in proteomics – *planned*	Edmonton	June 8 – 10, 2001
Proteomics	Edmonton	June 11 – 16, 2001
Genomics	Fredericton	July 16 – 21, 2001
Developing the Tools	Toronto	Aug 27 – Sept 1, 2001
NCBI toolkit – *planned*	Vancouver	Oct 15 – 27, 2001

REVIEW ENGAGEMENT REPORT

To the Members of
Canadian Genetic Diseases Network

We have reviewed the non-consolidated statement of financial position of Canadian Genetic Diseases Network as at March 31, 2000 and the non-consolidated statements of activities and changes in net assets and cash flows for the year then ended. Our review was made in accordance with generally accepted standards for review engagements and accordingly consisted primarily of enquiry, analytical procedures and discussion related to information supplied to us by the company.

A review does not constitute an audit and consequently we do not express an audit opinion on these financial statements.

Based on our review, nothing has come to our attention that causes us to believe that these financial statements are not, in all material respects, in accordance with generally accepted accounting principles.

COLLINS BARROW
CHARTERED ACCOUNTANTS
Vancouver, Canada
July 17, 2000

Non-Consolidated Statement of Financial Position
Year-end March 31, 2000
(Unaudited)

ASSETS		
Assets		
Cash and term deposits	$	464,694
Accounts receivable		6,686
Due from administrator (note 3)		958,191
		1,429,571
Investment in and advances to subsidiary (note 4)		51,402
Capital assets (note 5)		18,377
	$	1,499,350
LIABILITIES		
Current liabilities		
Accounts payable and accrued liabilities	$	4,000
Deferred contributions (note 6)		878,075
		882,075
CAPITAL		
Unrestricted net assets		617,275
	$	1,499,350

Approved by:

Ron Woznow
Chief Executive Officer & Director

Non-Consolidated Statement of Activities and Changes in Net Assets
Year-end March 31, 2000
(Unaudited)

Revenue		
Federal government grants (note 8(b))	$	4,668,271
Provincial government grants		241,000
Registration workshop fees-Bioinformatics		99,100
Industry/Foundations-Bioinformatics		80,584
Cost recoveries and other		89,543
		5,178,498
Expenditures		
Amortization		8,712
Bioinformatics workshops		289,055
Commercial research		623,046
Core research		3,145,510
Research administration and general		468,314
Research training		306,259
Start-up funding		44,840
		4,885,736
Excess of operating revenue over expenditures for the year		292,762
Gain on sale of investments (note 8(c))		300,000
Net results for the year		592,762
Unrestricted net assets, beginning of the year		24,513
Unrestricted net assets, end of the year	$	617,275

Notes to the Non-Consolidated Financial Statements
Year-end March 31, 2000
(Unaudited)

1. Nature of activities

Canadian Genetic Diseases Network ("CGDN") is a not-for-profit corporation incorporated on March 3, 1998 under the Canada Corporations Act. The corporation commenced its operations on April 1, 1998. The net assets and excess of revenue over expenses of the corporation are not available for the personal benefit of any member.

The federal government of Canada has selected CGDN to receive core funding under its Networks of Centres of Excellence Program ("NCE") and has charged the Medical Research Council with administrative responsibility for overseeing CGDN. The Medical Research Council, CGDN, and the University of British Columbia ("UBC") have entered into a Funding Agreement dated April 1, 1998 which outlines the terms and conditions pursuant to which the CGDN is to receive core funding of $4,500,000 during each of fiscal 1999, 2000, 2001 and 2002.

Under the Funding Agreement, UBC, on behalf of and as directed by CGDN, has agreed to: a) provide suitable space and facilities; b) receive and distribute grant funds to eligible participating institutions; and c) provide ongoing accounting and annual financial reporting for the NCE funds.

The specific objectives of CGDN are to:

- promote advances in genetics research related to common diseases;
- provide scientific participants with access to technology to derive insights on the molecular mechanisms of disease;
- develop the basis for novel therapies and related diagnostics;
- foster the application of genetic discoveries in health care;
- provide new Canadian venture investment opportunities and jobs;
- provide trainees with new skills related to emerging employment opportunities;
- build an endowment fund to support CGDN research and development after the current NCE mandate is completed.

The Biotechnology Canada Human Resource Council ("BHRC") has selected CGDN to develop and implement a Canadian bioinformatics capability development program in Canada. BHRC and CGDN have entered into a contract dated February 17, 1999 which outlines the terms and conditions pursuant to which CGDN is to receive a total of about $400,000 during fiscal 2000 and 2001 to fulfill the terms of the contract. The contract expires October 31, 2000.

2. Significant accounting policies

a) Capital assets

Capital assets are recorded at cost. Amortization is provided on a straight-line basis over the assets' estimated useful lives, which for furniture and equipment is 5 years and for computer equipment is 3 years.

b) Revenue recognition

CGDN follows the deferral method of accounting for contributions. Restricted contributions including federal grant revenue received under the NCE and BHRC programs are recognized as revenue in the year in which the related expenditures are incurred. Unrestricted contributions are recognized as revenue when received or receivable if the amount to be received can be reasonably estimated and collection is reasonably assured. Endowment contributions are recognized as direct increases in net assets. The benefit of donated services is not recognized in the financial statements.

3. Due from administrator

The amount due from UBC represents the balance of unexpended NCE and provincial government grants and other funds on hand as at March 31, 2000. These funds are committed to various research projects and will be expended in fiscal 2001.

4. Investment in and advances to subsidiary

The investment in subsidiary is recorded at cost. During the current year, the subsidiary was inactive and did not have any results of operations.

CGDN Ventures Inc. (100%)	
Shares	$ 1
Advances, without interest or fixed repayment terms	51,401
	$ 51,402

5. Capital assets

	Cost	Accumulated Amortization	Net Book Value
Computer equipment	$ 24,710	$ 8,236	$ 16,474
Furniture and equipment	2,379	476	1,903
	$ 27,089	$ 8,712	$ 18,377

6. Deferred contributions

Deferred contributions represent unspent funding from NCE, BHRC, provincial government, and Burroughs Wellcome Fund. The deferred contributions are committed to research and training projects in fiscal 2000.

NCE	$ 816,636
BHRC	–
Provincial government	–
Burroughs Wellcome Fund	61,439
	$ 878,075

7. Economic dependence and related party transactions

As described in note 1 CGDN receives substantially all of its funding from the NCE and the BHRC.

CGDN is dependent upon UBC for its administration of the NCE and provincial government grants and for the provision of office premises and certain capital assets on a rent-free basis. UBC does not receive fees for administrative services.

Substantially all of the core research and research training expenditures are paid to eligible participating institutions, including UBC, who are members of the corporation in their capacity as researchers.

8. Other information

a) Financial instruments

The carrying amounts of CGDN's financial instruments, which include due from administrator approximate fair value due to their short maturities. CGDN is not exposed to credit or interest rate risks.

b) Federal government grant revenue

NCE funds received	$ 4,500,000
BHRC funds received	190,000
	4,690,000
Add: deferred contributions recognized as Revenue in year	
BHRC	17,848
NCE	777,059
Less: deferred contributions, end of the year	(816,636)
	$ 4,668,271

c) Gain on sale of investments

CGDN received certain share investments as consideration for start up funds. All of the shares were sold during the year for a gain of $300,000.

d) Agency arrangement

CGDN acts as a nominee and agent on behalf of the Canadian Gene Cure Foundation, a registered charitable organization, in connection with certain investments. The entities are related due to certain directors being common to both.

In addition, CGDN acts as advisor for the Canadian Gene Cure Foundation and during the year ended March 31, 2000 received fees of $15,000.

Scientists & Institutions

John P. Robarts Research Institute, London
Dr. Robert Hegele

Hospital for Sick Children, Toronto
Dr. John Dick
Dr. Roderick McInnes
Dr. Brian Robinson
Dr. Chaim Roifman
Dr. Johanna Rommens
Dr. Stephen Scherer
Dr. Lap-Chee-Tsui

London Health Sciences Centre, London
Dr. George Ebers

McGill University, Montreal
Dr. Philippe Gros

Montreal Children's Hospital Research Institute
Dr. Rima Rozen
Dr. Charles Scriver

Montreal General Hospital Research Institute
Dr. Tom Hudson
Dr. Ken Morgan
Dr. Guy Rouleau
Dr. Erwin Schurr
Dr. Emil Skamene

McMaster University, Hamilton
Dr. Michael Rudnicki

Mount Sinai Hospital, Toronto
Samuel Lunenfeld Research Institute
Dr. Joseph Culotti
Dr. Andras Nagy
Dr. Tony Pawson
Dr. Janet Rossant
Dr. Kathy Siminovitch

Ottawa General Hospital
Ottawa Hospital Research Institute
Dr. Dennis Bulman
Dr. Ronald Worton

Laval University, Quebec
Centre Hospitalier Universitaire de Québec: Pavillon Saint- François d'Assise
Dr. Régen Drouin
Dr. François Rousseau

Centre de recherche; Pavillon Robert-Giffard
Dr. Chantal Mérette

University of Alberta, Edmonton
Dr. Diane Cox
Dr. Norman Dovichi
Dr. Michael Walter
Dr. Rachel Wevrick

University of British Columbia, Vancouver
Dr. Lorne Clarke
Dr. Pieter Cullis
Dr. Frank Tufaro

Centre for Molecular Medicine and Therapeutics
Dr. Michael Hayden
Dr. Phil Hieter
Mr. Francis Ouellette

University of Calgary
Dr. Leigh Field
Dr. Roy Gravel
Dr. Frank Jirik

University of Manitoba, Winnipeg
Dr. Barbara Triggs-Raine
Dr. John Wilkins

University of Montreal
Hôpital Sainte-Justine
Dr. Grant Mitchell
Dr. Daniel Sinnett

University of Ottawa
Children's Hospital of Eastern Ontario
Dr. Joh-E Ikeda
Dr. Robert Korneluk
Dr. Alex MacKenzie

University of Toronto
Banting & Best
Dr. James Friesen
Dr. Jack Greenblatt
Dr. David MacLennan
Centre for Research in Neurodegenerative Disease
Dr. Peter St George-Hyslop
Eye Research Institute
Dr. Elise Héon
Ontario Cancer Institute
Dr. Brenda Gallie
Dr. Jeremy Squire
Women's College Hospital
Dr. Steven Narod

University of Victoria
Dr. Benjamin Koop

Industrial Partners:

Allelix Biopharmaceuticals
Canadian Medical Discoveries Fund
IBEX Technologies Inc.
INEX Pharmaceuticals Corp.
GeneChem Technologies
Merck Frosst Canada Inc.
StressGen Biotechnologies Corp.

Industrial Affiliates:

Affymetrix
Alcan Aluminum Ltd.
Amgen Inc.
Apotex
Astra Zeneca
ApoptoGen Inc.
Bayer Corp.
Bristol-Myers Squibb
Burroughs Wellcome
CGDN Ventures Inc.
Caldwell
Computing Devices Canada
Ecogenix Inc.
Ellipsis
Exella Ventures Inc.
Genexyn Pharmaceuticals Inc.
Genzyme Corp.
Millennium Pharmaceuticals Inc.
NeuroVir Therapeutics Inc.
Pinnacle Reefs
RGS Genome Inc.
Rx&D
Schering Canada Inc.
Sequella Inc.
SignalGene Inc.
Solutions by Sequence Inc.
T^2C^2
University Medical Discoveries Inc.
Variagenics
XENON Genetics Inc.

Non-profit Affiliates:

Alberta Heritage Foundation for Medical Research
Amyotrophic Lateral Sclerosis Society
Armaurer Hansen Research Institute
Arthritis Society of Canada
Association Français Contres les Myopathies
B.C. Research Institute for Children's and Women's Health
Canadian Breast Cancer Research Initiative
Canadian Cystic Fibrosis Foundation
Canadian Dermatology Foundation
Canadian Diabetes Association
Canadian Gene Cure Foundation
Cancer Research Society
Children's Hospital of Eastern Ontario Research Institute
Families of Spinal Muscular Atrophy
Fondation Contre des Maladies du Coeur du Québec
Foundation for Fighting Blindness
Foundation for Gene and Cell Therapy
Glaucoma Research Foundation
Glaucoma Research Society of Canada
Heart & Stroke Foundation of Canada
Heart & Stroke Foundation of Ontario
Hereditary Disease Foundation
Hospital for Sick Children
Howard Hughes Medical Research Institute
Huntington Society of Canada
Huntington Disease Society of America
Juvenile Diabetes Foundation International
Kidney Foundation of Canada
Lloyd Carr-Harris Foundation
Lotte & John Hecht Memorial Fund
Macular Vision Research Foundation
Montreal General Hospital Foundation
Montreal General Hospital Research Institute
Muscular Dystrophy Association
Muscular Dystrophy Association (USA)
Multiple Sclerosis Society of Canada
Multiple Sclerosis Society of Canada Foundation
National Cancer Institute (USA)
National Cancer Institute of Canada
National Center for Human Genome Research
National Institutes of Health
Ottawa Hospital Research Institute
Parkinson Foundation of Canada
Restless Legs Syndrome Foundation
Terry Fox Foundation
University of Alberta
University of British Columbia
University of Toronto

Government Affiliates:

Biotechnology Human Resource Council
Fonds de la recherches en santé du Québec
Human Resources Development Canada
Medical Research Council of Canada / CIHR
National Research Council of Canada
Province of British Columbia
US Department of National Defense
US Army

Board of Directors:

Mr. David Arkowitz
Controller, MRL
Merck & Co., Rahway, NJ

Dr. Norman Dovichi
Professor of Chemistry,
University of Alberta, Edmonton

Mr. Richard Glickman
Vice-Chairman,
StressGen Biotechnologies Corp.,
Victoria

Dr. Michael Hayden
Scientific Director,
Canadian Genetic Diseases Network,
Vancouver

Dr. Robert Heft
President & Chief Operating Officer,
IBEX Technologies Inc., Montreal

Mr. Louis Lacasse
President,
GeneChem Technologies Venture Fund,
Laval

The Rt. Hon. Don Mazankowski, PC, OC
Vegreville, Alberta

Mr. Maurice Mourton
Tsawwassen, B.C.

Dr. Heather Munroe-Blum
Vice President of Research &
International Relations,
University of Toronto

Dr. Martha Piper
President,
University of British Columbia,
Vancouver

Dr. Calvin Stiller
Chairman & Chief Executive Officer,
Canadian Medical Discoveries Fund
Inc., London

Mr. Graham Strachan
President and Chief Executive Officer,
Allelix Biopharmaceuticals Inc.,
Mississauga
(to March 2000)

Dr. Ronald Worton
Associate Scientific Director,
Canadian Genetic Diseases Network,
Ottawa

Management – Scientific:

Scientific Director
Dr. Michael Hayden
Professor of Medical Genetics,
University of British Columbia
Director, Centre for Molecular Medicine
and Therapeutics, Vancouver

Associate Scientific Director
Dr. Charles Scriver
Alva Professor of Human Genetics,
McGill University, Montreal

Associate Scientific Director
Dr. Ronald Worton
CEO & Scientific Director
Ottawa Hospital Research Institute

Director, Scientific Advisory Board
Dr. Lap-Chee Tsui
Geneticist-in-Chief,
Head of Genetics and
Genomic Biology Program,
Hospital for Sick Children, Toronto
H.S. Sellers Chair in Cystic Fibrosis,
Professor of Molecular &
Medical Genetics,
University of Toronto

Management – Corporate:

Chief Executive Officer
Dr. Ron Woznow

Managers
Dr. Louise Desjardins
New Developments

Mr. Stephen Herst
Scientific Affairs & Training

Ms. Carol Smith
Finance & Administration

Office Administrator
Ms. Nicole Langlands-Kotnik

CANADIAN GENETIC DISEASES NETWORK
RÉSEAU CANADIEN DE MALADIES GÉNÉTIQUES

Canadian Bioinformatics Workshops

Canadian Genetic Diseases Network
NCE Building at UBC
351 - 2125 East Mall
Vancouver, B.C. Canada V6T 1Z4
Tel: (604) 822-7886
Fax: (604) 822-7945
email: admin.cgdn@ubc.ca
www.cgdn.generes.ca

Designed by Poissy Design Inc. Printed in Canada