

BC Research Institute for Children's & Women's Health
2002/2003 Report



Research that Matters.

OUR VISION:

Healthy children and women through excellence in discovery and application.

OUR MISSION:

To attract and support a community of researchers who will discover, disseminate and integrate new knowledge for the benefit of children's and women's health worldwide.

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Introduction

“Our aspirations are our possibilities,” said Samuel Johnson. At the BC Research Institute for Children’s & Women’s Health we aspire to the goal of healthy women and children in BC and around the world.

Our researchers are studying the entire spectrum of influences on the health of children and women in our complex world. In our multi-disciplinary environment, more than 230 investigators and their research teams are encouraged to seek novel research discoveries directly benefiting women and children. Their research spans the continuum of translational research – a long line of innovative enquiry that stretches from lab to clinic to community and beyond.



To support our investigators’ pioneering work, the Research Institute provides funding, infrastructure and state-of-the-art facilities. We are located on the site of the Children’s & Women’s Health Centre of BC, the largest clinical service of its kind in Canada, and most of our investigators hold faculty positions with our other partner, the prestigious University of British Columbia. Our investigators engage in collaborations locally, nationally and internationally.

In this report, we’ll tell you more about our thriving community of research excellence, and about some of the people who benefit from our work. We’ll also profile a few of the hundreds of investigators who work at our institute – people who daily transform inspiration into reality, conducting research that matters to the lives of children and women.

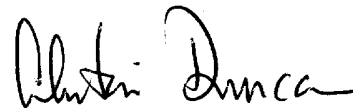
Board & Executive Message

BOARD MESSAGE

On any journey there are always milestones to mark important moments of passage. This last year has indeed been a landmark one for the BC Research Institute for Children's & Women's Health. With the infusion of new energy brought by the Research Institute's new Executive Director, Stuart MacLeod, and Scientific Director, Geoff Hammond, the Institute has an increased sense of momentum and purpose. The Research Institute is gaining a position as a major player in the larger research community, both nationally and internationally, and its researchers are expanding their knowledge daily – resulting in opportunities for improved health of women and children around the world. I know I express the view of all our Board members in saying it is very exciting to be involved in such an enterprise.

Of course, such progress is possible only through partnerships and collaborations. On behalf of the Research Institute Board, I extend thanks to our partners, the University of British Columbia, the Children's & Women's Health Centre of BC and its parent organization, the Provincial Health Services

Authority. Our continued partnership serves to encourage the creation and transfer of knowledge. Our appreciation also extends to B.C.'s Children's Hospital and Sunny Hill Health Centre for Children Foundations and several provincial and national funding agencies, who make possible our research. Special thanks go to Mike Mahony for an excellent term as Interim Executive Director while we recruited the Research Institute's new leadership. And of course, our continued appreciation goes to the Research Institute's staff, its investigators and their research teams; it is a great honour to work on their behalf.



Mr. Alistair Duncan
Board Chair



Mr. Alistair Duncan
Board Chair



Dr. Stuart MacLeod
Executive Director



Dr. Geoffrey Hammond
Scientific Director

EXECUTIVE MESSAGE

The spirit of discovery is one of curiosity, enthusiasm, courage and faith. As Joseph Campbell said, "Jump. It is not as wide as you think." He meant, of course, that forging ahead and making creative leaps into the unknown are the keys to success in life.

Every day at the BC Research Institute for Children's & Women's Health, researchers respond to the health needs of today's society, taking tremendous leaps forward in improving the health of women and children. Investigators at our Research Institute are studying the entire spectrum of health determinants, from the genetic and cellular interactions that regulate the body's development and determine susceptibility to disease, to the impact of community support and public policy on populations. While there is only room in this report to feature a handful of our researchers and those who benefit from their work, many hundreds more scientists and their research teams are working to benefit millions of children and women.

It has been our great pleasure in the last year to join this vibrant, rapidly evolving research culture, and to work with such dedicated investigators, research teams, staff and Board members.

We have taken many steps to solidify and enhance the structure of the Institute to support and improve its future research capacity. In addition to implementing a Scientific Steering Committee to work with us on setting direction, we have restructured our research programs to better capitalize on the diverse strengths at the Institute. We are in the final planning stages, preparing to add more than 100,000 square feet of lab space to accommodate the growth we are now experiencing and to support our investigators in their work.

The Research Institute has been incredibly fortunate to have, over the years, attracted many great talents – outstanding clinical, population health and biomedical investigators and trainees. Future research successes will depend on our ability to attract and retain these rising stars and international leaders. We can achieve this by ensuring their success in securing funding and facilitating rapid establishment and operation of their new laboratories and research programs. New support programs in research technology and development, informatics and research education training are currently being developed and implemented, with support from the Michael Smith Foundation for Health Research.

2002/03 Board & Board Committees

Board Members

Mr. Alistair Duncan (Chair)
Mr. Maurice Mourton (Vice Chair)
Mr. Dennis Bettiol (Secretary-Treasurer)
Dr. Don Brooks
Dr. John A Cairns
(Alternate: Dr. Alison Buchan)
Mr. David Choi
Mr. Alan D Grimston
Dr. David Hardwick
Ms. Helen Low
Mr. Michael Marchbank
(Alternates: Ms. Sharon Toohey/
Dr. Liz Whynot)

Mr. Jim Rattenbury
Ms. Ann Sturrock
Dr. Stuart MacLeod (ex officio)
Ms. Sue Carruthers (by invitation)

Board Executive Committee

Mr. Alistair Duncan (Chair)
Mr. Maurice Mourton (Vice Chair)
Mr. Michael Marchbank
(Alternates: Ms. Sharon Toohey/
Dr. Liz Whynot)
Dr. Stuart MacLeod (ex officio)

Finance and Audit Committee

Mr. Dennis Bettiol (Chair)
Ms. Helen Low
Mr. Jim Rattenbury
Mr. Alistair Duncan (ex officio)
Mr. Maurice Mourton (ex officio)
Ms. Donna Hart (non-voting member)
Dr. Stuart MacLeod (ex officio)
Mr. Richard Hunter (by invitation)

Nominating Committee

Mr. Alan Grimston (Chair)
Dr. John Cairns
Ms. Ann Sturrock
Mr. Alistair Duncan (ex officio)
Mr. Maurice Mourton (ex officio)
Dr. Stuart MacLeod (ex officio)

Notes:

1. Chair is ex officio on the Finance and Audit and the Nominating Committees.
2. Vice-Chair is ex officio on the Finance and Audit and the Nominating Committees.
3. Executive Director is ex officio on the Finance and Audit and the Nominating Committees.
Dr. MacLeod is also ex officio on the Board Executive Committee.

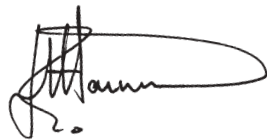
Each day the Research Institute's investigators expand their knowledge – resulting in opportunities for improved health of women and children around the world.

— MR. ALISTAIR DUNCAN, *Board Chair*

This past year, we've seen an increase in research funding, bringing to over \$27 million the external funding attracted by our researchers. The Institute has seen steady funding growth, and our goal is to double it again in the next five to six years. With increased funding, space and research infrastructure support, the Research Institute is poised for the future, in our role as one of the world's premier academic centres in women's and children's health. The gap is not wide at all – in fact, we have already taken the leap, and the solid foundation of higher ground is almost under our feet. With that said, we hope you'll join us in celebrating the Research Institute's past, continuing and future success.



Dr. Stuart MacLeod
Executive Director



Dr. Geoffrey Hammond
Scientific Director

Research Institute Overview

OUR INSTITUTE

Established in 1995, the BC Research Institute for Children's & Women's Health is dedicated to advancing the health of women and children. We operate in partnership with the University of British Columbia (UBC) and the Children's & Women's Health Centre of BC (C&W), part of the Provincial Health Services Authority.

We are situated on the 46-acre grounds of C&W, where many of our investigators have clinical practices. C&W is the largest maternal-fetal-newborn clinical service in Canada. It has more than 400 in-patient beds, and is the major referral centre in BC for acutely ill or injured children. More than 20,000 women are seen annually through its specialized women's health programs.

Our state-of-the-art facilities include a well-equipped education and study centre in support of our teaching mandate. We have 163,000 sq. ft. of wet and dry laboratory space, and an additional 110,000 sq. ft. research building is in the final planning stages. Once completed, our institute will be one of North America's largest and best-equipped research centres devoted to children and women.

A key role of the Research Institute is supporting individual investigators and research teams. A significant portion of our annual operating budget is allocated to merit-based awards, including career and establishment awards, as well as postdoctoral fellowships and graduate student awards. We also provide infrastructure and a number of core services – such as financial management, communications and contract negotiation support – to facilitate investigators' ability to conduct research. The Research & Education Services office coordinates all aspects of grants funding, from application to record keeping and reporting. It also provides advanced educational opportunities to researchers and trainees.

In addition, we've established a Research Technology Development office to foster collaborative research endeavours, and we are developing an Integrated Informatics Resource to provide researchers with better access to newly available databases and informatics approaches.



OUR RESEARCH

At the Research Institute more than 230 investigators work alongside hundreds of graduate students, postdoctoral fellows, research technicians and assistants. Their research activities are organized by programmatic and crosscutting themes.

Programmatic Themes

Our seven programmatic themes are areas of research excellence with focus on major fields of children's and women's health:

Community Child Health Research: Investigators with the Centre for Community Child Health Research work to understand the biological, behavioural and social determinants of health and to transfer research findings to practice in the broader health community. Areas of study include health promotion, injury prevention, biobehavioural research, and population health.

Diabetes: Through innovative and multi-disciplinary basic and clinical research, investigators aim to improve the lives of children with diabetes. Areas of focus are: genetics of type 1 diabetes; islet cell biology and transplantation; viral pathogenesis of diabetes; immunology of type 1 diabetes; and clinical diabetes research.

Health Innovation & Improvement: The focus of the Centre for Healthcare Innovation & Improvement is the effective translation of biomedical, clinical and population research into policies and practices that improve health care. Research concerns include evidence-based medicine, knowledge transfer through national information exchange networks, disease mapping, and drug safety.

Infectious & Inflammatory Diseases: Investigators with this program work to enhance care for children with infectious and inflammatory diseases. Their research focuses on increasing knowledge about the causes, therapies and prevention of infectious diseases, and on discovering the cellular and molecular interactions that underlie the normal and abnormal responses of the immune system.

Molecular Medicine & Therapeutics: The Centre for Molecular Medicine & Therapeutics is dedicated to understanding the molecular and cellular basis of disease and to transferring research into effective clinical and therapeutic strategies. The centre brings together scientists studying neurodegeneration, the genetics of behaviour, the genetics of cancer, the development of animal models of human disease, bioinformatics, and intracellular trafficking.

Oncology: Investigators are carrying out cutting-edge research on new and improved strategies for treating cancer in children and women. In particular, investigators are working to identify and target the genetic and molecular alterations that disrupt signal transduction pathways and give rise to childhood and female-specific cancers.

Reproductive Health: The focus of this program is basic science and clinical research of the reproductive health of women over the life span. Investigations are targeted at understanding infertility, early pregnancy loss, congenital anomalies, pregnancy complications, preterm birth, pre- and post-partum depression and reproductive cancers.

More than 230 investigators work alongside hundreds of research team members at the BC Research Institute for Children's & Women's Health. To support their work, the Research Institute provides funding and infrastructure, core services, and state-of-the-art facilities.



Crosscutting Research Themes

Our crosscutting themes represent research exploration across programs. Investigators associated with crosscutting research areas work collaboratively with one or more of the main programmatic themes:

Clinical Investigation: More than 2/3 of our researchers are clinically-based at the Children's & Women's Health Centre of BC, which is comprised of three leading health care facilities. Clinical investigators oversee clinical trials and assist in pre-clinical evaluation and validation of new technologies, diagnostics and therapeutic interventions.

Genetics: Investigators in this area are members of several programmatic themes and provide access to advanced platform technologies, allowing for the quick and efficient application of new discoveries in genetics.

Immunology & Transplantation: Researchers are working to better understand the immunophysiology and immunopathology of pediatric illnesses and develop new diagnostic techniques and treatment interventions.

Informatics: Bioinformatics combines biological information, with the help of computer tools, to further understanding of the data being generated on genetic sequences and biomedical structures and interaction. Health informatics is a rapidly expanding area that uses expertise in data management, computational sciences and information systems to link health databases and improve health care planning.

Neurobiology & Mental Health: This is an emerging crosscutting theme. A number of researchers at our institute specialize in areas such as child and adolescent psychiatry, neonatology, developmental pediatrics, rehabilitation medicine, neuropathology, and neuro-imaging.

Nutrition: The Nutrition Research Program works to develop innovative nutritional strategies for preventing and managing disease, and supporting children in reaching their maximum potential for physiological and neurological development and health throughout life. Nutrition-related health problems are addressed from the molecular and cellular level to that of clinical practice and population health.

In addition to our main programmatic and crosscutting themes, there are other areas of study for groups of researchers at our institute. For example, investigators with the Cardiovascular Sciences Program are working to identify and understand the genes responsible for congenital heart disease, and collaborate with pediatric cardiac surgeons and cardiologists to reduce the risks of open-heart surgery for babies born with heart disease.

For more information on research at our institute, please see our website at www.bcricwh.bc.ca

Our Partners

OUR PARTNERS

The BC Research Institute for Children's & Women's Health operates in partnership with the University of British Columbia and the Children's and Women's Health Centre of BC – part of the Provincial Health Services Authority.

University of British Columbia (UBC)

UBC is one of Canada's top research universities, with particular strength in the areas of medicine, biotechnology, and chemistry. UBC is associated with four major teaching hospitals in Vancouver: Children's & Women's Health Centre of BC, BC Cancer Agency, St. Paul's Hospital and Vancouver Hospital and Health Sciences Centre. UBC currently holds the first position in Canada Foundation for Innovation (CFI) funding for new research infrastructure, as well as the number one position among the top research-intensive institutions for overall funding from CFI.

For more information: www.ubc.ca

Children's & Women's Health Centre of BC (C&W)

The Children's & Women's Health Centre of BC is the primary site for the UBC Faculty of Medicine Departments of Pediatrics, Obstetrics and Gynecology, and Medical Genetics. C&W is the largest maternal-fetal-newborn clinical service in Canada. As a teaching hospital and major provincial health care resource, C&W has more than 400 in-patient beds and is comprised of three health care facilities: B.C.'s Children's Hospital, Sunny Hill Health Centre for Children, and BC Women's Hospital & Health Centre.

B.C.'s Children's Hospital (BCCH) is home to many specialized pediatric services available nowhere else in the province, including BC's trauma centre for children, neonatal intensive care, kidney and blood and marrow transplants, open heart surgery, neurosurgery and cancer treatment. The hospital also provides developmental and rehabilitation services to children throughout the province and offers a full spectrum of health services for child-bearing women and their babies.

Sunny Hill Health Centre for Children is a provincial facility that offers specialized services to children and youth with developmental disabilities. It offers interdisciplinary assessment, consultation, referral, and, in select cases, treatment for children with complex disabilities. Services are delivered on site, or in communities throughout the province through travelling clinics or telehealth consultations.

BC Women's Hospital & Health Centre is the province's only facility devoted exclusively to the health of women, newborns and families. It provides the highest level of care to pregnant women and newborns throughout BC, with province-wide services including its Medical Genetics program, the Centre for Prenatal Diagnosis and Treatment, the Maternal and Infant Transport services, and the Special Care Nursery (neonatal intensive care unit). It is one of the country's busiest and largest obstetrical centres. More than 20,000 women are seen annually through its specialized women's health programs, which include world-class services in breast health, substance dependency, osteoporosis, HIV/AIDS and reproductive health.

For more information: www.cw.bc.ca

DONATING TO RESEARCH

Research at our institute would not be possible without the support of generous donors through B.C.'s Children's Hospital Foundation.

Since 1982, **B.C.'s Children's Hospital Foundation** has raised funds to help pay for essential needs – such as equipment, research, patient programs and education – of the only pediatric hospital in British Columbia, B.C.'s Children's Hospital. The foundation also raises funds for Sunny Hill Health Centre for Children, which offers specialized services for children with complex disabilities.

To make a donation to support the research of the BC Research Institute for Children's & Women's Health, or for more information, see the B.C.'s Children's Hospital Foundation website at www.bcchf.ca

Research that Matters

From investigations into reproductive health and the genetic underpinnings of disease, to treatments for devastating childhood illnesses and the translation of research into policies and practices to improve health care, our researchers are making pioneering discoveries that make a difference in the lives of women and children.



At the Research Institute, we're inspired knowing our work makes a difference in the lives of women and children. On the following pages we feature a few of the institute's hundreds of researchers engaged in studying children's and women's health. We'll also tell you stories of a few of the women and children to whom this research matters.

As Stephanie Hart is well aware, pregnancy involves complex interactions between the mother and fetus - and it's even more complicated when the mother's health is compromised by disease. Stephanie thought she'd never be able to have children, but thanks to research advances and the exceptional care provided at our partner organization, Children's & Women's Health Centre of BC, Stephanie had a safe and fulfilling pregnancy.

In developed societies such as Canada, a variety of socio-economic factors have led many women to delay pregnancy. Unfortunately, these delays can lead to increased risk of infertility, miscarriage, and pregnancy complications. Our investigators are conducting research into these and other aspects of women's health, including cancers of the reproductive system.

Our investigations into childhood cancer have made all the difference for little Dominique Marcotte, who was diagnosed with neuroblastoma. As the provincial centre for childhood cancer research and a leader in many North American clinical trials of cancer drugs, we're making tremendous leaps in treating this devastating disease.

Children's health is the focus of many of our lab and clinical investigators. Research efforts in immunology and transplantation are exploring how defects of the immune

system underlie a number of pediatric illnesses. Molecular medicine and genetics researchers are making groundbreaking discoveries into the ways complex cellular functions are performed, and into methods to detect genetic susceptibility to disease. Nutrition is a factor in gene regulation as well as physical and cognitive development, and researchers are exploiting nutritional strategies to prevent and treat many chronic conditions. Other studies in areas of neurobiology and mental health are looking at the causes and treatments of autism, attention deficit disorders and neurological conditions.

Children are exposed daily to bacteria and viruses, and our research is also directed at infectious diseases such as tuberculosis, influenza, hepatitis, meningitis, HIV/AIDS and emerging problems such as SARS. In addition, we're home to unique programs such as the Vaccine Evaluation Centre, and a program to foster best use of antibiotics to slow the spread of antibiotic-resistant bacteria.

The translation of biomedical, clinical and population research into policies and practices that improve health care is important to Janice Bennett, who relies on the health system to provide her two boys with fast, effective care. Our community and population health researchers are working with collaborative networks of policy makers and clinicians to make the health system the best it can be, and are studying areas as diverse as population-based epidemiology, injury prevention, and drug safety and effectiveness.

Of course, this is just a brief introduction to the innovative research being done here. On the following pages, you'll see more. And for further information, be sure to see our website at www.bcriwh.bc.ca



Stephanie Hart and her husband Derek had always wanted children, but after a lengthy illness Stephanie was told at age 24 she had a vascular disease affecting blood flow to her legs, bowel and kidneys. Because the blood circulatory systems of the mother and fetus are intimately connected, Stephanie didn't think she'd ever be able to have a child. However, with recent advances in health care, Stephanie decided to give it a try.

Using innovative technologies and research methods, our lab and both the pregnant and non-pregnant state. Researchers are also improve diagnosis, prevention and treatment of both rare and



"Like all other living organisms, our biological imperative is to reproduce, and steroid hormones control almost all aspects of human reproduction," says **Dr. Geoffrey Hammond**, whose focus is the study of steroids.

Sex steroids, such as androgens and estrogens, control our sexual development even before we are born. They also influence our emotions and behaviours and are key regulators of gametogenesis (the production of eggs and sperm). After conception, progesterone produced by the ovary is essential to placental development and the implantation of the embryo into the uterus. Steroids produced by the fetus control its growth as well as the timing of the birth process.

Dr. Hammond is known for his pioneering work on how proteins control the amounts of active steroid hormones in the blood. His recent international collaborations have shown how proteins bind steroids at the atomic level, and to the discovery of how a naturally occurring variation in the sex hormone-binding globulin gene is linked to ovarian dysfunction. "I value collaborative work," says Dr. Hammond. "It is absolutely critical to the advancement of science today."

Using unique transgenic mice developed by students in his lab, Dr. Hammond's group is working with Research Institute investigator Dr. Sheila Innis to identify why the amount of sex hormone-binding globulin in blood is tightly linked to metabolic status. Says Dr. Hammond, "This work will answer fundamental questions about how genes are regulated by metabolic regulators, and could lead to dietary interventions that alter the activities of sex steroids during critical periods of life."



Chromosomes, contained in each of our body's cells, are the storage units of DNA – providing the information necessary for growth and function. Chromosome abnormalities are a significant cause of infertility, pregnancy complication, developmental delay, and cancer.

Medical geneticist **Dr. Wendy Robinson** is an expert on chromosomal abnormalities, including chromosomal mosaicism. Chromosomal mosaicism is a condition in which some cells have different chromosomal makeup; the most common kind of chromosomal mosaicism found at prenatal diagnosis involves trisomy, where the abnormal cells contain 47 chromosomes, rather than the usual 46. During pregnancy the abnormality may be confined to the placenta, and thus contribute to poor fetal growth, or it may be present in the growing fetus, and can lead to malformations or result in the child being born with Down syndrome or other trisomy-associated syndromes.

Little is yet known about the cause of trisomy – though it is often associated with advanced maternal age. Dr. Robinson's goal is to understand the causes and to identify strategies to reduce trisomy incidence. Her research also looks at the impact of chromosomal and other genetic abnormalities on pregnancy outcome, and at what occurs in development to allow some abnormalities to continue to term.

Premature ovarian failure, which Dr. Robinson is also studying, may also be associated with increased risk of trisomy at a younger age. Says Dr. Robinson, "My research will help women who want to conceive at any age. With this research we hope to give them more options for a healthy pregnancy."

Stephanie says her medical team was very supportive: “They told me they were here to help make my pregnancy as healthy as possible.” Throughout her pregnancy, the baby and Stephanie – who’s on medication and at increased risk for pregnancy complications such as pre-eclampsia – were regularly monitored. “I was really well taken care of. It was an awesome experience,” she says. Stephanie adds her 1 1/2 year old daughter Olivia is “just perfect – a lot of joy. She’s made our life complete.”

Now 32, and pregnant again, Stephanie travels monthly from northern BC to Vancouver for check-ups at C&W with health professionals and researchers, who make sure Stephanie’s blood pressure is controlled and her blood coagulating properly, and monitor the baby’s growth and blood supply.

The cause of her illness remains unknown, but Stephanie looks forward to a time when she doesn’t have to be on medication. She adds, “Research is the key to finding a diagnosis and cure. Research is my future.”

clinical investigators are studying how reproductive processes affect a woman’s health, in working to understand the complex interactions that occur within genes – with the goal to common diseases.



Perinatologist **Dr. Peter von Dadelszen** is investigating the hypertensive disorders of pregnancy, particularly pre-eclampsia. Pre-eclampsia is characterized by a sudden rise in blood pressure and loss of protein in the urine. Blood flow becomes restricted, damaging the woman’s organs, the placenta and the fetus; when severe, pre-eclampsia can cause seizures – called eclampsia – or death. Pre-eclampsia occurs in 7-10% of pregnancies, and is the most common cause of maternal death in North America.

The process of pre-eclampsia seems to involve inappropriate activation of the immune system. Dr. von Dadelszen is looking for the cause of the blood vessel inflammation, and ways to modify the inflammatory response to safely prolong pregnancies and accelerate recovery. He says, “Often we’re able to stabilize a woman’s health for even two weeks and that is enough additional time for a healthier delivery.”

Treatment includes medications to lower blood pressure. Currently, the only real cure is delivery – and severe cases may require immediate Caesarean section. Clinicians need to balance risks of prematurity for the fetus against risks to the mother; Dr. von Dadelszen’s translational research and collaboration with local and national networks is informing clinical decision-making about these risks.

Dr. von Dadelszen recently received industry funding for a clinical trial studying recombinant human activated protein C (rhAPC), which has been shown to increase survival in septicaemia (which shares many characteristics with pre-eclampsia), in women with severe pre-eclampsia. He hopes that a disease-modifying therapy, which will probably involve some way of switching off the inflammation of the blood vessels, is only a few years away.

In the body, cell characteristics are established by proteins that interact to perform critical functions. Diverse stimuli define the genetic activity within a cell, specifying which proteins will be produced. Subtle defects in the mechanisms by which cells translate these stimuli into gene activity can have dramatic impacts.

To understand this complex interplay, interdisciplinary fields such as bioinformatics are key. **Dr. Wyeth Wasserman** is a leading bioinformatics specialist focussed on identifying and characterizing the regulatory sequences controlling the activity of genes. He uses computer databases and statistical models to analyse DNA sequences and discover the “on-off switches” that define when genes will be active.

Now that his algorithms have proven effective at finding the switches, Dr. Wasserman is working to prove that mutations in “switches” cause childhood diseases. While most known gene mutations linked to disease change the amino acid sequence of a protein, the first examples of “switch” mutations are emerging – ones that impact the amount rather than the nature of proteins produced. Dr. Wasserman says, “Our research will lead to discovering defects in genes that seemed fine on first inspection.”

Once problems are found, further research can find mechanisms to compensate for, replace or repair altered genes. One project in the Wasserman lab addresses children with retinoblastoma (RB), a cancer affecting the eye. For families with a history of RB, detection of mutations during pregnancy leads to early treatments critical to cancer prevention. Dr. Wasserman’s research offers hope to the 10% of RB families in which the critical mutation in the RB gene hasn’t yet been found.



When **Dominique Marcotte** was diagnosed with neuroblastoma at 10 months of age, her parents Kim and Sylvain alternated between disbelief and imagining the worst. Says Kim, “We were shocked. I hadn’t known babies could get cancer.”

Dominique’s diagnosis came after she’d been brought to B.C.’s Children’s Hospital for what seemed to be the flu. X-rays to check for pneumonia revealed a tumour in her chest. “Things moved very fast,” says Kim. “Tests were done to check the extent of the cancer. When Dominique began the first of four rounds of chemotherapy to shrink the tumour, reality sunk in.”

Many of our researchers are clinically-based at Children’s & specialized pediatric services – including trauma services, are available nowhere else in the province.



Pediatric oncologist **Dr. Kirk Schultz** specializes in blood and marrow transplants in children with leukemia. He’s attempting to understand how the immune system works after transplantation and to discover ways to help a child’s immune system to fight leukemia.

“Blood and marrow transplantation – BMT – is currently the only successful immune-based therapy to treat childhood leukemia,” says Dr. Schultz. The difficulty with BMT is that a complication called graft-versus-host disease (GVHD) can occur; in contrast to the usual situation in which a patient’s immune system rejects a transplanted organ, GVHD results when the transplanted bone marrow immune system rejects the recipient patient.

Dr. Schultz is analysing how GVHD operates. A focus is on the role of the immune system’s recognition of antigens – substances capable of stimulating antibody production and immune response – and he is evaluating drugs targeted at the mechanisms involved in antigen presentation. His lab was the first to show that chloroquine, which is commonly used to treat malaria, can prevent GVHD by inhibiting presentation of antigens.

Combining lab studies of immune signalling processes with clinical trials of new drugs, Dr. Schultz’s lab acts as a reference for several international clinical trials on BMT. In addition, he is working on developing vaccines to augment immune responses against leukemia. He says, “Twenty-five years ago only one-quarter of children with leukemia survived – now the cure rate is 80%, due in part to transplantation. With vaccines we hope in the future to give children non-toxic treatments that utilize their bodies’ own defences to fight or even prevent leukemia.”



In the signal transduction process, signals from outside a cell, such as from hormones or neurotransmitters, interact with receptors on the cell’s surface. The receptor interactions in turn trigger changes within the cell. This signalling process regulates fundamental cellular processes; disruption of it can lead to development of various diseases.

Dr. Catherine Pallen is a molecular cell biologist focussed on a class of enzymes called protein tyrosine phosphatases (PTPs) – key regulators of the signal transduction process. PTPs and protein tyrosine kinases (PTKs) are involved in protein tyrosine phosphorylation, which controls a diverse array of cellular events, including cell growth and survival. It has been known for a while that malfunction of PTKs is involved in the development of cancer. It is also becoming apparent that PTPs are likewise critical. Dr. Pallen explains, “It was once thought that PTPs were involved only in a cell’s housekeeping processes, its routine functions. But we’re finding, for example, that PTP signalling is involved in cancer processes such as metastasis, where cancer cells spread from one part of the body to another.”

By studying PTPs, their regulation processes and the pathways through which they transmit information, Dr. Pallen is able to gain insight into how disease begins. Her aim is to identify specific PTPs as therapeutic targets. Says Dr. Pallen, “If we understand how defective or deregulated PTPs are involved in the development and progression of diseases like cancer, we can begin to develop specifically targeted drugs – ones that turn off or inhibit the functions of only those PTPs involved in cancer development.”

Neuroblastoma is a cancer that affects very young children. It usually begins in the nerve tissue in the chest or abdomen. By the time of diagnosis, it has often spread to the lymph nodes, liver, lungs, or bones and bone marrow. Luckily, Dominique's hadn't spread, but the tumour was too large to immediately remove.

While Dominique underwent chemotherapy, her parents worked to "have patience and faith and be strong for Dominique." They also agreed to participate in studies to further knowledge about childhood cancers. Says Kim, "We know research helped save Dominique's life." Dominique's own treatment

may directly contribute to saving lives – the video of her surgery is used to train new surgeons at UBC.

Dominique is now over two years old, and with each of her follow-up CT scans progressively better (and with a sibling on the way – Kim is pregnant), her long-term outcome looks good. Adds Kim, "The care Dominique has received is incredible. We are so very grateful."

Women's Health Centre of BC, which includes B.C.'s Children's Hospital (BCCH). BCCH offers kidney and blood and marrow transplants, open-heart surgery, neurosurgery, and cancer treatment – that



Geneticist **Dr. Elizabeth Conibear** is a specialist in intracellular trafficking. Her goal is to discover the genes that control the way lipids and proteins are carried between different parts of a cell.

Dr. Conibear examines what happens when the transport, storage and recycling of molecules within cells are blocked. The cells become damaged because proteins and lipids continue to be produced and have no means of travelling to where they are needed. For example, in children with Niemann-Pick Type C, cholesterol and other lipids accumulate in the liver, spleen and brain. She says, "Children with this disease may appear healthy for years. But, eventually they lose coordination and muscle control, and deteriorate mentally." The disease is fatal, and the majority of affected children die before age 20.

To understand how underlying defects in protein and lipid trafficking contribute to human disease, she studies transport mechanisms in the yeast *Saccharomyces cerevisiae*.

She explains: "It may seem surprising that I study a single-cell organism such as yeast to understand what's going on in a child's brain. But yeast cells act very much like human cells, using similar genes." Once she identifies the genes in yeast she studies the human equivalents in tissue cell cultures.

Says Dr. Conibear, "It's exciting to make discoveries, to learn how the molecules in a cell work together to keep us alive." Understanding the cellular and molecular basis of disease, she adds, can lead to new medicines and therapies to halt or reverse the damage to children with genetic diseases.

"In our society there is a growing number of overweight people, including children," says **Dr. Jean-Pierre Chanoine**. "I grew alarmed at how many obese children I was seeing in my practice, some of them as young as three, and began to worry about the long-term impact of their weight on their health."

Dr. Chanoine, an expert in endocrinology, growth and nutrition, is particularly concerned about the rise in childhood obesity and the increased number of overweight children with type 2 diabetes. Obesity is the major risk factor for type 2 diabetes. Once mostly seen in grown-ups, it is now commonly seen in predisposed children. "At the Endocrinology and Diabetes Unit, we follow more than 50 children and adolescents with type 2 diabetes – ten times the number we saw only five years ago," he says.

According to Dr. Chanoine, the two main factors in childhood obesity are inactive lifestyle and inappropriate eating habits. "While we know some children are predisposed to obesity, very few that I see have real endocrine problems."

Dr. Chanoine, who is recognized internationally for his clinical and basic research in trace element metabolism, has developed a research program investigating the effects of nutrition and hormones during pregnancy and in infants on the later development of obesity and diabetes in children. He hopes to find ways to prevent obesity and diabetes and is testing some newly discovered hormones and their impact on controlling appetite. He was also recently involved in community-based research studying the efficacy of a peer-led curriculum in the prevention of obesity in schoolchildren.



Before I had kids I never thought about how many things can go wrong in the human body,” says **Janice Bennett**, mother of Adriel, 9, and Lochlan, 4. “I think it’s every mother’s nightmare when their child gets sick. When symptoms appear, desperate fears come up.”

“For the most part we’ve been lucky,” she says. “My boys are pretty healthy. But they’re also very active, and sometimes they get hurt. Adriel wants to be a professional skateboarder, and there’s only so much protective padding he can wear. If he’s hurt I want to know he’ll receive fast, effective care. When emergencies arise, I put my trust in the health system.”

At the Research Institute, community, population and health clinicians to make the health system the best it can be, and and drug safety and effectiveness.



Dr. Ron Barr is a pediatrician specializing in infant development. His community-based and laboratory research is applied to clinical settings and public prevention programs.

For two decades Dr. Barr has studied infant crying. During the first few months, an infant’s crying has, he says, “very specific properties that can irritate caregivers.” He calls this time frame the “Period of PURPLE Crying.” Almost all cases of shaken baby syndrome occur while the baby is crying, and at least half of them occur in the first few months of life. Dr. Barr plans to mount an education campaign about this period to help parents deal with crying without shaking their baby. He adds, “This type of crying is part of normal development, but only occurs for a limited period – the amount of crying escalates in the first couple of months, and then begins to decrease.”

Another area of study includes observing how caregivers modify or support infant behaviours. The Baby’s Day Diary is used around the world to capture objective descriptions of an infant’s day; in an upcoming project Dr. Barr will translate that diary into a PalmPilot format, making it easier to record accurate descriptions.

Dr. Barr is also interested in infant memory. He’s been studying the capacity of newborns to remember spoken words and images, and has found an influence of feeding on memory – babies given glucose remember longer. Says Dr. Barr, “Fifteen years ago the concept of infant memory didn’t even exist. Now, we want to see what influences their memory.”



“Imagine taking your child for a vaccination and never seeing a needle,” says cellular immunologist **Dr. Jan Dutz**. “Instead a patch would be placed on your child’s skin to transmit the same vaccine a needle used to. This innovation may be five years away from practice.”

Dr. Dutz is referring to his recent work on skin surface immunization and how it can induce systemic immunity, and T cells in particular. Vaccination is one of the most efficient methods of promoting public health; vaccination through the skin offers potential for developing cost-effective vaccines that are easier to administer.

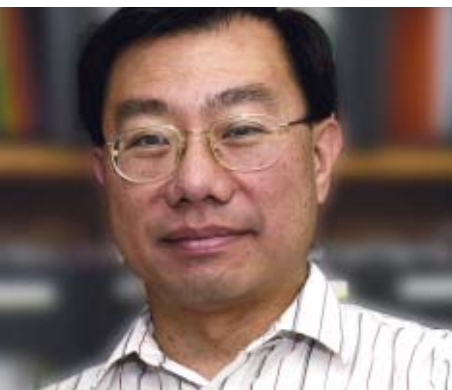
Over the last decade, says Dr. Dutz, it’s become clear that dendritic cells – a large number of which are present in the skin – are key players in immune response because they activate T cells, which work to destroy viruses and bacteria. More than one-third of the immune responses our bodies make are to antigens we encounter through the skin or mucous membranes. Dr. Dutz is working on ways to make practical use of the skin in controlling immune response. His lab is currently studying the skin application of peptides and proteins and methods to enhance their delivery and effectiveness.

Says Dr. Dutz, “In addition to being an ideal organ for initiating immune responses, the skin may be a place to turn them off.” Dr. Dutz, who is trained in rheumatology, immunology and dermatology, is also studying dendritic cells as a possible avenue for suppressing the damaging immune responses in autoimmune diseases like diabetes and lupus.

Janice's contact with the health system is mostly through her GP and hospital emergency departments when her kids are injured or sick. Both boys have asthma, a chronic disease in which the lining of the air passages becomes inflamed and swollen, and increased mucus blocks air from the lungs. Asthma is the number one cause of children's emergency room visits; a current Research Institute study is examining the regional variations in the use of asthma medication and the rates at which children are hospitalized.

"I want to know that care is going to be consistent wherever I go," says Janice. "It's important to me that hospitals and doctors in the community have access to new research so that my boys receive the best care. I support the newest research and am grateful to the research community for all the work they do to help children."

services researchers are working with collaborative networks of policy makers and are studying areas as diverse as population-based epidemiology, injury prevention,



"I look at ways to provide the best possible hospital care for babies," says **Dr. Shoo Lee**. The neonatologist and health economist founded the Canadian Neonatal Network (CNN) to collect standardized data from every neonatal intensive care unit in Canada; the result is a national database of best practices and health outcomes.

Using a system he calls EPIC (Evidence-based Practice, Identification & Change), Dr. Lee identifies areas where improved practices can effect improved outcomes. "Every neonatal care hospital has areas of excellence and areas where they could do better. Using CNN data, they can gauge how they're doing and what they can do better."

The CNN produces information used to guide health planning, policy, and practice. For example, the network provided data that changed the medical guidelines for screening premature babies for retinopathy, a condition that can lead to blindness. They found that only half the number of babies actually needed to undergo this specialized procedure, resulting in substantial health system savings without compromising infant care.

Dr. Lee has also established the Neonatal-perinatal Interdisciplinary Capacity Enhancement (NICE) team of health researchers, providers and decision makers researching new ways to improve quality of care for babies and mothers. In addition, he's developed a national neonatal-perinatal training program in the People's Republic of China.

"Neonatal intensive care units provide vital care for sick newborn infants and have been instrumental in helping Canada achieve one of the lowest infant mortality rates in the world. I hope to help create a legacy of collaboration that results in improved neonatal health care and planning," says Dr. Lee.

Dr. Martin Pusic is a pediatric emergency physician whose research interests lie in health informatics, knowledge translation and evidence-based practice. He explains, "There's a lot of research evidence available today. We're looking at ways to translate that evidence so it's accessible during diagnosis and treatment. One way is through health informatics, which uses computer science to integrate information."

Dr. Pusic's interest in computers extends to using them as teaching tools. In an upcoming project, medical students in the emergency department will do computer tutorials immediately after examining patients – Dr. Pusic calls this "just-in-time learning." Topics range from common health problems, such as throat infections, to rare conditions like neck fractures, which can be devastating if not recognized early. In a pilot project, Dr. Pusic found that the computer tutorials could increase student exam scores on tutorial topics by more than 50%.

In other research, Dr. Pusic is surveying pediatricians and general practitioners about evidence-based care. He says, "Many physicians are conversant with the idea of evidence-based care. We want to find out how to increase their use of it." He also wants to help pediatricians quickly sift through research data to find information relevant to children's treatment; for example, there might be lots of information on an asthma drug, but the drug may affect children differently than adults.

Says Dr. Pusic, "With more research data available now, to patients as well as clinicians, the practice of medicine is changing. That's a good thing. It's resulting in more informed decision-making, and improved care."



Health research generates hope for millions of women and children. At our institute, we foster ongoing research innovations by nurturing new and future independent investigators. More than 150 trainees (postdoctoral fellows and graduate students) from around the world work with our established investigators and benefit from our training programs.

Our Research/Education Training Centre provides a multidisciplinary curriculum, helping trainees build the skills, knowledge, and attitudes to enhance their health research careers. A significant portion of our annual operating budget is also allocated to studentship and fellowship awards. Through these awards we recruit and support exceptional research trainees, ensuring future excellence in care and research relating to children's and women's health.

To find out more, see our website at www.bcriwh.bc.ca

Bright Minds, Bright Futures

Each year more than 150 students and fellows work with our established investigators and participate in our training programs. The success of these up-and-coming researchers in biomedical, clinical and community research ensures a bright future for generations of women and children to come.



Postdoctoral fellow **Dr. Rebecca Devon** arrived in 2000 with funding from the UK Wellcome Trust. After completing her PhD in the genetics of schizophrenia in Edinburgh, she looked for a world-class genetics lab. "Dr. Michael Hayden's lab fitted the bill," she says.

Dr. Devon is examining the neurogenetics of juvenile onset Lou Gehrig's disease (ALS2), a rare neurodegenerative condition. ALS2 results in muscular weakness and progressive paralysis – affected children are usually wheelchair-bound by age ten. Dr. Devon has identified novel ALS2 gene mutations by screening the DNA of affected children. She is also developing a mouse model of the disease by knocking out the mouse ALS2 gene.

Once her postdoctoral training is completed, Dr. Devon hopes to continue her research on ALS2. She says, "Children with this disease suffer greatly. If we can discover how ALS2 gene mutations cause neurons to die, we can work towards finding therapies."

Hoa Le is a PhD student working with Dr. Catherine Pallen. Her previous training was in Singapore and Vietnam, and she is here with a two-year award from the Research Institute. She says, "There's a lot of studying required and we all benefit from competition for funding. I've learned a lot."

Ms. Le is studying the regulation of the NMDA (N-methyl-D-aspartate) receptor, a subtype of glutamate receptor channel, by a class of enzyme called protein tyrosine phosphatases (PTPs). NMDA receptor regulation is associated with excitotoxicity (over-stimulation of nerve cells, which often leads to cell damage), neurodevelopment, learning & memory.

Ms. Le is doing her research using both cultured cells and mice with and without PTPs' expression, to compare the differences. She says, "Laboratory work is a long process. It may be difficult to immediately see the benefits, but in ten years we will. All the research being done will help in treating diseases."

Health services research – PhD student **Ron Lindstrom's** area of focus – considers how various factors affect access to and quality and cost of health care, and ultimately our health. He is conducting research in the BC North West – a largely rural geographic area representing 27% of the province's landmass. He is exploring a more effective process of developing and utilizing child and youth health services using multiple-stakeholder, community-based participatory approaches.

Previously a senior health executive, Mr. Lindstrom has firsthand understanding of the challenges. He says, "Today the health system is even more complex. This demands innovative, interdisciplinary, and collaborative approaches."

Mr. Lindstrom is working with Dr. Robert Armstrong. He has funding from CIHR, UBC, the Northern Health Authority, the Western Regional Training Centre for Health Services Research, and the BC Ministry of Children and Family Development through the Human Early Learning Partnership.

Dr. Lucy Marzban is a postdoctoral fellow in the lab of Dr. Bruce Verchere. "We're trying to enhance survival of pancreatic islets transplanted to type 1 diabetic patients," she says. The goal of her current research is to inhibit formation of amyloid deposits, which can destroy the insulin-producing beta cells.

Dr. Marzban's main focus has always been diabetes. Her PhD thesis in pharmaceutical sciences at UBC was on insulin signalling pathways in diabetes, and while completing her medical degree in Iran she focused on gestational diabetes. She's recently been awarded a prestigious Canadian Diabetes Association postdoctoral fellowship.

She received Research Institute fellowship funding for her first two years. She says, "The environment here is friendly and collaborative, and these fellowships provide great opportunities. They give fellows time to prove themselves. The past two years I've presented eight abstracts and two papers – I feel I accomplished a lot."

Our Funding

The BC Research Institute for Children's & Women's Health has experienced steady growth in funding. The 2002/2003 budget was approximately \$37 million, of which just over \$27 million was external funding which included grants, contracts, agreements and clinical trials. Approximately \$9.7 million in internal funding was received from B.C.'s Children's Hospital Foundation and \$260K from the Sunny Hill Foundation. Funding in 2002/2003 was received from more than 100 agencies, recognised below.

Foundations and Granting

Agencies/Organizations

Alberta Heritage Foundation for Medical Research
Amyotrophic Lateral Sclerosis Association, US
Arthritis Society
BC Ataxia Society
BC Cancer Agency
BC Foundation for Non-Animal Research
BC Health Research Foundation
BC Lung Association
BC Medical Services Foundation
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Canadian League Against Epilepsy
Canadian Liver Foundation
Childhood Cancer Foundation Canada – Candlelighters
Crohn's and Colitis Foundation of Canada
Cystic Fibrosis US
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Genome British Columbia
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NCE: National Centers of Excellence

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Royal College of Physicians and Surgeons of Canada
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Government

BC Knowledge Development Fund
BC Ministry of Advanced Education, Training and Technology
BC Ministry of Children and Family Development
BC Ministry of Competition, Science and Enterprise
BC Ministry of Health
International Development Research Centre
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Hospitals/Universities

Capital Health Authority
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Hampton Research Endowment Fund
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Xenon Genetics Inc.

Other

Association of Canadian Medical Colleges
Canadian Paediatric Society

Our People

The outstanding success of the BC Research Institute for Children's & Women's Health is possible because of its community of committed investigators, trainees, support staff and administration. Every effort has been made to include correct names of all these people; please accept our apologies for any errors or omissions from this list.

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