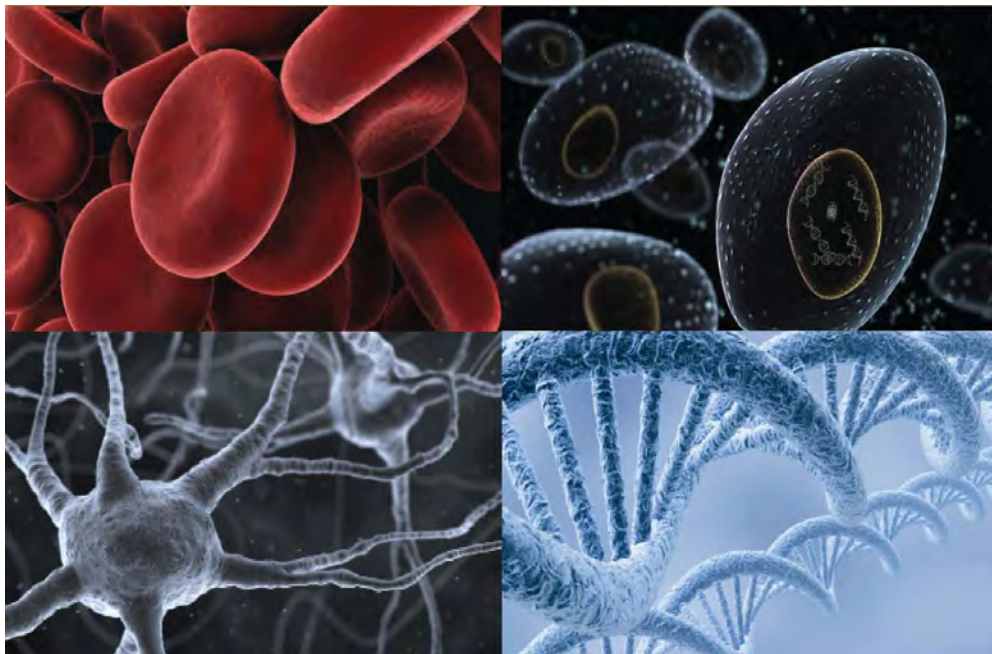


# Biomarkers for Precision Medicine Initiative Biomarqueurs pour la médecine de précision

NATIONAL WORKSHOP

ATELIER NATIONAL



November 19th and 20th, 2009  
19 au 20 novembre 2009



**CIHR IRSC**

Canadian Institutes of  
Health Research

Instituts de recherche  
en santé du Canada

Institute of Circulatory and  
Respiratory Health

Institut de la santé circulatoire  
et respiratoire

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## TABLE OF CONTENTS

|  |       |    |
|--|-------|----|
| Background   | ..... | 2  |
| Steering Committee Members   | ..... | 5  |
| Short Summaries – Current state of biomarker<br>research from various perspectives | ..... | 7  |
| Cancer   | ..... | 7  |
| Circulatory and Respiratory Health   | ..... | 9  |
| Gender and Health  | ..... | 12 |
| Health Services and Policy Research  | ..... | 14 |
| Infection and Immunity   | ..... | 16 |
| Longitudinal Study on Aging  | ..... | 17 |
| Musculoskeletal Health and Arthritis   | ..... | 20 |
| Neurosciences, Mental Health and Addiction   | ..... | 23 |
| Nutrition, Metabolism, and Diabetes  | ..... | 25 |
| Regenerative Medicine and Nanomedicine   | ..... | 27 |
| Workshop Program   | ..... | 29 |
| Participants   | ..... | 33 |

# Background

Biomarkers are critical tools for management of many risks, and acute and chronic diseases, specifically for defining baseline risk, identifying initiating factors, diagnosing disease, managing therapies, forecasting outcomes, and fostering new drug, device and care model delivery development. Predicting complications of illness and allowing risk modification to prevent complications is central to the hope for more robust and translatable biomarkers. The relevance to many health research arenas such as cancer, diabetes, musculoskeletal health, neurosciences, cardiopulmonary, infectious and inflammatory, and aging processes, to name only a few, is obvious. It has been our hope that this national workshop would bring together many diverse and expert people from CIHR Institutes, partners, public research institutions, private sector therapeutic and diagnostic companies, not-for-profit, policy domains and others to work collaboratively and shape a unique and powerful direction for Canada in regards to biomarkers and human health. This initiative will also contribute to CIHR's mission by creating programs that advance world-class excellence in genomics, proteomics and clinical phenotyping, as well as chronic disease management and early risk and disease identification.

At present, there are many promising marker candidates available including those derived from biological experiments, genomics, proteomics, metabolomics, DNA sequence analysis, epigenetic changes, imaging, and phenotypic excellence, as well as many databases. The context of systems of health and science is pertinent, and the relationship between genes, environments and behavior is also part of this quest. Hence, it is now the time to link platforms of discovery with networks of validation, with well-phenotyped and followed cohorts and trial data for the modern emergence of predictive and precision medicine to reach full bloom. The workshop will bring basic and clinical researchers, health services and population health researchers, and other key stakeholders together to learn, discuss and try to identify compelling research priorities, defining gaps in the arena of biomarker discovery, development and implementation wherein a Canadian initiative can make a distinctive impact here and elsewhere.

We thank you so much for your participation and the many contributions you will make to this important workshop and to the directions the partners will ultimately take!

CIHR- Institute of Cancer Research (ICR)

CIHR- Institute of Circulatory and Respiratory Health (ICRH)

CIHR- Institute of Gender and Health (IGH)

CIHR- Institute of Health Services and Policy Research (IHSPR)

CIHR- Institute of Infection and Immunity (III)

CIHR- Institute of Musculoskeletal Health and Arthritis (IMHA)

CIHR- Institute of Neurosciences, Mental Health and Addiction (INMHA)

CIHR- Institute of Nutrition, Metabolism, and Diabetes (INMD)

CIHR- Canadian Longitudinal Study on Aging Initiative (CLSA) & Institute of Aging (IA)

CIHR- Regenerative Medicine and Nanomedicine Initiative (RMNI)

# Contexte

Les biomarqueurs sont des outils essentiels à la gestion de nombreux risques et maladies aiguës et chroniques, notamment pour définir les risques de base, déterminer les déclencheurs, diagnostiquer les maladies, gérer les thérapies, établir des pronostics et promouvoir la création de nouveaux médicaments, instruments et modèles de prestation des soins. La possibilité de prévoir les complications des maladies, et de les prévenir en agissant sur les facteurs de risque, alimente l'espoir de découvrir des biomarqueurs plus fiables et applicables. Les biomarqueurs sont évidemment utiles à de nombreux secteurs de la recherche en santé, notamment le cancer, le diabète, la santé de l'appareil locomoteur, les neurosciences, les maladies cardiopulmonaires et les processus d'infection, d'inflammation et de vieillissement. Cet atelier national devrait réunir des experts nombreux et variés des instituts des IRSC, notamment des organismes partenaires, des établissements de recherche publics, de l'industrie du traitement et du diagnostic médical, d'organismes sans but lucratif et du secteur des politiques publiques, qui joindront leurs efforts pour établir une orientation unique et solide pour le Canada dans le domaine des biomarqueurs et de la santé humaine. Cette initiative contribuera aussi à la réalisation de la mission des IRSC par la création de programmes qui stimuleront l'excellente recherche de calibre mondial en génomique, en protéomique et en phénotypage clinique, en gestion des maladies chroniques et sur le dépistage précoce des risques et des maladies.

Il existe actuellement de nombreux marqueurs candidats prometteurs, y compris ceux qui sont dérivés d'expériences biologiques, de la génomique, de la protéomique, de la métabolomique, de l'analyse de séquences d'ADN, de changements épigénétiques, des technologies d'imagerie et de phénotypage de pointe, ainsi que de nombreuses bases de données. Le contexte des systèmes de santé et de recherche est pertinent, et la relation entre les gènes, l'environnement et le comportement fait aussi partie de l'énigme. C'est pourquoi le temps est venu de relier les plateformes scientifiques avec des réseaux de validation, des cohortes bien suivies avec phénotype bien déterminé et des résultats d'essais cliniques pour que la médecine prédictive et de précision puisse atteindre son plein potentiel. Les participants à l'atelier – chercheurs en sciences fondamentales, cliniciens-chercheurs, chercheurs sur les services de santé et la santé des populations et autres intervenants clés – pourront apprendre, discuter et tenter de définir des priorités de recherche mobilisantes et de cerner les lacunes de la recherche, du développement et de l'application de biomarqueurs, là où une initiative canadienne pourrait avoir un impact distinct ici et ailleurs.

Nous vous remercions à l'avance de votre participation et de vos contributions à cet important atelier et aux orientations qui seront finalement retenues par les partenaires!

IRSC - Institut du cancer (IC)

IRSC - Institut de la santé circulatoire et respiratoire (ISCR)

IRSC - Institut de la santé des femmes et des hommes (ISFH)

IRSC - Institut des services et des politiques de la santé (ISPS)

IRSC - Institut des maladies infectieuses et immunitaires (IMII)

IRSC - Institut de l'appareil locomoteur et de l'arthrite (IALA)

IRSC - Institut des neurosciences, de la santé mentale et des toxicomanies (INSMT)

IRSC - Institut de la nutrition, du métabolisme et du diabète (INMD)

IRSC - Étude longitudinale canadienne sur le vieillissement (ELCV) & Institut du vieillissement (IV)

IRSC - Initiative de recherche en médecine régénératrice et nanomédecine

# Steering Committee Members

## BIOMARKERS WORKSHOP STEERING COMMITTEE MEMBERS

| Name                  | Institute Rep | Expertise   |
|-----------------------|---------------|---|
| Bruce McManus (Chair) | ICRH          | Transplant Vascular Disease, Valve Disease, Proteoglycans, Coxsackievirus, Myocarditis, Histopathology, Cardiovascular Pathobiology, Death Pathways, Molecular Biology/Genomics, Imaging        |
| Jean-Claude Tardif    | ICRH          | Atherosclerosis, Cardiovascular Disease, Oxidative Stress, Clinical Trials, Inflammation, Intravascular Ultrasound, Coronary Imaging, Endothelial Function                                      |
| Gillian Einstein      | IGH           | Cognitive Neuroscience, Aging, Memory, Estrogens and Cognition, Sex Differences, Women's Health, Systems Neuroscience   |
| Katherine Siminovitch | IMHA          | Signal Transduction, Genomics, Murine Models of Disease, Autoimmunity, Cancer Biology, Tyrosine Phosphatase, Protein-protein interaction, Positional Cloning, Flow Cytometry, Molecular Biology |
| Jolanda Cibere        | IMHA          | Osteoarthritis, Epidemiology, Rheumatoid Arthritis, Randomized Trials, Cohort Study, Alternative Medicine, Reliability  |
| Ernest Seidman        | INMD          | Intestinal Immunology, Cell Biology, Cytokines, Inflammation, Crohn's Disease, Ulcerative Colitis, Absorption, Pediatrics, Molecular Biology, Cancer  |
| Mark Silverberg       | INMD          | IBD, Crohn's Disease, Ulcerative Colitis, Genetics, Genomics  |
| Cynthia Balion        | CLSA          | Clinical Chemistry, Carnosinase, B-Type Natriuretic Peptide, Systematic Reviews, Quality Control, Aptamers, Point of Care Tests, Method Evaluation  |
| Trevor Young          | INMHA         | Bipolar Disorder, Depression, Post Mortem Brain Studies, G-Proteins, Signal Transduction, Lithium, Sodium Valproate, Adenylyl Cyclase, Clinical Trials, Antidepressants                         |
| Georg Northoff        | INMHA         | Functional Brain Imaging, Psychiatric Disorders, Depression, Schizophrenia, Neuroethics, Neurophilosophy  |
| Fiona Miller          | IHSPR         | Health Policy Analysis<br>Health Biotechnology<br>Health Services Research<br>Mixed Methods<br>Genetic Health Services<br>Resource Allocation<br>Health Policy Ethics<br>Public Health          |
| John Wilkins          | III           | Systems Biology, Lentivirus and ShRNA, Inflammation, Cellular Immunology, High Content Imaging, Autoimmunity, Monoclonal Antibodies, Proteomics   |
| Amit Bar-Or           | III           | Autoimmune Disease, Neuroimmunology, Multiple Sclerosis, B Cells & T Cells, Myeloid Cells, Immune Regulation, Biomarker   |

|                      |  |  |
|----------------------|--|--|
|                      |  | Development, Immune Neural Interaction, Cell Culture, Flow Cytometry   |
| Peter Watson         | ICR  | Breast Cancer, Pathobiology, Biomarkers, Tumor Banks, Biobanks, Biobank Networks   |
| James (Jim) Woodgett | ICR  | Signal Transduction, Oncogene, Microarray, Functional Genomics, Protein Kinase, Phosphorylation                                      |
| Christopher Yip      | Regenerative Medicine and Nanomedicine Initiative (RMNI) | Protein Structure, Molecular Self-Assembly, Scanning Probe Microscopy, Spectroscopy, Organic Solid-State, Microscopy, Bioinformatics |

# Biomarkers from CIHR Partners' Perspectives

## Cancer

Morag Park (ICR), Jim Woodgett (U. of T), Peter Watson (BCCA), Jacques Corbeil, Anne-Marie Mes-Masson (ICR IAB)

Background – In current clinical practice, cancer therapies are often administered without first attempting to predict which patients will respond to a given treatment. The pre-treatment detection of response predictive markers could allow for a more strategic application of treatment helping to maximize the therapeutic index. The elucidation of predictive and prognostic biomarkers for the identification of patient subsets, treatment and improved survival has become a major goal of clinical research. This, together with the use of imaging, is key to the development and use of biomarkers in the cancer field. Biomarker activity can be classified into four areas within the cancer field: Discovery, Technology Development, Validation, and Policy. Development and evaluation of new biomarkers involves the basic biological and genomic sciences and extends into clinical laboratory and imaging areas. For most applications single biomarkers are unlikely to provide the necessary sensitivity and specificity. Hence it is necessary to develop rigorous bioinformatic approaches to establish panels of biomarkers. Challenges include the need for clinical standards in quality control, the need for large prospective clinical trials for validation and the development of technologies suitable for use in the health care setting.

Current activity in Canada and elsewhere – Canada has important local, provincial and national assets. These include:

Clinical resources: Cancer registries, outstanding Clinical trials groups, Pathology practice patterns

Biospecimen/data initiatives: National networks – CTRNet, Provincial frameworks, Pan Canadian projects - Tomorrow Project

Research initiatives: National breast cancer framework biomarker priorities (CBCRA), Terry Fox Research Initiative (TFRI) nodes and networks activities, as well as provincial activities, Ontario Institute of Cancer Research (OICR).

International initiatives: The NIH biomarkers consortium ([www.biomarkersconsortium.org](http://www.biomarkersconsortium.org)), NCI Early Disease Research Networks, The Human Proteome Organization (HUPO) (<http://www.hupo.org/>), Cancer Genome Sequencing Consortium as well as large scale population based initiatives (Luxembourg Initiative).

Gaps and opportunities – Access to biospecimens is a common issue for all fields and phases of biomarker discovery, development, validation and deployment. ICR-CIHR has supported significant progress in the form of a linked cancer biobank network (CTRNet). Expansion of this concept and model could be an area where the cancer field can provide expertise. The NCIC-clinical trials group networks clinical trials across the country and is recognized as international leaders<sup>i,ii</sup>. There is a need to coordinate our SOPs across the country<sup>iii</sup> and facilitate better discussions with the pharmaceutical industry to make better use of the Canadian cancer biomarker research data and discoveries and facilitate the translation into the market<sup>iv</sup>. At this stage it is critical to evaluate new technologies and international population based initiatives such as the Luxembourg initiative that will impact in the long term on prevention and prediction of many disease states<sup>v</sup>.

Challenges- It is clear that the Canadian Health Care System is not ready to implement the discoveries and treatments that will arise from current cancer biomarker research. Research into biomarkers across all research areas is rapidly advancing and there is great need to adapt our policies and health system to effectively implement new discoveries and take advantage of the cost-saving opportunities that biomarker research will bring. If research discoveries in biomarkers are to help improve the health of Canadians and

improve health care costs then there is need to focus on health policy and economics research and this area should be a major component of any biomarkers initiative.

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## Circulatory and Respiratory Health

Bruce McManus (UBC), Jean-Claude Tardif (MHI), Peter Liu (CIHR-ICRH), Rob Hegele (UWO), Todd Anderson (U Calgary), Arthur Slutsky (U Toronto), Louis-Philippe Boulet (Laval U), Dean Befus (U Alberta), Danuta Radzioch (McGill U)

Background – Evaluation of risk factors, including biomarkers, to both predict risk and monitor response to therapy, is a central component of clinical care administered in cardiovascular and cerebrovascular disease clinics. Well-established risk factors include family history, elevated plasma low-density lipoprotein, depressed plasma high-density lipoprotein, diabetes, tobacco use, high blood pressure, and obesity. More recently, newer biomarkers with potential clinical utility to predict atherosclerotic risk have emerged, including serum concentrations of C-reactive protein, homocysteine, Lp(a), triglyceride and quantitative imaging markers. Numerous risk algorithms have been developed primarily based on the known risk factors, including the Framingham Risk Score, Reynolds Risk Score, Prospective Cardiovascular Munster equation and the European Society of Cardiology Systematic Coronary Risk Evaluation. Overall, these risk engines have proven clinical value across jurisdictions and clinical situations, principally by helping to stratify patients into risk categories, which then drive decisions for interventions using evidence-based pharmaceutical-, procedure- and device-based therapies. The association of risk profiles with the subsequent occurrence of end points has been well-described. For instance, the APOE E4 isoform is consistently associated with increased susceptibility to later-onset Alzheimer disease. Also, the only apparently effective biomarker currently for chronic obstructive pulmonary disease (COPD) is the time-honoured measure of forced expiratory volume in one second (FEV1), although it is insensitive for early stages of COPD, and appears only to be useful once the condition is quite advanced. Both COPD and asthma have no reliable or specific blood based markers. It is well-recognized that there are many phenotypes of asthma and that the phenotype can influence response to drugs and management approaches. Given the absence of reliable biomarkers of asthma or the spectrum of its phenotypes, there is extensive biomarker research on sputum, exhaled gases, and using olfactometry. The few markers purported to predict the prognosis of patients with sepsis or systemic inflammatory response syndrome (SIRS) are similarly inconsistent with respect to sensitivity and specificity. So, in general, individual risk factors or biomarkers poorly predict risk, due to the overlapping distributions of these variables among disease cases and healthy individuals. For this reason, combinations of multiple risk factors have been considered to hold greater discriminatory potential. For instance, the recent INTERHEART study showed that a bundle of nine common risk factors, including clinical and demographic variables, together with biomarkers such as the apo B/A1 ratio, contributed ~90% of population attributable risk (PAR) for myocardial infarction. But the utility of risk scores in managing individual patients with risk for or suffering from heart and blood vessel disease is modest, as evaluated by such (admittedly limited) methods as improvement in receiver-operator characteristic (ROC) curves or net reclassification index (NRI). Another potential application of biomarkers is in pharmacogenomics to predict individual response to a medication type or dose. For instance, the FDA recently approved CYP2C9 and VKORC1 genotyping to direct the appropriate warfarin regimen, although this appears to be most helpful for a minority of individuals who require extreme warfarin doses. For these reasons and others, there is a strong belief that emerging novel biomarkers spanning genetic, “-omic”, or molecular imaging – perhaps individually but more likely as part of marker panels - would improve the performance of existing risk prediction engines and clinical decision-making tools. In parallel, issues such as cost-effectiveness and ease of use, including minimally invasive sampling and point-of-care measurement need to be considered. The road to realize the potential of biomarker solutions remains long, and includes discovery, development, commercialization and implementation. Rigor at each step further requires extensive multi- and inter-disciplinary collaboration, with new alliances and partnerships across stake-holders and interested sectors, with universal commitment to integrated and harmonized processes, including pre-analytical, analytical and post-analytical phases of development. Early alignment with regulatory agency frameworks, such as the FDA’s Critical Path is crucial. Ultimately, clinical trials, systematic evaluation of outcomes and economic analyses will be essential to

determine whether a biomarker or panel of markers can improve clinical practice and the health of Canadians

Illustrative activities in Canada and elsewhere – Canada is a leader in biomarker discovery and development. A partial list of relevant contributors and stakeholders would include:

Overall – Publicly funded healthcare system, frequently track-able patients and patient data, many collaborative clinical and research networks, governmental investments in infrastructure and platforms, centres and networks, and people with complementary skills and knowledge, an uneven but potentially enabling ethics environment, many biobanks and databases and the commitment to link these electronically. Notable national and international biomarker-focused enterprises – funded by the NCE CECR Program, include the PROOF Centre of Excellence for the Prevention of Organ Failure (based in Vancouver – mainly -omics), and CEPMed Centre of Excellence in Personalized Medicine (based in Montreal – omics and non-omics); the Duke Translational Medicine Institute, Partnership in Personalized Medicine, Critical Path Institute, Biomarker Consortium, International Partnership for Critical Markers Of Disease (CMOD), CHILD birth cohort study jointly funded by Allergan NCE Inc, and CIHR, etc.

Many clinical networks – Canadian Atherosclerosis Imaging Network (CAIN, CIHR-funded), Can COLD, Canadian Heart Failure Network, Canadian Critical Care Trials Group, Canadian Stroke Network, etc. Biospecimens/dry data – Internationally (ISBER), nationally (Tomorrow Project), provincially (e.g., BC BioLibrary), Montreal Heart Institute Hospital Cohort, etc.

Gaps and opportunities – Quality standards and ready acquisition, maintenance and optimal use of clinical cohorts, biospecimens, capacity for new technology platforms, computational strategies, regulatory frameworks, health system entry points, health economics characteristics, and links to industry where needed are uneven. Collaborative frameworks to make more efficient and effective use of the many resources in order to find solutions to important, and sometimes niche, problems need to be strengthened. Resolving the challenges that relate to levels of assessment and validation, as well as qualification in various disease contexts, requires concerted attention to layered evaluation by tools aimed at marker-disease associations, hazard ratios, receiver-operator performance, reclassification capability and other features. This activity is a foundational piece for any national program, regardless of clinical disciplinary focus.

Challenges – Education of those involved in the complexity of biomarker discovery, development, commercialization and implementation will need to be ongoing and preferably developed as a national curriculum or forum held yearly. Similarly, health professionals are just beginning to struggle with the reality of the genetic and genomic landscape and how patients and the public need to be guided. Being competitive in a global push towards biomarker solutions requires collaboration, cooperation and economies of scale if Canada is to have a consistent, sustainable footprint in this domain. It is also crucially important that we do not lose sight of the need for corresponding or contemporaneous biological studies of mechanisms underlying certain biomarkers or biomarker panels. Such will help us understand the real roles of given biomarkers in disease pathogenesis and as surrogates, and also help to identify new drug targets. Providing industry with the kind of support that allows the drug discovery pipeline to improve its performance is also a strong consideration.

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## **Gender and Health**

Gillian Einstein, PhD

In any discussion about the development, testing, and use of biomarkers—and in any conversation about personalized and precision medicine—it is imperative to include chromosomal sex and its social partner, gender. This position is supported by the FDA’s “Critical Path Initiative” [1] and by the Institute of Gender and Health’s publication, “Better Science with Sex and Gender” [2]. The position is also supported by empirical and clinical evidence on known differences in etiologies and response to treatments of numerous diseases. It was summarized as early as 2001 in the Institute of Medicine’s report “Exploring the Biological Contributions to Human Health: Does Sex Matter?” [3].

In fact it would not be out of place to consider chromosomal sex and gender as biomarkers themselves.

It is well-known, for example, that whether you are XX or XY can affect the likelihood, age, and presentation of cardiovascular disease [4]. If a biomarker is developed for the detection of CVD or a best response to a treatment for CVD, and chromosomal sex is not taken into account, one could reasonably question its precision.

Chromosomal sex also affects the efficacy of therapeutics. The Arizona Center for Education and Research on Therapeutics lists 34 currently marketed drugs that present an increased risk of causing Torsades de Pointes [5]. Of these, 17 (a full 50%) do so more often in women than in men. These drugs include antibiotics and treatments for heart disease and psychosis. The US General Accounting Office reported that 8 out of 10 drugs withdrawn from the market between Jan. 1, 1997 and Jan. 1, 2001 were removed because they had greater adverse effects in women than in men [6].

X-inactivation in XX individuals may create even further necessary levels of precision—since the XX genome is a mosaic, with each cell having its own genomic complement.

In genomics it is critical to understand the role of steroid hormones on a particular genetic marker. Steroid hormones—estrogens and androgens—act on the cell nucleus to modify gene expression and production of proteins. In their groundbreaking work on the hippocampus, Woolley and McEwen [7] demonstrated that estrogens regulate the production of MNDAs receptors and the number of spine synapses on CA1 pyramidal cells, making hyper-excitability of these neurons more likely during the luteal stage of the ovarian cycle. Liu [8] posits that androgen exposure in early development may predispose XY individuals to an earlier onset of atherosclerosis than XX individuals, who are not exposed to early high androgen levels. It is not unreasonable to believe that novel therapeutic targets may arise from understanding how androgens enhance early plaque formation and cause vasodilatation via genomic and nongenomic androgen effects on vascular smooth muscle. Pioneering work by Goldstein and Tobet is exploring the respective roles of early estrogens and androgens in the development of mental illness [9].

Epigenetics is also gendered. The groundbreaking Whitehall study demonstrated that illness from every kind of disease rose as level on the working hierarchy diminished [10]. Those at the lowest rung—with the lowest control over their work—had higher levels of disease than those at the top. Many XX individuals are at the low rung on the hierarchy. African-American women—even those with high economic status—have more premature births and lower birth-weight babies than Caucasian women. There is some suggestion that this is due to life context rather than prenatal nutrients. The different environments in which XX and XY find themselves may affect biomarker expression.

It is IGH's position that promulgating and supporting a serious consideration of sex and gender in CIHR's biomarker initiative will give Canada a strong innovative edge and critical research and clinical advantage in the development of truly personalized medicine.

## Recommendations

1. Carry out early experimental work on biomarkers on XX and XY animals;
2. Control for sex in the study of biomarker efficacy in cell cultures;
3. Consider chronobiological information—such as stage of ovarian cycle, age, and time of day—in animal models and human trials;
4. Consider life context in which biomarkers are successful or unsuccessful;
5. Record chromosomal sex, age, stage of ovarian cycle, and context in all registries.

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# Health Services and Policy Research

Fiona Miller

## Health Services and Policy Research for Biomarkers: Ensuring effective health care

Developments in biomarker science, including research in genomics, metabolomics and imaging, hold promise for improved health and health care through more effective prediction, prevention, prognostication and treatment. Yet obstacles to the translation of developments in biomarker science and technology into effective health care are considerable. These include (i) the challenge of efficacy – that is, the need for evidence that the intervention can work under ideal conditions; (ii) the challenge of assessment – that is, the need for evidence on the likely efficacy, effectiveness and efficiency of biomarkers, to justify market access or public investment; and (iii) the challenge of translation – that is the need for evidence for translating the intervention into effective health care practice in real-life conditions. Yet despite these several challenges we face a growing evidence gap, where far more research pursues biomarker discovery than translation to the clinic.<sup>i</sup> Further, as basic research knowledge accumulates, initial discoveries may come to look less promising,<sup>ii</sup> increasing the need for caution before the ready uptake of un-validated technology.

Biomarkers can accomplish many different things in health care, including (i) prediction for the purpose of prevention, potentially through population screening; (ii) prediction for the purpose of prognosis in clinical care; (iii) prediction for the purpose of treatment, identifying indicated or contra-indicated therapeutic regimens; and (iv) monitoring of treatment response. Evidence requirements differ for these different purposes and different service delivery issues arise.

The challenge of efficacy: The validation of individual biomarkers and biomarker combinations is a complex science, demanding substantive and methodological advance. Guidance for reporting and grading the strength of evidence for medical tests is growing (e.g., STARD, REMARK, GRADE),<sup>iii</sup> and collaborations seeking to synthesize and evaluate the existing evidence base exist (e.g., HuGENet, [cdc.gov/genomics/hugenet/](http://cdc.gov/genomics/hugenet/)). Yet the evidence base to support the rigorous evaluation of biomarker discoveries remains limited.

The challenge of assessment: The assessment of medical technologies occurs at two levels: at the federal level for safety and efficacy to justify market access, and at the national or provincial level to assess clinical and economic effectiveness to justify public subsidy, typically before widespread uptake. Research is needed to assess the appropriateness of different regulatory regimes for biomarkers and biomarker platforms, to develop methods and evidence concerning clinical and cost effectiveness of existing and emerging biomarkers,<sup>iv</sup> and to assess the relevance of different coverage mechanism (e.g., coverage conditional on evidence development<sup>v</sup>) for the early introduction and continued evaluation of biomarker technologies.

The challenge of translation: The ultimate effectiveness of even validated biomarkers depends on a complex web of service delivery and system level factors, <sup>vi</sup> including (i) the coordination of financial incentives and accountability mechanisms (i.e., oversight, accreditation) for service delivery for uptake and obsolescence; (ii) the coordination and validation of platforms for service delivery (e.g., laboratory or imaging capacity),<sup>vii</sup> (iii) the coordination of clinical practice, including referral, result integration and interpretation,<sup>viii</sup> and (iv) support for patient care, including information or decision aids.

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# Infection and Immunity

John Wilkins and Amit Bar-Or

**Background:** Diseases of immune dysfunction or infectious agents can involve virtually any tissue of the body. The effects of these diseases can range from localised to systemic. Thus while nuances of the tissue specific processes may vary, the underlying immunological contributions to pathological processes may be very similar. Establishment of the details of these processes offer a basis for identifying commonalities as well as differences between a number of diseases with immunological components. The challenges then relate to developing discriminators with sufficient levels of sensitivity and specificity to be clinically useful.

**Challenges:** Many of the challenges are the same ones faced by other areas relating to disease process [e.g. disease and patient heterogeneity, incomplete knowledge of natural history of a disease, inability to access affected tissues, staging of disease, and clinical confounders such as other medical conditions] or experimental aspects [e.g. sample acquisition, access to analytical platforms, data analysis].

**Opportunities:** The potential commonalities afford the opportunity to incorporate information from a number of different diseases with immune components. Conversely comparisons offer an accelerated mechanism of defining differentiators between disease entities. The implementation of standard approaches to processing and handling of clinical samples, application of analytical techniques and sharing of datasets could benefit the study of a broad range of diseases. Clearly this approach does not preclude the need for disease specific research projects but it would reduce the duplication of capabilities.

Cohorts of fully characterized patients are essential to any effort to identifying useful biomarkers. Thus establishment of universal ethical guidelines for sample acquisition with sufficient flexibility to allow for their further analysis as new techniques arise.

If high content analytical approaches are to be successful there is a critical need for the Institute to foster training and research in computational biology and statistical analysis.

Much of the necessary infrastructure is in place but there is a critical need to coordinate access and operating support. Equally important is the need to provide resources for specimen acquisition, patient characterization, and data interpretation. This highlights the importance of support for clinician scientists and trainees to during these studies.

As immune processes may play an important role in the initiation phases of many of the subsequent tissue specific pathological events, the identification of immune related biomarkers may have broad disease based applicability.

# Longitudinal Study on Aging

Cynthia Balion

**Background and History:** The Canadian Longitudinal Study on Aging (CLSA) is a key strategic initiative of the CIHR. They have funded the development and implantation of the baseline CLSA data collection activities. In the fall of 2001, CIHR's Institute of Aging in partnership with Health Canada held an invitational research symposium, From Cell to Society. As a result of the meeting, a Request for Applications to develop the protocol for the CLSA was officially launched. The research team was selected in 2002 to begin the development of the CLSA. The CLSA has been conceptualized as a national project bringing together major Canadian Universities from across the country as participants in a national research program in Healthy Aging. The CLSA is lead by a lead Principal Investigators (Parminder Raina) and two Co Principal Investigators (Drs. Christina Wolfson and Susan Kirkland), and 160 co-investigators from across Canada. The CLSA has also formed key collaborations with Statistics Canada, Health Canada and many provincial agencies. CLSA has also been funded by Canadian Foundation for Innovation to establish infrastructure across Canada to carry out CLSA. The CLSA has undergone multiple international peer-reviews to meet the scientific standard set by the CIHR. During the developmental phase of the studies, many feasibility studies were funded by CIHR and have been recently published by the Canadian Journal on Aging (see references).

**Introduction:** Advances in biosciences, informatics and population health research herald exciting opportunities to conduct interdisciplinary high-impact research that, only a decade ago, were not possible. On a background of technological and scientific innovation, the CLSA is a research program and a research platform designed to enhance the investigation of the complexities of the aging process with a view to improving our understanding of the transitions and trajectories of aging. The CLSA is a Canada-wide, 20-year follow-up study of 50,000 people between the ages of 45 and 85 years at baseline. Thirty thousand of the 50,000 will also be asked to provide in-depth information through physical examinations and blood and urine specimens. The remaining 20,000 will provide the core CLSA information set through questionnaires only. This research initiative will unify biosciences and population health and create a "Legacy Research Platform" that will provide scientists with the resources essential to pursue leading-edge research. The CLSA comes at a time when the baby boomers are moving into late middle age and towards retirement, a demographic shift that has created a critical need for aging research to inform interventions, programs and policies, and to promote healthy aging for today's and tomorrow's seniors. Acceleration of our understanding of the aging process, its modifiers and consequences is essential if future interventions and policies are to reach the objectives of improving health, allowing individuals to maintain desired levels of activity into late life, and increasing the lifespan as well as quality of life. The CLSA will foster cutting edge research into understanding how risk factors individually, and in combination, influence the biological, physical (circulatory, brain, musculoskeletal, respiratory and endocrine/metabolic systems), psychological, and social functions that determine the health and well-being of individuals as they age. The overall aim of the CLSA is to understand the dynamic process of aging and adult development. The depth and breadth of data collection in the CLSA will enable the examination of a host of research hypotheses, far too many to be included here. Nevertheless, some examples of key overarching research questions that the CLSA has been designed to answer include: 1) What are the determinants of changes in biological, physical, psychological and social function over time and across ages? 2) What is the magnitude of the role of genetic and epigenetic factors in the aging process? 3) What factors distinguish individuals who experience healthy aging from those who do not? 4) Are there identifiable patterns of cognitive functioning in midlife that predict the onset of dementia in later life? 5) How do work and family transitions intersect with negative/positive changes in social networks and social support and how do these transitions influence overall health?

**Current Activity:** In collaboration with Statistics Canada, the CLSA team launched the CLSA baseline in November 2008 to recruit initial batch of the 20,000 participants for the CLSA. The remainder of the recruitment (N=30,000) will commence in early 2011. The CLSA team is in process of getting REB approvals

across Canada, developing IT solutions for data capture, implementing Computer Assisted Telephone interview (CATI) modules, programming questionnaires in CATI, develop privacy and confidentiality protocols, data access and utilization policies, finalize terms of references for various management committees, training manuals, standard operating procedures and establish plans and agreements for establishing infrastructure across Canada. All of the measurement tools have been selected and are in process of being finalized.

Gaps and Opportunities: CLSA is also positioned as a research platform that will allow researchers to carry out sub-studies within CLSA taking advantage of core rich data while at the same time facilitating the collection of new data relevant to given area of research. Some of the key areas that might be included in some of the sub-studies are imaging data, tissue samples including brain and environmental biomarkers. Other areas where CLSA may have opportunities may include the initiation of 1) an intergenerational study by including children of the participants and their children, and 2) opportunity to establish collaborative partnerships with private sector.

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# Musculoskeletal Health and Arthritis

Jolanda Cibere and Katherine Siminovitch

Background/Current Research Activity in Canada: Musculoskeletal (MSK) diseases include over 100 forms of arthritis. Of these, osteoarthritis (OA) is most common. Of the inflammatory arthritides, rheumatoid arthritis (RA) and ankylosing spondylitis (AS) and psoriatic arthritis (PsA) are most prevalent. The summary below will be limited to these conditions, although biomarkers have been evaluated in other autoimmune diseases. For many MSK diseases, the search for biomarkers that aid in diagnosis, prognosis and in the evaluation of treatment efficacy has intensified over the past decade (1, 2, 3, 4, 5, 6, 7).

In OA, the development of assays for the detection of cartilage synthesis and degradation markers, targeting specific molecules, such as type II collagen, aggrecan and other extracellular matrix components, has led to an improved understanding of the pathophysiology (8, 9, 10, 11, 12). Several of these biomarker assays were developed in Canada (1, 8, 9, 10) and are currently used in international OA cohorts for determination of their utility in diagnosis, prognosis and as outcome measures in OA clinical trials. In OA, biomarkers relating to bone, cartilage and synovium have been investigated, with the majority of studies evaluating biomarkers for prognostic purposes (3). Of these, c-telopeptide of type II collagen (CTX-II), cartilage oligomeric matrix protein (COMP), hyaluronic acid (HA), type II collagen cleavage neoepitope (C2C), type I and II collagen cleavage neoepitope (C1,2C), c-propeptide of type II procollagen (CPII), as well as ratios of biomarkers are predictive of OA progression. There is a scarcity of investigation of biomarkers for diagnostic purposes. In the Vancouver cohort of early knee OA, increases in urine C2C and C1,2C were both found to be associated with early pre-radiographic stage of OA, determined by magnetic resonance imaging (MRI) (13).

Cartilage degradation and synthesis assays have been employed in RA studies, together with inflammatory markers such as cytokines, matrix metalloproteinases (MMPs) and acute phase reactants. Diagnostic markers such as anti-cyclical citrullinated peptide (anti-CCP) antibodies and anti-Sa antibodies have high specificity for RA. Anti-Sa antibodies were first identified in a French Canadian patient (14) and have subsequently been reported to be present in early disease and associated with aggressive RA. Multicytokine profiling in conjunction with autoantibody status determination has been proposed for prognostication in RA (15). Specific biomarkers of interest in RA are those predictive of disease progression, such as acute phase reactants (CRP, ESR), markers of degradation/turnover of affected joint tissues, e.g. CTX-II, c-telopeptide of type I collagen (CTX-I), glucosyl-galactosyl-pyridinoline (Glc-Gal-PYD), COMP, MMP-1, MMP-3, osteoprotegerin :RANKL ratio and genetic typing for HLA-DRB1 (4). Short-term changes in collagen markers (C2C, C1,2C and CPII) were predictive of long-term clinical and radiographic treatment response to biologics in RA (16).

In addition to biochemical tools, genetic and immunologic “biomarker” discovery efforts are a very active facet of national autoimmune/inflammatory disease research. Genetic association data emerging from genome-wide association surveys have identified a myriad of RA, PsA and AS associated risk alleles, a number of which may predict disease course and/or outcome as well as risk (17, 18, 19, 20, 21). Newly-emergent phosphoflow cytometry tools have also revealed the potential for flow cytometry to identify/quantify disease activity and possibly severity in autoimmune/inflammatory conditions such as RA.

Gaps and opportunities: Clearly, there are strong ongoing Canadian initiatives conducting clinical research on biomarkers in MSK diseases. National and international networks already exist to evaluate the prognostic value of biochemical/imaging markers in MSK diseases. However, several gaps exist. No biomarker has yet been shown to have sufficient predictive capacity for disease progression in any of the chronic joint diseases. The assessment of select biomarkers in different disease cohorts, rather than a systematic evaluation of multiple biomarkers is an important gap. There is a need for expanded Canadian collaboration across

institutions and disciplines to optimize biomarker research. The translation of knowledge from the basic sciences into the clinical realm represents a critical step to enhance the current biomarker research agenda. Yet Canadian companies face serious financial constraints that limit further R&D as a result of a lack of federal/provincial funding opportunities. The opportunity to link genetic biomarker research with biochemical biomarker research exists, but requires more input from statisticians capable of designing algorithms enabling these data to be shaped into clinically useful diagnostic tools. There is a need for standard terminology, which has resulted in a proposal to classify OA biomarkers in the US (22). Clear definition of cohorts with regards to stage of disease is critically important, as it will allow for appropriate interpretation of the utility of biomarkers in the clinical context. While biomarkers have been investigated extensively for prognostication, they are not currently accepted as surrogate outcomes for drug approval processes. There is an ongoing Osteoarthritis Research Society International initiative to develop a guidance document for the U.S. FDA which will include the development of criteria for use of OA biomarkers in preclinical studies, detection of early onset of OA and in phase I, II and III trials as surrogate outcome measures, a crucial step towards integration of biomarkers into the evaluation of efficacy of disease-modifying drugs in OA. Similarly, the Outcome Measures in Rheumatology (OMERACT) 9 Soluble Biomarker Group, which includes many Canadian researchers, has proposed levels of evidence and a study design template for biomarker research in RA, AS and PsA (23). These initiatives highlight current gaps, but also provide opportunities to further enhance the biomarker research agenda.

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# Neuroscience, Mental Health and Addiction

L. Trevor Young and G. Northoff

Although the impact of mental illness on the health of Canadians is well established and efforts such as those by the Mental Health Commission of Canada have renewed focus on reducing stigma, prevention and making treatment available and effective, there is a clear need for biomarkers which may help confirm diagnosis, help in selection of treatment and predict outcome. The field of biological psychiatry has lagged behind in establishing neurobiological models of specific illnesses but advances in molecular pharmacology, genetics and brain imaging are rapidly improving our understanding.

The need for biomarkers is illustrated by many issues which include: a) reliance on patient self-report for diagnosis, b) increasing evidence that there are many genes of small effect which predispose to mental illness rather than a smaller number of genes with large effects, c) a trial and error approach to choosing the right treatment for the right patient based initially on tolerance to adverse effects but only much later to outcome, d) the increased familiarity among patients and clinicians on the promising data from recent research studies which are not yet translated into practice.

Several promising leads which have taken a “biomarker” approach in psychiatry include:

Decreased microstructural integrity of white matter tracts measured with magnetic resonance diffusion tensor imaging in frontal and temporal regions in patients with schizophrenia may predict disease progression (Rowland LM et al Neuropsychopharmacology, 2009)

A relationship between mood-induced changes in neuronal activation measured with functional MRI and glutamate levels in major depression (Walter M et al Arch Gen Psych 2009)

Blood levels of the expression of myelin-related gene expression may be related to the clinical severity of mood symptoms in bipolar disorder (Le-Niculescu et al Mol Psychiatry 2009)

A broad range of findings in patients with mood disorders on the importance of serum BDNF levels in assessing illness progression (many refs including Kauer-Sant’Anna M et al Int J Neuropsychopharm)

The findings from PET that monoamine oxidase A binding potential may be a diagnostic biomarker for major depression (Meyer J et al Arch Gen Psychiatry)

In order to account for relevant neurobiological progress, the concept of endophenotypes has recently been introduced in psychiatric research. An endophenotype describes the linkage from gene to expression of specific proteins at a biochemical level to processes which can be observed at the symptomatic and clinical level. This suggests specific pathophysiological mechanisms may result in one or more single symptoms which are detectable in clinical practice. Consider for instance the symptom of anhedonia. Anhedonia describes the inability to experience pleasure and positive emotions which may be of central importance in depression but also in schizophrenia with regard to residual symptoms. Imaging techniques singled out abnormal hyperactivity in a particular region in the brain, the perigenual anterior cingulate cortex (PACC), to be crucial to constituting anhedonia. In addition, BDNF and others cellular marker may also be important in mediating anhedonia.

Additionally there is a lot of interest in a number of susceptibility genes for schizophrenia and mood disorder which have been replicated by large scale genome wide association studies and how those may be of clinical relevance. These include careful analyses of several large scale multicentre clinical trials funded by NIMH included the STEP-BD and STAR\*D programs.

There are several excellent Canadian established and junior investigators (Kennedy J and Voineskos A, Toronto; Alda M, Halifax). Internationally there is a remarkable degree of interest in biomarkers and centres of excellence in Britain (Bullmore E, Fletcher P at Cambridge for Schizophrenia), Germany (Heinz A in Berlin

for Addictions) and the USA (McMahon, F, NIMH; Le-Niculescu, Indianapolis). A workshop is timely and will strongly support the development of a program for biomarkers in mental illness and addictions.

Though not having achieved the status of biomarkers that are able to predict subsequent diagnosis and therapeutic effects, e.g., diagnostic and therapeutic markers, developments such as this and many others point towards this direction. One may consequently expect the development of valid diagnostic and therapeutic markers in the field of mental health within the next 5-10 years.

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# Nutrition, Metabolism, and Diabetes

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## Background

Biomarkers are relevant to the study of health and disease processes across the INMD mandate, including autoimmune disorders of organs in the human digestive system, renal system and diseases such as diabetes mellitus. The availability of accurate, non-invasive biomarkers will serve to improve diagnosis of a variety of illnesses and provide targeted delivery of care. For nutrition, identifying biomarkers to characterize micronutrient status and the biological impact of nutrition interventions, both at clinical and programmatic level, has gained importance. For kidney diseases, a number of candidate biomarkers already have been identified. However, there remains a pressing need to study such markers both singly and in combination in relation to the pathophysiology of kidney diseases. This will result in the development of better and more targeted therapies.

## Current Activity in Canada and Elsewhere

Canadian investigators have been world leaders in the identification of susceptibility genes for various clinical disorders, as well as in validating serodiagnostic tests that distinguish between types of chronic inflammatory bowel diseases (IBD). These biomarkers may also serve as prognostic indicators. Canadian scientists have access to genome wide expression arrays in high throughput screening studies. Canada also has resources in terms of large, well defined patient registries, bioinformatics, and statistical genetics. Outside of Canada, there are a number of IBD consortia, in North American, Europe, and elsewhere internationally.

## Gaps and Opportunities

The identification of valid biomarkers will serve to improve several dimensions of patient care including the prediction of disease susceptibility and the potential for subsequent prevention of disease onset, assist in earlier diagnosis, and prognostic information related to the severity of clinical phenotype and disease complications. Such information could influence decisions about interventions, the development of novel therapies, and predict therapeutic outcomes, drug toxicities (pharmacogenetics), and drug resistance. The IBD field is still at a stage of gene discovery, but there is a gap between gene discovery and clinically relevant outcomes for affected patients. With the advent of biologic agents for various autoimmune disorders, possessing the potential to alter disease expression and natural history, it has become increasingly clear that a better ability to accurately predict disease phenotypes and measure disease activity are critical for an assessment of therapeutic efficacy. However, the absence of reliable markers of disease outcomes has hampered assessments of efficacy of novel therapeutics. One of the key goals of future biomarker studies is to obtain longitudinal assessments of available biomarkers following specific therapeutic interventions and to correlate these with validated disease activity indices.

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# Regenerative Medicine and Nanomedicine Initiative

Christopher Yip and Eric Marcotte

## Novel Tools and Technologies for Biomarker Detection, Analysis, and Characterization

Given the complexity of biological systems, research programs and strategies that integrate different disciplines of knowledge, different types of technology and informatics, and different levels of biological organization are increasingly making the greatest advances in answering previously inaccessible questions of broad significance and application. The power and importance of a multidisciplinary approach to healthcare innovation is not only evident in nanotechnology and its attendant benefits to medicine, but in a wide range of far-reaching areas of life science inquiry - including systems biology, chemical biology, cancer research, regenerative medicine, stem-cell biology, and the technology platforms that support these initiatives in critical ways.

To date, most of the strategic CIHR funding for multi-disciplinary research at this interface (with direct application to biomarkers) has been provided by the Collaborative Health Research Projects (CHRP) – co-funded by CIHR and NSERC – and by various Invention, Tools, and Techniques RFAs and New Discoveries/Catalyst Grant RFAs offered by several CIHR branches – most notably the Institute of Genetics and the Regenerative Medicine and Nanomedicine Initiative. A number of recent grantees of these programs have been suggested as participants for this workshop.

The interface between clinical/biomedical research and the physical/applied science domains needs to be explicitly considered in any discussion of biomarkers, as the application of novel technologies will undoubtedly have a profound impact on our ability to detect, assess, measure, and apply new biomarkers for health benefit. Indeed, powerful new tools for health research are now emerging from the physical, computational and applied sciences. These include:

exciting new data assembly and modeling strategies for systems biology

bio-imaging and photonics technology for monitoring, manipulating and measuring biological systems

micro-patterned surfaces for manipulating and analyzing cellular systems

next-generation high-throughput platforms for genome sequencing, association genetics, and structural genomics

methods for miniaturization and integration of physical and (bio)chemical processing steps (e.g. multilayered soft lithography, micro-fluidics, electro-optical sensing, etc.) to decrease cost and sample volumes, and increase throughput.

It is expected that inclusion in this workshop of participants from the tool/technology development research domains will enhance and facilitate discussions of biomarker detection, analysis and characterization.

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Collaborative Health Research Projects (CHRP): [http://www.nserc-crsng.gc.ca/Professors-Professeurs/Grants-Subs/CHRP-PRCS\\_eng.asp](http://www.nserc-crsng.gc.ca/Professors-Professeurs/Grants-Subs/CHRP-PRCS_eng.asp)

Catalyst Grant: Invention and High-Risk, High-Benefit Research: <http://www.researchnet-recherchenet.ca/rnr16/viewOpportunityDetails.do?prog=621>

Integrating the Physical and Applied Sciences into Biomedical Research Workshop III - <http://www.cihr-irsc.gc.ca/e/38735.html>

# Workshop Program

## Vision for the Workshop

To define and refine the focuses of biomarker research and development that could underpin a Request for Applications (RFA). Such an RFA will be issued to the Canadian health research community with the intent of enabling excellence and distinction in Canada's biomarker solutions aimed at more precise personalized health care.

## Objectives of the Workshop

1. To examine the current state of knowledge regarding the realm of biomarkers related to more precise healthcare interventions, reaching from prevention through to management of advanced stages of disease.
2. To deliberate and advise about the most important themes related to biomarkers wherein programmatic funding could move the field forward in Canada, especially in niche domains where we can compete and contribute distinctively.
3. To discuss and prioritize the best funding vehicles to use in offering a Request for Applications to the Canadian health research community.
4. To develop the framework for a Request for Applications on the topic of biomarkers for better human health.

## Thursday November 19 (Day 1)

|         |  |
|---------|--|
| 7:00 am | Registration and Breakfast [Alpine Foyer]  |
| 7:55 am | Welcome and Introduction to the Workshop [Alpine Room]<br>Drs. Peter Liu, Bruce McManus, and Glen Roberts  |
| 8:15 am | Brief Perspectives on Biomarkers from Partnering Institutes and Initiatives – Institute or Initiative Delegate [Alpine Room]<br>Institute or Initiative Delegate |

[A series of 3-minute introductory statements focused on what the Precision Medicine Initiative could mean to each research community]

|         |  |
|---------|--|
| 9:15 am | Plenary Session I: The Personalized Healthcare Imperative – Where Biomarkers Fit (What are biomarkers, that is, how are they currently defined? Why are they important in the public and private sectors? Where are the great opportunities to make a difference through biomarker solutions?) [Alpine Room] |
|---------|--|

Chairs: Drs. Tim Triche, Pavel Hamet

[10-minute presentations]

Drs. Tim Triche, Jean-Claude Tardif, Mohammed Karmali, Pavel Hamet

|          |                             |
|----------|-----------------------------|
| 10:15 am | Health Break [Alpine Foyer] |
|----------|-----------------------------|

- 10:30 am Respondents [Alpine Room]  
[Fiona Miller, Mark Silverberg, for 3 minutes each, followed by Open Moderated Discussion]
- 11:00 am Plenary Session II: Quality Measurement of Biomarkers  
(How do we assess and measure biomarkers? What are key considerations in this regard?) [Alpine Room]
- Chairs: Drs. Peter Liu, Christoph Borchers
- [10-minute presentations]
- Drs. Cynthia Balion, Peter Kavsak, Shana Kelley, Christoph Borchers
- 12:00 pm Respondents [Alpine Room]  
[Dan Holmes, Olga Vitek, Sean Higgins, Rob Beanlands, for 3 minutes each, followed by Open Moderated Discussion]
- 12:30 pm Lunch and Informal Discussion [Alpine Foyer]
- 1:15 pm Plenary Session III: Taking Biomarkers from Discovery to the Clinic (How do we extract value from complex data sets? How should multi-disciplinary teams work? Which cohorts for which question? Which molecular signature should we measure? How do we manage biospecimens? How do we achieve rigour in analysis without paralysis? How do we followup on biological leads? What is pharma's perspective on biomarkers? What are the social and economic considerations in developing biomarkers? How do new biomarker tests/panels reach the healthcare systems?) [Alpine Room]
- Chairs: Jean-Claude Tardif, Sean Higgins
- [10-minute presentations, a few done as a duet]
- Computational Excellence – Rob Balshaw  
Seamless Teams –Janet Wilson-McManus  
Cohort Identification & Management – Don Sin, Jolanda Cibere  
High Performance Platforms – John Wilkins, John Rioux  
Harnessing Engineering & Nanosciences – David Juncker  
Biospecimen Management – Peter Watson  
Validation & Qualification – Agnes Klein
- 2:30 pm Health Break [Alpine Foyer]
- 2:45 pm Plenary III Continues... [Alpine Room]
- Extracting Biological Value – James Woodgett  
Perspective of Investigators –Jennifer Van Eyk  
Perspective of Imagers – Robert Bartha  
Pharma's Needs – David Brener  
Diagnostic Industry's Perspective – Sean Higgins, James Donnelly  
Social & Economic Considerations – Carlo Marra  
Bioethical Consideration – Ron Heslegrave  
Bridging into the Healthcare Systems – Bruce McManus

- 4:10 pm Stretch Break
- 4:15 pm Respondents [Alpine Room]  
[Michael Kobor, David Juncker, Anne Goodbody, for 3 minutes each, followed by Moderated Open Discussion]
- 5:00 pm Summarization, Work for the Evening & Day Two [Alpine Room]
- 6:30 pm Cash Bar Reception [Geneva Room]
- 7:00 pm Dinner and Special Presentation (20 minutes) [Geneva Room]  
  
Speaker: Dr. Sergio Baranzini, "How do biomarkers, systems biology and better medical care connect?"

## Friday November 20 (Day 2)

- 7:30 am Registration and Breakfast [Alpine Foyer]
- 8:15 am Reprise on Day One and Outline of Today's Work [Alpine Room]  
Drs. Peter Liu, Bruce McManus, Glen Roberts and all participants
- 8:40 am Shawnmarie Mayrand-Chung: "An NIH Perspective on Biomarkers Discovery and Development" [Alpine Room]
- 9:00 am Breakout Groups for RFA Formulation  
  
Participants will have an opportunity to self-select a minimum of four sessions (depending on time) and move to different sessions throughout the day.
- |                |    |  |
|----------------|----|--|
| Boardroom 348  | A. | What types of biomarkers should be measured? How are the approaches different/same for different disease types or research communities? Host: Pavel Hamet  |
| Boardroom 349  | B. | How does one measure biomarkers, and how does one move them onto clinically relevant platforms? Host: Christoph Borchers   |
| Boardroom 353  | C. | What computational tools and skills are necessary? Host: Robert Balshaw  |
| Alpine Room    | D. | How can public health needs and industry needs be concurrently met through biomarker discovery and development (weighing social and economic benefits)? Host: Sean Higgins   |
| Alpine Room    | E. | How can investigative teams work with regulatory authorities to move biomarkers ahead most effectively? Host: Agnes Klein  |
| Alpine Room    | F. | Why does research into biomarkers fail to translate into clinical practice? How can new, effective biomarkers make it expeditiously into the healthcare system? Host: Fiona Miller                                 |
| Zurich Room    | G. | How are observational and other clinical trials set up to evaluate biomarker utility, and how can biomarker solutions be sought more consistently in accompaniment of therapeutic clinical trials? Host: Mark Loeb |
| Neuchatel Room | H. | What is/are Canada's niche/s in regards to biomarkers? What priorities are there for each of the clinical specialties or disciplines? Host: Peter Liu  |

Montreaux Room

I. How can ethical consideration be handled well for potential subjects, for researchers, for the private sector, and for others? Host: Ron Heslegrave

|          |  |
|----------|--|
| 10:15 am | Health Break and Refreshments [Alpine Foyer]   |
| 10:30 am | Breakout Groups for RFA Formulation – Cont'd   |
| 12:30 pm | Lunch [Alpine Foyer]   |
| 1:15 pm  | Breakout Reports (5 minute presentations by the rapporteur from each Breakout Group) [Alpine Room]   |
| 2:00 pm  | Moderated Open Discussion and Key Elements of the RFA (priority setting) [Alpine Room]<br>Led by Drs. Glen Roberts, Bruce McManus, Peter Liu |
| 3:30 pm  | Health Break   |
| 3:45 pm  | Final Reflections – All participants [Alpine Room]   |
| 4:15 pm  | Next Steps [Alpine Room]   |
| 4:30 pm  | Adjournment  |
| 4:45 pm  | Debrief of Planning Team [Alpine Room]   |

# Participants

| Picture  | Name  | Contact Information   | Research Interests   |
|--|---|---|--|
|   | Fred Apple<br>Professor                             | Department of Laboratory Medicine & Pathology<br>University of Minnesota<br>Medical Director Clinical Laboratories, Hennepin County Medical Center<br>HCMC, Clinical Labs P4 ,<br>701 Park Ave<br>Minneapolis, MN 55415<br><br>Phone: 612 873 3324<br>Email: apple004@umn.edu<br>Website: mmrf.org                            | Application of cardiac and vascular biomarkers and assays for the detection of myocardial cell damage, ischemic and inflammatory injury, reperfusion, and risk stratification and outcomes assessment.   |
|  | André Arsenault<br>Professor                        | Département de médecine nucléaire<br>Institut de Cardiologie de Montréal<br>5000 rue Bélanger<br>Montréal, QC<br>Email: andre.arsenault@icm-mhi.org   | Nuclear Cardiology, Pharmacological, Thermal & Mental Stress, Experimental Design, R&D Medical Instrument, Multivariate Statistics, Organizational Behavior.   |
|  | Stephanie Atkinson<br>Professor and Associate Chair | Department of Pediatrics<br>McMaster University<br>HSC 3A42, 1200 Main St W<br>Hamilton, ON L8N 3Z5<br><br>Phone: 905-521-2100 x 75644<br>Email: satkins@mcmaster.ca<br>Website:<br><a href="http://www.fhs.mcmaster.ca/pediatrics/stephanie_atkinson.html">http://www.fhs.mcmaster.ca/pediatrics/stephanie_atkinson.html</a> | Dr. Atkinson's research centres on nutrition and disease (or drug) exposures during fetal, neonatal and early childhood life as determinants of metabolic programming that leads to sub-optimal growth and risk of adult-onset diseases. This includes a prospective, longitudinal birth cohort study of the early determinants of obesity, diabetes, and risk of cardiovascular disease and osteoporosis in over 900 children. The "late effects" of disease and drug therapy on growth and development is investigated in prematurely born infants and in children with various cancers, cystic fibrosis or epilepsy.  |
|  | Cynthia Balion<br>Associate Professor               | Department of Laboratory Medicine<br>Hamilton General Hospital<br>McMaster University<br>Hamilton, ON L8L 2X2<br><br>Phone: 905- 527-4322 x 46120<br>Email: balion@hhsc.ca  | Dr. Balion is actively involved in basic and clinical research including evidence-based laboratory medicine (EBLM). Her research interests are in the discovery and evaluation of biomarkers for neurodegenerative diseases, systematic reviews of diagnostic test accuracy, geriatric clinical biochemistry and enhancing laboratory test reporting. As a clinical biochemist consultant her focus areas are in quality control and point of care tests. She is a co-investigator for the Canadian Longitudinal Study on Aging (CLSA) sharing responsibility for sample collection, biobank operation, and test methodology for high-throughput biomarker analysis of the stored samples. |



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Dr. Balshaw's research encompasses multivariate analytical methods for the analysis of health data, decision analytic modeling for multi-state chronic diseases, economic analysis and modeling, and innovative methods for the analysis of high dimensional microarray genomic and proteomic data. Dr. Balshaw is the senior statistician for many international research initiatives, and a key advisor to the pharmaceutical and biotechnology industry on many aspects of advanced methodology and statistical analysis.



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ICR fosters research based on internationally accepted standards of excellence, which bear on preventing and treating cancer, and improving the health and quality of life of cancer patients.

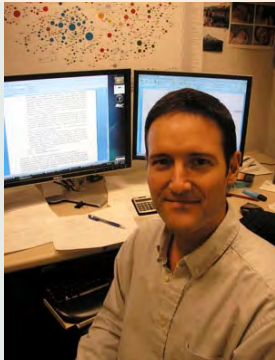
III supports research and helps to build research capacity in the areas of infectious disease and the body's immune system. Through the Institute's programs, researchers address a wide range of health concerns related to infection and immunity including disease mechanisms, disease prevention and treatment, and health promotion through public policy.



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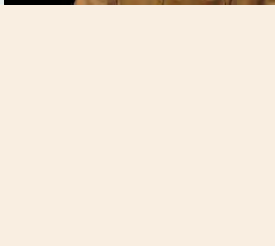
A neurologist and neuro-immunologist, conducts laboratory research directed at understanding principles of immune regulation including B cell, T cell and APC interactions, and how these might relate to inflammatory neurological diseases, primarily multiple sclerosis. A strong interface with neuroscience laboratories provides opportunities to investigate principles of immune-neural interactions and their relevance to CNS injury, repair and regeneration. Dr Bar-Or coordinates several multi-center research studies in multiple sclerosis including, a CIHR new emerging team (NET) in autoimmunity that studies similarities and differences in pathophysiology of different human autoimmune diseases in children and adults.



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My interests include genetics and genomics of multiple sclerosis. Our lab has contributed to mapping MS susceptibility genes, and to creating extensive gene expression profiles of different disease stages. In addition, animal models are being used to validate our findings. We have also identified markers of the pary response and disease progression.



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Dr. Bartha's group at the Robarts Research Institute develops methods in magnetic resonance (MR) imaging and spectroscopy to investigate anatomical and chemical changes that occur in brain tissue as a result of disease or injury. These methods can be applied to conditions such as stroke, cancer, epilepsy, mental illness, and

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As the Director of the University of Victoria – Genome BC Proteomics Centre, - the only solely proteomics devoted - platform our research is focused on the development, improvement and application of mass spectrometry (MS) based proteomics technologies. Particularly, our research is centered on the development of approaches for targeted, multiplex, fast and absolute protein quantitation (concentration!) in clinical specimen. Special interest is dedicated to approaches using Multi-Reaction Monitoring (MRM) and those combining immuno-affinity enrichment of peptides and MS (SISCAPA and iMALDI). These approaches are currently being used for biomarker verification and discovery.



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ICR fosters research based on internationally accepted standards of excellence, which bear on preventing and treating cancer, and improving the health and quality of life of cancer patients.  
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ICRH supports research into causes, mechanisms, prevention, screening, diagnosis, treatment, support systems, and palliation for a wide range of conditions associated with the heart, lung, brain (stroke), blood, blood vessels, critical care and sleep.



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Marjorie is The PROOF Centre's Chief Development Officer and is responsible for the Centre's business development activities. With fourteen years of business and legal experience, Marjorie's prior involvement in the biotechnology industry includes business development roles at Twinstrand Therapeutics, Inc. and Forbes Medi-Tech, Inc., two Vancouver-based biotechnology companies developing therapies to treat cancer and cardiovascular diseases, respectively. Additionally, Marjorie's prior private practice experience included providing legal advice to Canadian biotechnology companies.



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My primary research area is the development of diagnostic products used in the screening, diagnosis and monitoring of disease. Specifically, we are focusing on areas where we can improve health care effectiveness and safety through the integration of informatics, in vivo and in vitro testing. We identify opportunities for improvement in clinical workflow, the reduction of risk for medical errors and medical complications which add to the health care burden. By improving patient management we can better manage limited health care resources.



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The Laboratory of Cognitive Neuroscience and Women's Health focuses on women's health issues, sex differences in the brain, and the effects of estrogens on cognition. An underlying assumption is that the adult CNS is plastic and particularly responsive to circulating steroid hormones as well as experience. Convergent methods such as standard psychological tests of memory and pain response, psychophysical tests, genetic tests, steroid hormone assays, fMRI, and qualitative interviewing are used to explore CNS changes with prophylactic oophorectomy in women who carry the BRCA1/2 genes, cutting of the genitalia as in female genital circumcision/mutilation/cutting, and with the menstrual cycle.

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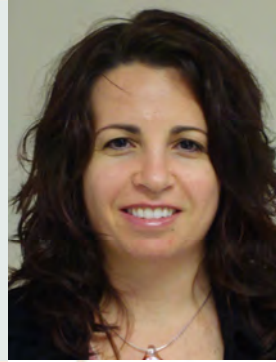
IGH's mission is to foster research excellence regarding the influence of gender and sex on the health of women and men throughout life, and to apply these research findings to identify and address pressing health challenges.

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ICRH supports research into causes, mechanisms, prevention, screening, diagnosis, treatment, support systems, and palliation for a wide range of conditions associated with the heart, lung, brain (stroke), blood, blood vessels, critical care and



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1) The translation of personalized medicine into healthcare practice. 2) Ethical issues in biobanking and related research 3) Using public engagement and deliberative democracy to inform policy on novel biotechnologies

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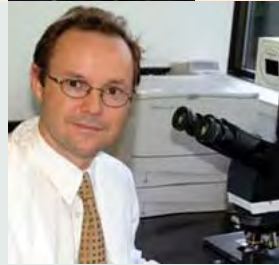


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My research work is in clinical, analytical and statistical aspects of laboratory medicine - ranging from development of assays, their interpretation and investigation and understanding of analytical interferences. I am appointed as a Medical Officer of the PROOF trial and I am charged with assisting the migration of biomarker panels into the clinical laboratory.



David Huntsman  
Associate Professor

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Faculty of Medicine  
BC Cancer Agency  
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Our laboratory uses genetic and genomic approaches to identify new biomarkers to improve cancer control. We are currently focused in two areas: the development of improved tools to identify individuals at increased risk for gastric cancer and the development of tissue based biomarkers to improve the classification and treatment decisions for women with ovarian carcinoma. We are currently using next generation sequencing as a discovery platform and have a long track record of taking discoveries from basic genomic research into large cohorts of clinically annotated samples to determine their clinical relevance.



David Juncker  
Assistant Professor

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<http://wikisites.mcgill.ca/djgroup>

Design, development and use of Micro and Nanobiotechnologies, and specifically microfluidics, in biology and medicine. One important focus is on scalable technologies which includes a novel antibody microarray platform for biomarker validation and diagnosis that can be scaled to comprise thousands of antibody pairs against candidate biomarkers.



Mohamed Karmali  
Director General

Public Health Agency of Canada  
Office of Biotechnology Genomics  
and Population Health  
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aspc.gc.ca  
Website: [www.phac-aspc.gc.ca](http://www.phac-aspc.gc.ca)

The Office of Biotechnology, Genomics and Population Health, Public Health Agency of Canada, has three main research interests: (i) correlating single nucleotide polymorphisms in innate immunity pathways and inflammatory biomarker levels with health outcomes in chronic diseases (e.g., metabolic syndrome and type 2 diabetes) and infectious diseases (e.g., influenza and tuberculosis). This work is conducted through bioinformatics analysis of Genome-Wide Association study data in publicly available databases and collaborative clinical studies; (ii) investigating the role of micronutrients in modulating innate immune responses as measured by inflammatory biomarker levels; and (iii) public opinion research on direct-to-consumer marketing of nutrigenomic tests.

Shana Kelley  
Professor

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Nanoscale biosensors and nanobiomaterials; development of new technologies for biomarker analysis and clinical diagnostics

Jonathan Kimmelman  
Assistant Professor

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|---|--------------------------------------|---|--|
|   |                                      | Website:<br><a href="http://www.mcgill.ca/biomedicaethicsunit/faculty/kimmelman/">http://www.mcgill.ca/biomedicaethicsunit/faculty/kimmelman/</a>   |  |
|   | Agnes V. Klein<br>Director           | Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics Health Canada<br>200 Tunney's Pasture Driveway, AL 0700C<br>Ottawa, ON K1A 0K9<br><br>Phone: 613-954-5706<br>Email: <a href="mailto:agnes_v._klein@hc-sc.gc.ca">agnes_v._klein@hc-sc.gc.ca</a>  | I am primarily a regulator. My primary responsibilities are in the biotherapeutics and radiopharmaceuticals area. Radiopharmaceuticals are one form of imaging that can lead to development of biomarkers and surrogate endpoints. In addition to my primary regulatory responsibilities, I also lead the regulatory part of Genomics and Personalized Medicine. The role is appropriate because of the responsibility of my centre for radioisotope imaging, primarily and because monoclonal antibodies, or biotherapeutics can also be used as carriers of imaging molecules.   |
|    | Michael Kobor<br>Assistant Professor | Department Medical Genetics University of British Columbia CMMT - 950 West 28th Avenue, Room 2024<br>Vancouver, BC V5Z 4H4<br><br>Phone: 604-875-3803<br>Email: <a href="mailto:msk@cmmt.ubc.ca">msk@cmmt.ubc.ca</a><br>Website: <a href="http://www.cmmt.ubc.ca/">http://www.cmmt.ubc.ca/</a>  | Dr. Kobor's laboratory touches on some of the fundamental questions in chromatin biology, applying innovative genomic and proteomic technologies. These queries include how distinct chromosomal neighbourhoods are established, how they function and interact with enzymes involved in DNA metabolism, what the functional differences between histone variants and canonical histones are, and how chromatin-remodeling complexes are regulated. Most recently, Dr. Kobor has begun investigating epigenetic variation in humans, with a particular focus on the effects of social environment and aging, as well as testing for epigenetic patterns correlated with respiratory disease. |
|   | Tina Lawton<br>Project Manager       | Institute of Circulatory and Respiratory Health, CIHR<br>585 University Avenue, NCSB 11-1268<br>Toronto, ON M5G 2N2<br><br>Phone: 416-340-4536<br>Email: <a href="mailto:tlawton@uhnresearch.ca">tlawton@uhnresearch.ca</a>   | ICRH supports research into causes, mechanisms, prevention, screening, diagnosis, treatment, support systems, and palliation for a wide range of conditions associated with the heart, lung, brain (stroke), blood, blood vessels, critical care and sleep.  |
|  | Peter Liu<br>Scientific Director     | Institute of Circulatory and Respiratory Health, CIHR<br>585 University Avenue, NCSB 11-1268<br>Toronto, ON M5G 2N2<br><br>Phone: 416-340-3035<br>Email: <a href="mailto:peter.liu@utoronto.ca">peter.liu@utoronto.ca</a>   | ICRH supports research into causes, mechanisms, prevention, screening, diagnosis, treatment, support systems, and palliation for a wide range of conditions associated with the heart, lung, brain (stroke), blood, blood vessels, critical care and sleep.  |
|  | Mark Loeb<br>Professor               | McMaster University<br>1200 Main St West<br>Hamilton, ON L8N 3Z5<br><br>Phone: 905-525-9140 x 26066<br>Email: <a href="mailto:loebm@mcmaster.ca">loebm@mcmaster.ca</a><br>Website:<br><a href="http://fhs.mcmaster.ca/pathology/contact_us/faculty/faculty_bios/loeb.html">http://fhs.mcmaster.ca/pathology/contact_us/faculty/faculty_bios/loeb.html</a> | My research interests include epidemiologic and genomic population-based studies on viral infections including influenza, West Nile, and dengue. I am particularly interested in the use of biomarkers in epidemiological infectious disease studies to further knowledge of biological processes (helping to bridge bench discovery to population research) and as tools with direct potential clinical utility.  |

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|---|--|---|---|
|   | <p>Mary-Jo Makarchuk<br/>Assistant Director</p>          | <p>CIHR Institute of Nutrition, Metabolism and Diabetes<br/>Banting Bldg, 100 College St., Suite 207L<br/>Toronto, ON M5G 1L5</p> <p>Phone: 416-978-1324<br/>Email: mary-jo.makarchuk@sickkids.ca</p>   | <p>INMD supports research to enhance health in relation to diet, digestion, excretion, and metabolism; and to address causes, prevention, screening, diagnosis, treatment, support systems, and palliation for a wide range of conditions and problems associated with hormone, digestive system, kidney, and liver function.</p>   |
|    | <p>Simone Marcantonio<br/>Project Officer</p>            | <p>Institute of Circulatory and Respiratory Health, CIHR<br/>160 Elgin Street, 9th Floor<br/>Ottawa, ON K1A 0W9</p> <p>Phone: 613-946-0892<br/>Email: simone.marcantonio@cihr-irsc.gc.ca</p>  | <p>ICRH supports research into causes, mechanisms, prevention, screening, diagnosis, treatment, support systems, and palliation for a wide range of conditions associated with the heart, lung, brain (stroke), blood, blood vessels, critical care and sleep.</p>  |
|   | <p>Eric Marcotte<br/>Associate Director</p>              | <p>Regenerative Medicine and Nanomedicine, CIHR<br/>160 Elgin St, 9th Floor<br/>Ottawa, ON K1A 0W9</p> <p>Phone: 905-467-1822<br/>Email: eric.marcotte@cihr-irsc.gc.ca</p>  | <p>Regenerative Medicine and Nanomedicine</p>   |
|  | <p>Carlo A. Marra<br/>Associate Professor</p>            | <p>University of British Columbia<br/>2146 East Mall<br/>Vancouver, BC V6T1Z3</p> <p>Phone: 778-229-5480<br/>Email: cmarra@exchange.ubc.ca<br/>Website: <a href="http://core.ubc.ca/">http://core.ubc.ca/</a></p>   | <p>Carlo is a Tier II Canada Research Chair in Pharmaceutical Outcomes and holds a Michael Smith Foundation for Health Research Scholar Award in Health Services Research. Carlo's main research interests have been in health economics, quality of life research, and pharmacoepidemiology. Also, he is interested in research defining and evaluating the role of pharmacists in health care delivery.</p> |
|  | <p>Shawnmarie Mayrand-Chung<br/>NIH Program Director</p> | <p>The Biomarkers Consortium<br/>National Institutes of Health<br/>9000 Rockville Pike<br/>Bethesda, Maryland 20892</p> <p>Phone: 301-435-1705<br/>Email: mayrands@od.nih.gov<br/>Website: <a href="http://ppp.od.nih.gov/">http://ppp.od.nih.gov/</a> and <a href="http://www.biomarkersconsortium.org">www.biomarkersconsortium.org</a></p> |   |



Linda Mealing  
Associate Director

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The overall aims of the CLSA are:

- To examine aging as a dynamic process.
- To investigate the inter-relationship among intrinsic and extrinsic factors from mid life to older age.
- To capture the transitions, trajectories and profiles of aging: successful aging.
- To provide infrastructure and build capacity for sustained high quality research on aging in Canada.



John McLaughlin  
Vice President

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He leads interdisciplinary teams in large population-based studies to identify cancer causes by examining the interaction of environmental and genetic factors. Dr. McLaughlin also works to improve our knowledge and apply it in population-based cancer prevention, screening and surveillance programs with the ultimate goal of reducing the risk and burden of cancer in Ontario.



Bruce McManus  
Director

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Ravi S. Menon  
Deputy Director and  
Canada Research Chair

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My research area lies in the development of technology for ultra high field functional magnetic resonance imaging (fMRI) as well as understanding what it measures and tells us about human brain function. Driven by neuroscience questions posed by our colleagues, we develop new hardware (such as new radio frequency coils) and software solutions (novel pulse sequences) for fMRI. We utilize MRI scanners at 3 Tesla (T), 7 T and 9.4 T to understand the normal anatomy and function of both humans and animals as well as to understand the changes in anatomy and function that accompany disease and degeneration in the brain.



Fiona Alice Miller  
Associate Professor

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Fiona A. Miller (PhD) is an Associate Professor in the Department of Health Policy, Management and Evaluation and a member of the Joint Centre for Bioethics at the University of Toronto. She holds a New Investigator Award from the Institute of Health Services and Policy Research of the Canadian Institutes of Health Research (CIHR). Fiona leads a research program centred on health technology policy, especially for diagnostic and screening technologies.



Tommy Nilsson  
Director

Proteomics and Systems Medicine Program  
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Dr. Nilsson's main research area is Cell Biology focusing on adipose and hepatic tissues in disease. He has made significant contributions to the understanding of basic mechanisms of protein transport and processing in the secretory pathway. He has published some 50 articles which have received more than 6000 citations and he has an H-index of 36. Dr. Nilsson is an investigator and Director of the Proteomics and Systems Medicine Program at the Research Institute of the McGill University Health Centre and Professor at McGill University. In 2009, he was awarded a Tier-1 Canada Research Chair in Proteomics and Systems Medicine.



Morag Park  
Scientific Director

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Receptor Tyrosine Kinase; Scaffold Proteins; Signal Transduction; Actin Remodelling; Cell Migration and invasion; tumor metastases

Linda Piazza  
Director, Research

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Through the Federation Research Fund, HSFC funds research targeted to three priority areas: stroke, resuscitation and obesity. In particular, research questions related to secondary prevention of stroke; obesity and the built environment; knowledge translation in resuscitation; and monitoring and optimizing CPR are currently being addressed.

The HSF grant-in-aid program is "investigator-initiated" and provides opportunities for operating grants in any area relevant to the HSF Mission.



Parminder Raina  
Professor/Lead Investigator

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Website: <http://www.clsa-elcv.ca/en/welcome> and [http://www.fhs.mcmaster.ca/ceb/faculty\\_member\\_raina.htm](http://www.fhs.mcmaster.ca/ceb/faculty_member_raina.htm)

Dr. Raina specializes in the epidemiology of aging with emphasis on developing the interdisciplinary field of geroscience to understand the processes of aging from cell to society. Dr. Raina has expertise in epidemiologic modeling, systematic review methodology and knowledge transfer.



Jennifer Ralph  
Project Manager

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ICRH supports research into causes, mechanisms, prevention, screening, diagnosis, treatment, support systems, and palliation for a wide range of conditions associated with the heart, lung, brain (stroke), blood, blood vessels, critical care and sleep.



John D. Rioux  
Associate Professor of  
Medicine

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Chronic immune-mediated diseases affect approximately 3-5% of the population worldwide. Cardiovascular diseases (CVDs) remain the leading cause of mortality in the world, with more than 15 million deaths each year. The Laboratory of Genetics and Genomic Medicine of the Université de Montréal and Montreal Heart Institute aims to identify the causes of these common diseases and to identify relevant biomarkers and therapeutic targets to improve the health of patients with these debilitating diseases.



Eve A. Roberts  
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My biomedical research focus is the pathogenesis and diagnosis of metabolic liver diseases. My recent laboratory research has examined Wilson disease. Wilson disease provides an important perspective on copper disposition; moreover, it resembles drug hepatotoxicity. Therefore I have proposed investigating Wilson disease as an example of endogenous hepatotoxicity. Appropriate biomarkers might provide expedited diagnosis of Wilson disease, and technologies already developed for drug hepatotoxicity may be relevant. Identifying biomarkers poses important conceptual problems relating to experimental design and interpretation. These issues are within the domain of my current research in philosophy of biology.



François Rousseau

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His research interests cover population genetics, the genetics of complex traits, translational medicine and genetic health services. Funded by CIHR since 1992, he realized large molecular epidemiology studies for FMR1 mutations in the general population (>40000 subjects). He studied FMR1 transmission in 25000 mother-child pair. CIHR funds the validation new DNA markers for osteoporosis and he is part of the international GENOMOS/GEFOS consortium. He has CIHR funding for health economics studies on the cost/effectiveness of genetic screening for different diseases.

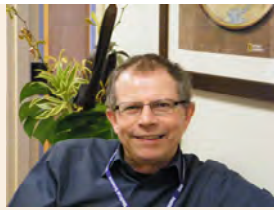


Ernest Seidman  
Professor

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My research has been concentrated on 4 main areas: i) gene-environment (microbial) interactions in the pathogenesis of chronic inflammatory bowel disease (IBD); ii) immune dysregulation and the pathogenesis of IBD, iii) the effect of inflammation on enterocyte cell biology and function, and its potential role in the prevention of colon cancer, and iv) novel diagnostic biomarkers & therapeutics for immune-mediated luminal GI disorders, including pharmacogenetics and serodiagnosocs. I am the principal investigator in the recently established Canadian Institute of Health Research New Emerging Team Grant: in Clinical Autoimmunity on Immune Mediated Intestinal Disorders.



Philip Sherman  
Scientific Director

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INMD supports research to enhance health in relation to diet, digestion, excretion, and metabolism; and to address causes, prevention, screening, diagnosis, treatment, support systems, and palliation for a wide range of conditions and problems associated with hormone, digestive system, kidney, and liver function.



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Genetics/Biomarkers and Clinical Outcomes in Inflammatory Bowel Disease

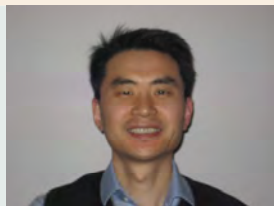


Katherine Siminovitch  
Professor/Senior Investigator

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A geneticist who studies the molecular mechanisms underpinning development of immunologic disease. Dr. Siminovitch aims to provide new knowledge and technologies enabling more efficacious and "individualized" therapies for major immunological diseases.

Dr. Siminovitch's research programme is directed at identifying the molecular factors which regulate normal immune responses and which, when disrupted, result in immune deficiency or autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease. Using both basic research tools and clinical sample sets, Dr. Siminovitch focuses on defining the genetic lesions predisposing to these diseases and the molecular pathways which couple these lesions to cell dysfunction and disease.



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Associate Professor

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Finding new biomarkers to enhance discoveries of novel therapeutic compounds in chronic obstructive pulmonary disease (COPD)

Bhagirath Singh  
Scientific Director

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III supports research and helps to build research capacity in the areas of infectious disease and the body's immune system. Through the Institute's programs, researchers address a wide range of health concerns related to infection and immunity including disease mechanisms, disease prevention and treatment, and health promotion through public policy.

Liz Stirling  
Assistant Director

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IMHA supports research to enhance active living, mobility and movement, and oral health; and addresses causes, prevention, screening, diagnosis, treatment, support systems, and palliation for a wide range of conditions related to bones, joints, muscles, connective tissue, skin and teeth.



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Director

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mhi.org

1- Personalized medicine and  
pharmacogenomics  
2- Biomarkers including integrative  
biology, metabolomics and  
molecular imaging  
3- Atherosclerosis assessment and  
regression



Scott J. Tebbutt  
Assistant Professor &  
CSO

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<http://www.proof.hli.ubc.ca/>

As Chief Scientific Officer for  
PROOF, I am involved in research  
that discovers, develops,  
commercializes and implements  
biological markers (biomarkers) to  
better prevent, diagnose, predict,  
manage and treat heart, lung and  
kidney failure. I also lead a research  
program focused on the genomics of  
complex respiratory disease,  
including the early and late reactions  
in allergic asthma. My research  
combines hypothesis-driven study of  
biological mechanisms with the  
development of advanced tools and  
technology to better facilitate basic  
and translational research.



Timothy J. Triche  
Chairman

Department of Pathology and  
Laboratory Medicine  
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My research focuses on genetic  
aspects of cancer biology and their  
biologic consequences. Current  
research emphasizes whole genome  
approaches to gene expression  
profiling and genomic  
polymorphisms using DNA  
microarrays and software developed  
by our group to analyze this data.  
Laboratory studies typically utilize  
tumor cell lines expressing  
transfected genes, or with silenced  
genes. Gene targets and biologically  
active small molecules are often  
analyzed in biologic context by these  
same methods. Clinical correlative  
studies utilize tumor tissue with  
linked clinical data.



Jennifer E. Van Eyk  
Professor

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Dr. Van Eyk, Ph.D. is an Professor  
of Medicine, Biological Chemistry  
and Biomedical Engineering at  
Johns Hopkins University, Baltimore  
and Director of both the Hopkins  
NHLBI Proteomics Innovation Group  
and the JHU Bayview Proteomics  
Center that has the mandate to  
facilitate application of proteomics in  
medicine. Her research laboratory  
studies the underlying molecular  
mechanism of cardiovascular  
disease using a large number of  
proteomic methodologies allowing  
development of better therapeutic  
intervention and robust biomarkers  
for the diagnosis, prognosis and risk  
stratification of heart disease.



Olga Vitek  
Assistant Professor

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Our lab focuses on statistical and  
computational methods for  
bioinformatics and systems biology.  
We are particularly interested in (1)  
accurate interpretation of high-  
throughput spectral measurements  
generated, e.g. by mass  
spectrometry-based proteomic,  
metabolomic and ionic  
experiments; (2) integration and  
interpretation of multiple  
heterogeneous measurements of a  
same biological system, and (3)  
development of informative and  
statistically motivated designs of

subsequent follow up experiments. We apply this methodology to a variety of investigations, which include discovery of biomarkers of cardiovascular disease.

Kimberly Walker  
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ICRH supports research into causes, mechanisms, prevention, screening, diagnosis, treatment, support systems, and palliation for a wide range of conditions associated with the heart, lung, brain (stroke), blood, blood vessels, critical care and sleep.



Peter H. Watson  
Director, Chief Physician, Senior Research Scientist, Adjunct Professor, Staff Pathologist

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Website: <http://www.bccrc.ca/drc/>

Our laboratory studies breast tumor progression with the medium term goal of improving our understanding of the important events that occur in breast tissues that promote the development and progression from pre-neoplastic lesions to pre-invasive and invasive tumors. Our overall approach is to identify cellular and molecular changes that occur in human tissues and then to correlate, connect, and understand the functional and clinical significance of these factors through exploration of factors within laboratory models and repeated cross referencing of findings to human tissues. The overall goals are to identify indicators of diagnosis, markers of risk, and functional targets that will improve our ability to diagnose, predict, and treat breast cancer at its early stages.

John A Wilkins  
Director  
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Email: [jwilkin@cc.umanitoba.ca](mailto:jwilkin@cc.umanitoba.ca)

- 1) Lymphocyte cell biology with specific emphasis on the cell surface, cell migration, adhesion and polarization.
- 2) Identification of biomarkers using proteomic approaches with emphasis on autoimmune diseases and transplantation.
- 3) Proteomic and functional genomics approaches to the characterization of cell virus interactions.
- 4) Proteomic and activity based profiling for characterization of microbes as potential biofuels sources.
- 5) Interfacing proteomics and immunology for the rapid identification of antibody specificity with application to hybridoma production, autoantibody and transfusion related alloantibody identification.

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The underlying common feature of the biological projects relates to developing descriptions of dynamic and complex biological processes. Policy research regarding evaluation of the impacts of personalized medicine and determining the appropriate federal responses.



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My primary focus in research is in program management of large-scale initiatives. At the current time, I am involved in discovering, developing, and implementing biomarkers of heart, kidney and lung failure and/or transplant into the clinical arena for improved patient care. I bring more than 26 years of hands-on research and program management experience from the clinical laboratory and basic and translational health research environments. Successful past initiatives range from laboratory renovations and equipment installation to operational infrastructure for research centres and institutions and in international, inter-disciplinary genomics initiatives.

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Single molecule biophysics /  
molecular imaging / molecular self-assembly