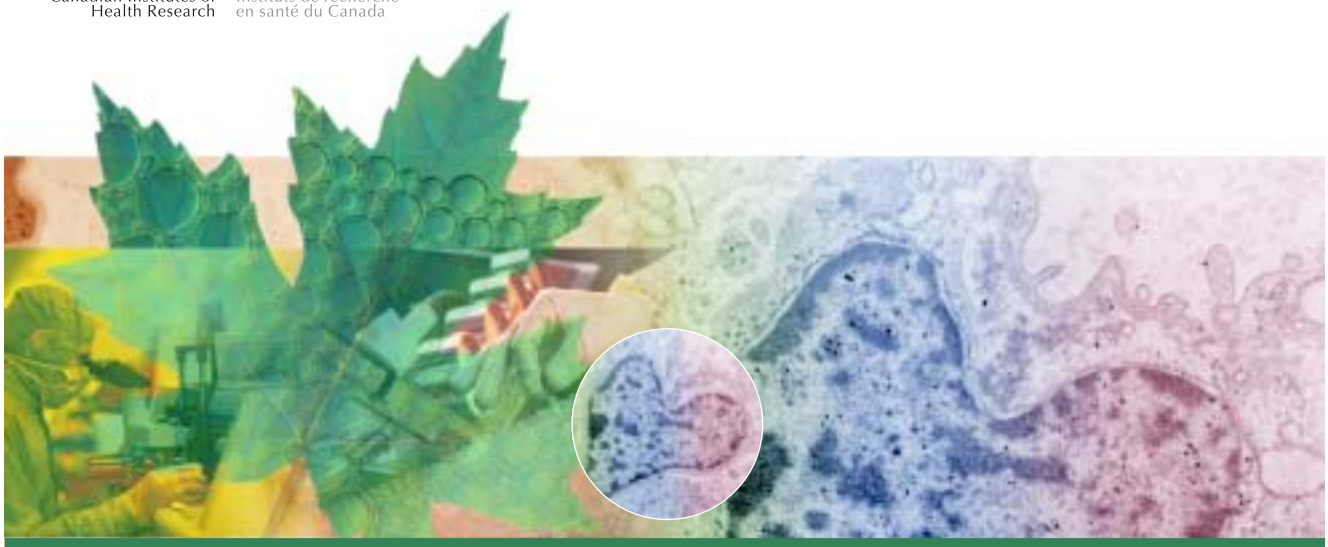
CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Health Canada
Santé Canada



Research Symposium on Integrating Discovery Platforms in Autoimmune Diseases

Kingbridge Centre
King City (Toronto), Ontario

December 4-5, 2003

Canada

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Health Canada
Santé Canada

Research Symposium on Integrating Discovery Platforms in Autoimmune Diseases

Kingbridge Centre
King City (Toronto), Ontario

December 4-5, 2003

Canada

CIHR Institute of Infection and Immunity
Siebens-Drake Research Institute, Suite 214
The University of Western Ontario
1400 Western Road
London, ON N6G 2V4
Fax (519) 661-4226
www.cihr-irsc.gc.ca

Cat. No.: MR21-53/2004E-PDF
ISBN 0-662-37745-1

Symposium Chairs

Dr. Katherine A. Siminovitch
Professor, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto

Dr. Eleanor Fish
Professor, Department of Immunology, University of Toronto

Symposium Organized by

CIHR Institute of Infection and Immunity
Dr. Bhagirath Singh
Scientific Director

Symposium Co-sponsored by

CIHR Institutes of
Aging, Gender and Health, Nutrition, Metabolism and Diabetes

Contents

Executive Summary

Introduction

The research symposium Integrating Discovery Platforms in Autoimmune Diseases aimed to develop a framework for a Canadian health research agenda in autoimmune diseases by targeting the following objectives: to explore the current situation in autoimmune diseases, and in particular basic mechanisms leading to, and commonalities among, these diseases; to identify strategic directions and potential research questions to be used, for example, as the basis for CIHR and partner-sponsored Requests for Applications and for integration of autoimmune diseases into the Canadian Lifelong Health Initiative; and to enhance collaboration and partnerships among stakeholders in the autoimmune diseases community.

Part I: Presentations

The presentations informed participants on the current situation in autoimmune research and set a framework for discussions related to strategic planning.

Session I: Autoimmune Diseases: Basic Mechanisms and Commonalities

Dr. Paul Fortin and **Dr. Luanne Metz** co-chaired Session I. **Dr. Amit Bar-Or** of the Montreal Neurological Institute presented Multiple Sclerosis: The Neuroimmune Interface. He discussed emerging themes in multiple sclerosis, a chronic inflammatory disease of the central nervous system that specifically targets the brain and spinal cord. **Dr. Charles Elson,** University of Alabama at Birmingham, spoke about The Inflammatory Bowel Diseases: Disorder of the Host (self) – Microbial (non-self) Interface, noting that the gastrointestinal tract has a number of immune-mediated inflammatory diseases such as autoimmune gastritis and celiac disease for which the target antigens have been defined. **Dr. Jayne Danska** from the University of Toronto discussed Type 1 Diabetes: Immunogenetic Mechanisms and Prospects for Deconstructing Complex Disease, stressing the need to identify more human markers (both cellular and genetic) of pre-diabetic autoimmunity. Immunopathogenesis of Rheumatoid Arthritis was discussed by **Dr. Peter Lipsky,** National Institute of Arthritis and Musculoskeletal and Skin Diseases. He described what he called the "Chaos Model of Autoimmunity." This model could be applicable to the pathogenesis of several autoimmune diseases and serve as a common basis for discussion. **Dr. Hani El-Gabalawy** chaired the final presentation in this session, in which **Dr. John McLaughlin** from the Samuel Lunenfeld Research Institute and the University of

Toronto presented Plans for Cohort Studies of the Canadian Lifelong Health Initiative. He described a cross-cutting, strategic, multi-institute initiative of the CIHR, the Canadian Lifelong Health Initiative, which will include two longitudinal studies—the Canadian National Birth Cohort and the Canadian Longitudinal Study on Aging—to investigate the hypothesis that disease burden is jointly determined by individual genetic endowment and complex environmental factors.

Session II: Immunological Principles

Co-Chairs **Dr. Karen Madsen** and **Dr. Ken Croitoru** directed Session II. **Dr. Stephen D. Miller,** Northwestern University Medical School, presented Immunological Principles Underlying the Pathogenesis and Immunoregulation of T Cell-Mediated Autoimmune Disease, discussing insights from his group's study of animal models of multiple sclerosis, the immunological principles underlying disease pathogenesis, and recent data on disease intervention using antigen-directed immunotherapies. **Dr. Andrew Macpherson,** University of Zürich, explained the Comparmentalisation of Immune Responses to Commensal Intestinal Bacteria, noting that non-pathogenic environmental organisms shape the immune system. **Mr. Steve Kerfoot** spoke on behalf of **Dr. Paul Kubes** from the University of Calgary. He discussed Trafficking of Leukocytes in the Brain: Learning by Watching Leukocyte Behaviour. He explained techniques used in Dr. Kubes's laboratory to image inflammation and leukocyte recruitment *in vivo.* Mr. Kerfoot concluded that *in vivo* imaging is a powerful tool to understand leukocyte recruitment by permitting direct observation of the process.

Session III: Science and Technology Platforms

Dr. Steve Collins and **Dr. Pere Santamaria** co-chaired Session III. The session opened with a presentation by **Dr. Claire Bombardier** (in association with **Dr. Sheilah Hogg-Johnson**), of the Toronto General Research Institute, who used the example of rheumatoid arthritis to illustrate Epidemiological Prognostic Models. She discussed classic predictors of disease outcome; disease activity at presentation, spread in terms of structural damage; functional ability; and variables such as socio-economic status apart from biological factors that have impact on disease outcome. **Dr. John A. Wilkins** from the Manitoba Centre for Proteomics presented three specific examples of The Application of Proteomics to the Study of Human Disease and discussed issues related to patient selection and sample acquisition, remarking that our proteomic capabilities are rapidly increasing. **Dr. Alexandre Montpetit**, of McGill University

and the Genome Quebec Innovation Centre, spoke about Emerging Genomic Tools to Study Autoimmune and Other Complex Diseases. He noted that the phenotype associated with a given disease and the underlying genetic defect can be studied by linkage analysis or association; however, due to the large size of the human genome, linkage analysis is more appropriate for mapping on a genomic scale. **Dr. Igor Jurisica**, University of Toronto and Queen's University, presented Towards an Integrated and Intelligent Molecular Medicine, discussing the computational aspects, challenges and possibilities that high throughput data obtained from microarray and protein array analyses afford in the characterization of complex diseases.

Session IV: US National Institute of Allergy and Infectious Diseases

Dr. Jack P. Antel chaired the final session in which **Dr. Daniel Rotrosen,** of the National Institutes of Health, USA, presented an overview of NIAID/NIH Funding and Strategic Planning as Related to Autoimmune Disease. In the 2003 fiscal year the NIH awarded an estimated $591 million dollars for autoimmunity research, which represents about 2.2% of the $27 billion dollar NIH budget. Approximately 45% of the autoimmunity expenditures are in projects examining pathogenesis and immune dysfunction, while 3% of the funds are allocated to the development of new animal models. The ultimate goal of the NIH's clinical research programs is to bring new vaccines, immune-based therapies and diagnostics to clinical practice.

Part II: Consultation Report
Supports, Opportunities and Challenges

Following the presentations, participants worked in small, mixed groups to discuss the following two issues with the goal of selecting strategic research directions. Some groups noted overlap between these two areas. The following is a summary of the discussions.

a) supports (e.g., infrastructure, capacity building) and opportunities for a Canadian health research agenda with a focus on integrated discovery platforms in autoimmune diseases

b) key challenges and considerations when developing a framework for a Canadian health research agenda with a focus on integrated discovery platforms in autoimmune diseases over the next ten years

Conference Recommendations

	New Research Questions	Supports Required
Methods for Early Case Findings	Benefits and drawbacks of doing direct-to-consumer advertising to generate cases, including analysis of retrieval numbers and false positives. Value of billing databases in identifying early diagnosis. Benefits of networks with general practitioners to identify early cases, e.g., through continuing medical education.	
Biometrics	Development of a clean, standardized, agreed-upon set of common variables for the determinants of health. Methods for cohort research, e.g., statistical analysis for innovative data mining of biometrics, patterns of care, patient outcomes. Innovative study designs, e.g., crossover designs with strategies for selecting control groups. Common, across-disease, early case definitions and innovative statistical methods for grouping clusters of early disease classifications.	

	New Research Questions	Supports Required
Cohort Methodologies	Innovative data collection methods that facilitate participation and retention, e.g., data collection that is integrated into practice, with value added for participating clinicians and applications to community practice. Research into methods for addressing practical issues related to cohort retention and follow-up, e.g., what to do when patients change physicians or move to another province, incentives for patients to remain involved in data collection processes. Issues related to methods of targeted sampling, e.g., to achieve community representation or to support standard tissue collection across various sites. Investigator-initiated research questions, e.g., on courses and prognosis of patients.	Supports are required to ensure that the research questions in this and the two following sections are addressed. A top priority in terms of capacity development involves the creation of a funded standing group or superstructure that enables integrated approaches among autoimmune disease researchers. Clinical researchers in autoimmune disease face many similar problems across Canada, both within individual diseases and across diseases. The purpose of this standing group would be to identify, clarify and address issues such as information technology, bar codes, privacy, data security, standards for tissue collection and handling, innovative methods for data collection and access to billing data.
Tissue Regeneration and Repair	Mobilization of progenitor cells to enhance repair. Manipulation of pre-existent cells to promote down regulation of cytopathic receptors, or upregulation of growth receptors. Molecular response during damage, recovery, repair and remodeling. The process of tissue response to damage (fibrosis, gliosis), when it ceases to be beneficial and becomes detrimental to repair.	Effective collaboration and cohesion among the agendas of hospitals, research institutes, universities, as well as public and private funding agencies. Coordinated access to relevant tissues to optimize research. Rational integration of the multiple federal programs in existence to facilitate and optimize hiring practices and initiation of research.

	New Research Questions	Supports Required
Biomarkers	Biomarker identification and validation (risk, activity, progression, response to drugs, and disease). Development and implementation of biomarkers and bioassays in well-designed clinical trials. Hyper-accelerated progression of biomarkers in clinical trials. Tissue- and species-specific biomarkers. Population-based studies involving the building of new, early cohorts to identify/develop biomarkers. Interface with chemical genomics – array data (gene) and screen library. Imaging biomarkers including molecular biomarkers for *in vivo* imaging of target organs. Development of methodology for dealing with large data sets that are unique to Autoimmune Diseases (AID).	There is a need for infrastructure and core facilities and the development of national consortia to enable integrated approaches to AID that can minimize duplication among the agencies involved. Integrated technology platforms in core facilities are required to develop partnerships and collaborations for accessing, developing and standardizing specialized assays. Hyper-accelerated programs are needed to support the development and implementation of bioassays into clinical trials of AID. Academic and clinical consortia/teams are required to build on Canadian traditions of collaborative projects, e.g., to - enable support for clinician buy-in - facilitate standardization of bioassays - help with the mechanics of getting patient samples, i.e., blood draws, information technology, ethics.
Immunopathogenesis	Exploring regulatory pathways for treatment from the genetics to expression and function. Immunotherapies that alter and cure disease. Correlate lessons learned from oncology.	Capacity building through training and recruiting. Exploration of linkages to established immune tolerance networks.
Functional Genomics	How to validate the functional impact of genetic polymorphisms identified in human or animal models. How to harness outputs of large-scale genomic/proteomic data sets to translate to molecular phenotype and pathophysiology of disease. Genetic regulation of pre-clinical phenotypes (based on biomarkers).	Organizational infrastructure for a data coordinating centre, including financial administration, communication between research centres, information and ready access to core facilities for genomics, proteomics, imaging. Sustained funding adequate to allow new teams to organize, establish platforms, produce data and take the risks required for innovation.

	New Research Questions	Supports Required
Microbial Autoimmune Pathogenesis	Construction of new animal models of autoimmune disease (including non-GI) using proscribed infections with well-defined microbial constituents. Looking at responses to infection and products of replicated fetal/immediate newborn in a gnotobiotic controlled environment. Determinants of immunoreactivity throughout life. Translation to human neonatal physiology/biology imprinting.	Gnotobiotic facilities for experimental animals. Data bases, e.g., mining and construction of appropriate questions. Cryopreservation of animal models for interprovincial transfer. Free availability of new animal models. Viral/microbial bank.

Conclusion

Drs. Siminovitch, Finegood and Singh each addressed the participants with closing remarks, emphasizing the importance of the meeting as a foundation for developing new research initiatives on integrated discovery platforms. Dr. Singh confirmed the cross-cutting nature of autoimmune diseases and the need to have Voluntary Health Organizations (VHO) involved in the development and implementation of research frameworks. He also acknowledged the benefits of having VHO representatives at the symposium and referred to their remarks on the second afternoon, when VHO participants emphasized the importance of inclusive, collaborative approaches to research that would result in clear health outcomes for both patients and caregivers. He further noted the presence of researchers across the four CIHR themes and the importance of following through on new relationships developed at this session. He will be sharing the results of the workshop with all parties in attendance, and will also be holding further discussions with the NIH to follow through on suggestions made regarding possible long-term infrastructure partnerships.

Introduction

The purpose of the research symposium "Integrating Discovery Platforms in Autoimmune Diseases" was to develop a framework for a Canadian health research agenda in autoimmune diseases. The following objectives were targeted:

- to explore the current situation in autoimmune diseases, and in particular basic mechanisms leading to, and commonalities among, these diseases
- to identify strategic directions and potential research questions to be used, for example, as the basis for CIHR and partner-sponsored Requests for Applications (RFAs) and for integration of autoimmune diseases into the Canadian Lifelong Health Initiative
- to enhance collaboration and partnerships among stakeholders in the autoimmune diseases community

Part I: Presentations

The following presentations informed participants on the current situation in autoimmune research and set a framework for discussions related to strategic planning.

Session I: Autoimmune Diseases: Basic Mechanisms and Commonalities

Co-Chairs: Dr. Paul Fortin and **Dr. Luanne Metz**

Topic	Presenter
Multiple Sclerosis: The Neuroimmune Interface	Dr. Amit Bar-Or
The Inflammatory Bowel Diseases: Disorders of the Host (self) - Microbial (non-self) Interface	Dr. Charles Elson
Type 1 Diabetes: Immunogenetic Mechanisms and Prospects for Deconstructing Complex Disease	Dr. Jayne Danska
Immunopathogenesis of Rheumatoid Arthritis	Dr. Peter Lipsky

Chair: Dr. Hani El-Gabalawy

Topic	Presenter
Plans for the Cohort Studies of the Canadian Lifelong Health Initiative	Dr. John McLaughlin

Multiple Sclerosis: The Neuroimmune Interface

Dr. Amit Bar-Or, Montreal Neurological Institute

Dr. Amit Bar-Or discussed emerging themes in multiple sclerosis (MS). MS is regarded as a chronic inflammatory disease of the central nervous system (CNS) that specifically targets the brain and spinal cord. Damage to the CNS is associated with injury to both myelin and myelin-producing cells (oligodendrocytes) as well as axonal loss. MS is the major cause of neurological disability in young adults, with diagnosis in the 20's or 30's being quite common. Most patients stop working within 10 to15 yrs of diagnosis, which causes a great burden in terms of their life, their families and society in general. Interestingly, the prevalence of disease is non-randomly distributed with the incidence increasing as one moves either north or south of the equator. Ethnicity is also an important consideration, with Caucasians suffering from MS most commonly. Moreover, within the Caucasian population, the incidence is approximately 1.5 to 2.5 times higher in females.

One of the clear features of MS is its highly variable and unpredictable course. Magnetic resonance imaging (MRI) has aided diagnosis and has allowed clinicians and researchers to monitor some aspects of the disease. The incorporation of gadolineum (Gd) enhancement into MRI scans has provided a window into understanding disease activity, whereby seepage of Gd reveals areas where the blood brain barrier (BBB) is compromised. Gd enhancement has also been used as a surrogate marker to study clinical trial outcomes in phase II trials. Dr. Bar-Or noted that recent studies in pathology and particularly imaging have suggested a possible degenerative component of this disease (tissue compromise with little immune cell infiltration) which may start early in the illness and might occur relatively independently of inflammation. These findings have resulted in a paradigm shift in treatment such that patients now begin treatment much earlier. Ideally, such treatments will target neuroprotection/repair in addition to immune modulation. Another method for studying the disease course employs magnetic resonance spectroscopy which allows the assessment of metabolites in the brain. In the white matter of a normal brain one would expect to see a characteristic signature of the chemical composition which is abnormal in the MS brain, indicating axonal compromise. To add to the complexity of MS, it has recently been proposed that there are four distinct patterns of tissue injury associated with demyelination. This implies that the disease could present as one of four different pathophysiological entities or perhaps the patterns represent snapshots of predominant processes occurring in patients that change over time. This is a very important point to delineate.

Dr. Bar-Or remarked that MS fits the model of the delicate balance between genes, pathogens and failed immune regulation. For example, three genome screens have

revealed that multiple genes contribute to the risk of developing the disease, and with respect to the environment, researchers have considered a role for toxins, nutrients and infectious agents such as viruses. MS is considered to be a disease in which there is peripheral activation of CNS reactive cells, which are associated with waves of inflammation in the brain. The most commonly used animal model of MS is the experimental autoimmune encephalomyelitis (EAE) model. This model has shown that $CD4^+$ T cells that react to the immunizing CNS antigen can transfer disease. With respect to the Th1/Th2 paradigm it appears that Th1 cells can induce disease while Th2 cells with the same specificity may be protective in EAE. The T cell autoimmune model of MS can be broken down into the following steps: 1) peripheral immune cell activation; 2) upregulation of adhesion molecules; 3) attraction through chemokine/chemokine receptor interaction; 4) active invasion of immune cells into the brain by elaboration of lytic enzymes; and 5) reactivation of T cells by local or invading antigen presenting cells (APCs) that then participate in the injury process. Molecules that can potentially act as therapeutic targets at each of these steps have been identified in MS patients; however, to date no single biomarker of the disease exists. Dr. Bar-Or concluded by highlighting a theme common to all autoimmune diseases which involves the need to develop and integrate bioassays into clinical trials. Such assays would provide insight into the therapeutic mode of action as well as open a window into the disease pathophysiology. Lastly, Dr. Bar-Or noted that clinical trials have revealed that some treatments should be used with caution. For example, anti-TNF-α therapies have been used to successfully treat several autoimmune diseases. However, in some patients there is an emergence of demyelinating disease and in early trials of these agents in patients with MS there have been reports of disease exacerbation.

The Inflammatory Bowel Diseases: Disorder of the Host (self) – Microbial (non-self) Interface

Dr. Charles Elson, University of Alabama at Birmingham

Dr. Elson noted that the gastrointestinal (GI) tract has a number of immune-mediated inflammatory diseases such as autoimmune gastritis and celiac disease for which the target antigens have been defined. Ulcerative colitis and Crohn's disease are chronic inflammatory diseases that affect the colon or most of the intestine respectively. There is some evidence for autoreactivity in these diseases, as autoantibodies against self-antigens have been identified in ulcerative colitis, such as pANCA, while antibodies against bacterial antigens, such as ASCA, have been characterized in Crohn's disease. Approximately 10 years ago, mouse models of inflammatory bowel disease (IBD) began to emerge, which emphasized two common themes: $CD4^+$ T cells are the effector cells that mediate disease, and bacterial flora drives the $CD4^+$ T cell response such that when the animals are rendered germ-free they no longer develop the

disease. Dr. Elson discussed a current hypothesis for IBD pathogenesis, which suggests that disease results from an abnormal mucosal immune ($CD4^+$ T cell) response to enteric bacterial antigens in a genetically susceptible host. Interestingly, the dichotomy between Th1 and Th2 cells is not apparent in IBD as either subset can induce disease. Recent studies have shown that regulatory T cells may play a protective role suggesting this subset could be harnessed as a therapeutic to treat autoimmune disease. In general, if one refers back to the mouse models, disease can be said to result from either impaired T cell regulation or excessive T cell effector function.

A second hypothesis, that Dr. Elson termed the epithelial hypothesis, suggests that abnormal function of the epithelial layer could result in chronic intestinal inflammation even in the presence of a normal immune system. This concept is supported by findings such as the abnormal barrier function for small molecules in Crohn's disease. In fact, it is now recognized that there are dynamic interactions between enteric bacteria, the epithelium and lymphocytes in the gut, although these interactions have yet to be clearly defined. However, it has been shown that enteric bacteria can induce altered gene expression in the epithelium. Epithelial cells then transduce signals not only to lymphocytes but also back to the bacteria themselves. Interestingly, CARD15/NOD2 was the first susceptibility gene identified in Crohn's disease. CARD15/NOD2 is a pattern recognition receptor (PRR) that binds bacterial peptidoglycan thereby activating NF-κB, which upregulates downstream genes, such as TNF-α. PRR and Toll-like receptors (TLR), recognize pathogen associated molecular patterns (PAMP) expressed by microorganisms. It is important to note that even commensal bacteria express PAMPs, for example flagellin that binds TLR5. Dr. Elson's group identified a locus on chromosome 3 that regulates the response to bacterial antigens in IL-10 deficient mice. This suggests that the susceptibility to colitis may be governed by how the immune system responds to commensal bacteria.

Dr. Elson made the interesting point that the immune system evolved in filth. Over time, microbes have acquired host genes and in order to mount a defense the host must be able to respond to self, which is why we have autoimmunity. This is supported by the observation that in areas where infections are endemic there is decreased incidence of autoimmunity. In his concluding remarks Dr. Elson noted that there are tremendous opportunities to develop new technologies to dissect microbial-epithelial-lymphocyte interactions to gain improved understanding of IBD.

Type 1 Diabetes: Immunogenetic Mechanisms and Prospects for Deconstructing Complex Disease

Dr. Jayne Danska, University of Toronto

Dr. Danska discussed type 1 diabetes (T1D), a T cell-mediated autoimmune disease. An incredible benefit to the study of T1D is the availability of spontaneous inbred animal models that recapitulate several aspects of human disease, namely the NOD mouse and BB rat. These models have been critical in understanding T1D pathogenesis and have permitted genetic and immunologic studies. T1D is probably the best studied autoimmune disease at the genetic level. It is clearly multigenic, with polymorphism at the major histocompatibility (MHC) locus playing an important role both in humans and animal models. Researchers have also dissected several cellular mechanisms underlying T1D susceptibility and progression including dysregulated lymphocyte homeostasis, requirement for immunoregulatory T cells, and defective macrophage and dendritic cell (DC) differentiation and function.

Dr. Danska also mentioned that the animal models have permitted the disease to be examined as a progression of steps. The disease course is predictable in NOD mice, taking place in a time frame of months. It is well established that a number of critical events must take place before ß cell death is accomplished, which actually occurs late in the disease process. This suggests that identifying the molecular basis of these steps will provide multiple opportunities for therapeutic intervention. Specifically, Dr. Danska's group has studied the recruitment of T cells to the early lesions. Using a series of genetic and genomic approaches, they identified several regions of the murine genome that control this single step, which underscores the complex genetics of this disease. Through recombinant congenic and genomic strategies it is possible to narrow these regions, but there is still a large number of genes to be vetted as individual candidates. Ultimately, this would require platforms to evaluate the functionality of the genetic variants. Using these types of approaches it should be possible to dissect the function of specific regions of the genome that control specific steps in T1D. Moreover, a collaboration funded by Genome Canada was established with the goal of identifying shared pathways in T1D pathogenesis between NOD mice, BB rats and T1D families using gene expression microarrays.

In terms of moving forward, Dr. Danska mentioned the need to identify more human markers (both cellular and genetic) of pre-diabetic autoimmunity. With respect to Canada's position, Dr. Danska emphasized the need to build on existing infrastructure to support national and international collaboration in discovery research and clinical trials. Dr. Danska concluded by encouraging collaborations that merge disciplines and platforms to examine: 1) rodent modeling and population based human studies; 2) genomic analysis of heritable susceptibility with epidemiology of potential

environmental triggers; 3) molecular biology of host-pathogen interactions and response to autoantigens; and 4) sex bias and developmental determinants of autoimmune disease.

Immunopathogenesis of Rheumatoid Arthritis

Dr. Peter Lipsky, National Institute of Arthritis and Musculoskeletal and Skin Diseases

Dr. Lipsky began his talk with the remark that "autoimmunity is everywhere" and noted that in a *Newsweek* article of the top 10 most important medical stories of the past year, autoimmunity was listed as number 6. Dr. Lipsky described a model which he felt would be applicable to the pathogenesis of several autoimmune diseases and serve as a common basis for discussion. This model could conceivably be called the "Chaos Model of Autoimmunity" whereby in complex diseases, genetic polymorphisms create a subtle but profound difference in the host. These changes must be subtle as disease can take years to develop, which is in stark contrast to animal models where a single gene can be manipulated to reproduce disease in a defined time frame. In humans, the entire array of polymorphisms that are characteristic of certain diseases creates a responsive unit in each individual that deals with the environment in a unique manner. In this model it can be envisioned that non-specific inflammation could lead to tissue alterations caused by 1) altered homing of inflammatory cells; 2) stromal cell maturation such that the cells function in a way that fosters immune reactivity (i.e., they function like follicular DCs); 3) neoantigen expression in the inflammatory sites; and 4) DC maturation (i.e., protolerogenic DCs become proinflammatory DCs). Ultimately, this leads to activation of autoreactive T cells and formation of germinal centre-like structures leading to autoantibody production. Dr. Lipsky explained that ectopic germinal centres are lymphoid aggregates that form in places where they do not belong. For example, in patients with rheumatoid arthritis (RA) germinal centres can develop in the synovium. In these structures, B cells encounter autoantigens and are positively selected. Therefore, unlike germinal centres in secondary lymphoid organs, ectopic germinal centres do not delete autoreactive B cells. The net effect of these activities is augmented inflammation resulting in tissue damage. The implications of such a model are that 1) there is no specific causative agent for individual autoimmune/rheumatic diseases; 2) organ involvement relates to genetics, the site of non-specific inflammation and the nature of the immune response; 3) similar but distinct processes drive all autoimmune/rheumatic diseases (a radical idea that needs to be considered); and 4) effective therapies target pathologic processes and not causation, which suggests that many of the same therapies will work in these diseases. Actually, the preceding statement is contradicted by our current knowledge of the response of various immune-mediated inflammatory diseases to therapeutic interventions. One example of this would be methotrexate, which is effective in patients with RA but does not work in those with psoriasis or IBD.

Finally, Dr. Lipsky cited a study from Holland which taught an important lesson about RA. In this study the researchers wanted to address whether an abnormal immune response could be identified in persons with RA before they presented with symptoms. Critical to the success of this study was the fact that Holland has a very organized medical system with thorough records of blood donors. The group wrote letters to RA patients asking them to give blood and of the 80 people who responded, 79 had been blood donors before RA onset. Next the researchers looked for the presence of autoantibodies in the serum samples and they found that about half of the patients had detectable autoantibody titers (anti-rheumatoid factor, anti-citrolynated peptide or a combination of both) as early as 8 to10 years before the onset of symptoms. This suggests that the disease process starts very early as B cells are activated to produce specific antibody years before symptoms occur. More importantly this information could be used to identify a population at risk and later study what causes a person to go from autoantibody production to disease development.

Plans for Cohort Studies of the Canadian Lifelong Health Initiative

Dr. John McLaughlin, Samuel Lunenfeld Research Institute, and the University of Toronto

Dr. McLaughlin described a cross-cutting, strategic, multi-institute initiative of the CIHR, the Canadian Lifelong Health Initiative. Included within this program are two longitudinal studies, the Canadian National Birth Cohort (CNBC) and the Canadian Longitudinal Study on Aging (CLSA), which are currently being considered and designed. Dr. McLaughlin discussed the status of these studies with respect to the concept, design and progress towards creating the cohorts. Identified as one of the main underlying themes is the study of gene/environment interactions; this concept relates to the theory that most disease burden is jointly determined by individual genetic endowment and complex environmental factors. These gene/environment interactions require decades to fully manifest over the life course. Moreover, diseases and conditions of later life occur in some individuals and not others because of the relationship between particular genetic constitutions and exposure to certain social and physical environments. Little is known, however, about the underlying causes of several conditions and why they are increasing in frequency (e.g., asthma). To understand the causal pathways and develop disease prevention and control strategies, sequential events must be studied in large numbers of people on whom baseline genetic and repeated environmental exposures are taken over time. The determinants of disease represent the genetic component, environment, diet and lifestyle, and from the population and public health perspective, the social structure. Ultimately, this web of causation can be approached by studying population genetics and by genetic epidemiology. Considering the life course perspective, from pregnancy through infancy

to adulthood there are several factors which influence the development and occurrence of subclinical and clinical conditions that ultimately affect health outcomes.

The CLSA concept was initially led by the CIHR Institute of Aging; several other Institutes have agreed to assist in the development of this cohort. The CLSA design and procedures are being developed by a research team consisting of 3 principal investigators, 20 co-investigators and 200 collaborators representing 26 universities in 10 provinces. The rationale behind the CLSA includes the reasoning that longer life expectancies seen in the Canadian population create serious burdens for the health care system and social programs. This presents the need to characterize aging beyond the presence of disease, disability and frailty. In fact, little is known about the aging process. The preliminary aims of the CLSA are to examine aging as a dynamic process; investigate the interrelationship among intrinsic and extrinsic factors from midlife to old age; capture the transitions, trajectories and profiles of aging; and provide infrastructure and build the capacity for high-quality research on aging in Canada. More specifically the goal would be to determine how changes over time in things such as genetic and biochemical factors and exercise, nutrition or other health behaviors, are interrelated and influence disease states and how they might contribute to "healthy aging." If funded, the study is likely to involve a longitudinal design of Canadian men and women aged 40 and over, with a large sample size (e.g., up to 50,000) and requiring a long period of follow-up, possibly 20 years. It should also be noted that embedded within this large infrastructure would be the opportunity for more detailed substudies. The fundamental goal would be to generate a publicly accessible national database.

In contrast, the CNBC is at an earlier stage of development and it will probably be several years before the study is implemented. The CNBC presents an exciting opportunity to be recognized internationally as unique by designing a multigenerational birth cohort. The objective of designing this cohort would be to study common genetically complex/multifactorial outcomes up to age 15. In conclusion, Dr. McLaughlin remarked that ethical, legal and social issues are clearly a concern for both cohorts. In order for these studies to benefit Canadians and the scientific community they must have very strong foundations. Public trust is required for public participation and is therefore vital to the success of such endeavors. Ways to deal with informed consent and disclosure issues related to the use of biological samples must be addressed. Ultimately, it would be of utmost importance to create a useful link between the findings of both the CLSA and CNBC studies.

Session II: Immunological Principles

Co-Chairs: Dr. Karen Madsen and Dr. Ken Croitoru

Topic	Presenter
Immunological Principles Underlying the Pathogenesis and Regulation of T Cell-Mediated Autoimmune Disease	Dr. Steve Miller
Compartmentalisation of Immune Responses to Commensal Intestinal Bacteria	Dr. Andrew Macpherson
Trafficking of Leukocytes in the Brain: Learning by Watching Leukocyte Behaviour	Mr. Steven Kerfoot (for Dr. Paul Kubes)

Immunological Principles Underlying the Pathogenesis and Immunoregulation of T Cell-Mediated Autoimmune Disease

Dr. Stephen D. Miller, Northwestern University Medical School

Dr. Miller discussed insights from his group's study of animal models of multiple sclerosis (MS), the immunological principles underlying disease pathogenesis, and recent data on disease intervention using antigen-directed immunotherapies. As a CD4 T cell-mediated autoimmune disease, MS attacks myelin in the CNS. There are thought to be two possible triggering events in MS: one is the loss of immune regulation leading to the activation of autoimmune responses against neuroantigens, while the other is an infectious agent trigger for at least some forms of disease. The latter hypothesis is suggested by epidemiological evidence. Dr. Miller's laboratory studies two mouse models of MS, experimental autoimmune encephalomyelitis (EAE) and Theiler's virus-induced demylinating disease. In SJL mice, EAE has a relapsing-remitting clinical course whereas Theiler's virus-induced demylinating disease has a chronic-progressive course. It is interesting that in the same genetic background there are two autoimmune diseases which present themselves clinically in completely different ways; however, it is difficult to distinguish between them by examining the lesions in the CNS. Moreover, both diseases are characterized by epitope spreading. In the EAE model, where disease is induced by the defined proteolipid protein (PLP) 139-151 peptide, CD4 T cells specific for the initiating antigen are responsible for the acute phase. The primary relapsing episode is caused by T cells specific for non-cross reactive epitopes of PLP, and is termed *intramolecular spreading.* As disease progresses to the secondary relapse, the response switches to an epitope of myelin basic protein (MBP); this is termed *intermolecular spreading.* The same phenomenon drives the induction of autoimmunity in the virus-induced model, where disease onset is induced by T cells recognizing viral antigens and by the late chronic phase the response is against myelin and viral epitopes. Epitope spreading is initiated in the CNS and is associated with the

appearance of what are believed to be CD11c$^+$ DCs. The implications of epitope spreading to the pathogenesis and immunotherapy of MS include the intimation that these autoimmune responses are dynamic and evolve over the course of this chronic disease and that it would be problematic to use peptide-induced tolerance as an antigen-specific therapy because determining which epitope would be next in the pathologic sequence would be practically impossible. This suggests that treatments targeting co-stimulatory molecules which do not require prior knowledge of autoreactive epitopes, but which can result in antigen-specific tolerance, may be effective in treating MS. The current clinical treatments employed in MS include the use of corticosteroids, interferon-ß, copolymer 1 and bone marrow transplantation in severe cases. Unfortunately, these approaches are largely ineffective and are non-antigen-specific.

Dr. Miller's laboratory is interested in designing specific therapies to intervene in the epitope spreading cascade which leads to chronic disease. One of their approaches involves using antibodies to block co-stimulatory molecule interactions or the CD3 signalling complex. Another strategy would be to use antigen-specific tolerance to prevent the activation of initiating T cells or in animals with ongoing disease to inhibit epitope spreading. Studies in SJL mice have shown that intervention using the F(ab') fragment of the anti-B7.1 molecule, which blocks the B7/CD28 interaction, effectively decreases the number of relapses if mice are treated during disease remission. This also correlates with a period of unresponsiveness in the T cells specific for the region of the PLP molecule that is involved in epitope spreading. One of the complications that can arise from antibody therapy is exemplified by anti-B7 molecules. Disease can be exacerbated if the intact anti-B7.1 molecule is used, suggesting that the intact antibody may signal, whereas the F(ab') fragment blocks signalling. This strategy has also been successful using anti-CD40L. If anti-CD40L is applied at the time of disease priming, it can very efficiently prevent the initiation of EAE; but more importantly, if given at the peak of the acute phase or during a relapse anti-CD40L, it can prevent further relapses. It is believed that therapies that block costimulation inhibit the differentiation of proinflammatory Th1 cells. In collaboration with other laboratories, Dr. Miller's group has shown that non-mitogenic anti-CD3 F(ab')2, if given at the time of disease onset or at the peak of the acute phase, can efficaciously inhibit disease onset or relapses respectively. Interestingly, if anti-CD3 is given at the time of disease priming it has no effect, suggesting that it targets previously activated T cells, which would be ideal for treating autoimmune disease. Lastly, Dr. Miller discussed the possibility of inducing antigen-specific tolerance. This can be achieved using APCs pulsed with peptide and treated with a chemical cross linker to prevent the delivery of the co-stimulatory signal. If antigen-specific tolerance is applied at the time of disease remission following the acute phase, it can very effectively prevent the progression of EAE.

Compartmentalisation of Immune Responses to Commensal Intestinal Bacteria

Dr. Andrew Macpherson, University of Zürich

Dr. Macpherson addressed how non-pathogenic environmental organisms shape the immune system. For example, germ-free animals kept in isolator cages and fed sterile food and water have no intestinal bacteria. However, post-colonisation these animals have hardly any IgA in the small intestine, the Peyer's patches are hypoplastic with relatively few germinal centres, and there are differences in the T cell content of the intestine. Despite a strong local immune response, clean mice are systemically ignorant of their commensals. These features denote the profound differences in the mucosal immune system, which is not to say that microorganisms comprising the flora are ignored; actually, they have a very important effect on the mucosal and systemic immune systems. This raises two very interesting questions: 1) How can the mucosal immune response to the commensals be separated from the systemic response? and 2) Does breaking systemic ignorance prime autoimmune pathology? Dr. Macpherson's group has addressed the first issue by demonstrating that small numbers of commensal bacteria are carried to the mesenteric lymph nodes (MLN) in DCs. The evidence for this is provided by a simple, reproducible experiment whereby mice are inoculated with *Enterobacter cloacae* by gavage or intravenous injection in the tail vein and various tissues are examined for live bacteria at different time points. In mice that are gavage fed, a peak in bacteria in the MLN can be seen for about 72 hours, while there are none in the spleen. In contrast, mice receiving an IV injection clear the organisms to the spleen. This shows that there is absolute preservation of the geographical containment of these organisms in the challenge dose unless the animals have the MLN surgically removed, and then the gavage dose appears in the spleen. Upon FACS-sorting of MLN cells, the organisms appear in the DC fraction while surprisingly not in the macrophage fraction. Commensals are not found within macrophage because they are rapidly killed. In contrast, the pathogen *Salmonella typhimurium*, which can survive intracellularly by subverting bacteriocidal mechanisms, can be found within these cells, suggesting that there is a Trojan Horse effect for the commensals existing within DCs. Using a Thirry Vella loop system, Dr. Macpherson's group has shown that commensal bacteria travel to the MLN within DCs and do not just penetrate as free organisms. The functional effect of DCs carrying bacteria as passengers is shown by stimulating the mucosal immune system with repeated challenges with the organism resulting in substantial IgA induction. The induced IgA has a protective role to limit the penetration of commensals. Interestingly, the $CD11c^+$ DCs may be $CD8\alpha^+$ or $CD8\alpha^-$ but in either case the cells have upregulated the co-stimulatory molecule CD86, suggesting that they are activated.

In his conclusion, Dr. Macpherson summarized the following points: 1) separate priming of the mucosal compartment is essential to maintain relative systemic

ignorance of the commensals since the consequences of unwanted systemic priming are profound but how they influence classical autoimmune models are yet to be explored; 2) commensals find their evolutionary niche in the lumen and unlike pathogens do not subvert microbiocidal killing mechanisms; and 3) compartmentalisation is achieved by the DCs retaining very low numbers of commensals within the mucosal circuit, allowing them to prime the mucosal compartment selectively and locally, but this can probably be broken to a small extent in immunopathology.

Trafficking of Leukocytes in the Brain: Learning by Watching Leukocyte Behaviour

Mr. Steve Kerfoot on behalf of Dr. Paul Kubes, University of Calgary

Mr. Kerfoot discussed techniques used in Dr. Kubes's laboratory to image inflammation and leukocyte recruitment *in vivo*. Specifically, he described intravital microscopy of the brain and emerging technology for imaging leukocytes *in vivo*. Leukocytes are recruited to sites of inflammation through a well-characterized cascade of events. In response to inflammation, endothelial cells are activated to express adhesion molecules, which allows leukocytes in circulation to initially tether to the endothelium followed by rolling. If the leukocyte encounters an appropriate signal, such as a chemokine, the cell will upregulate surface integrins, flatten out and then transmigrate into the tissue. Each step of this cascade is a prerequisite for the next with a few exceptions; for example, a previously activated cell can tether and immediately adhere, bypassing the rolling step. Furthermore, different types of adhesion molecule are important at different steps: selectins are required for tethering and rolling while integrins are necessary for firm adhesion. These steps can be imaged *in vivo* using intravital microscopy. In the case of the brain, a piece of the skull is removed along with the dura mater to reveal the underlying microvasculature. Rhodamine 6G is then administered intravenously to label all of the circulating leukocytes. Finally, using fluorescence microscopy, it is possible to watch the leukocyte/endothelial cell interactions in the blood vessels. When visualizing the cerebromicrovasculature of a healthy control mouse there is little baseline leukocyte recruitment. This is contrasted when examining a mouse that is developing EAE, where a tremendous number of rolling and adherent leukocytes can be seen. These cells will then transmigrate into the tissue causing demyelination and destruction associated with disease. It is possible to study disease development using an actively induced model of EAE in C57BL/6 mice, whereby the mice are immunized with MOG peptide and pertussis toxin (PTx) resulting in a very predictable disease course. Symptoms begin around day 12 and this developing phase is followed by an acute phase after which point the mice do not improve. However, their condition does not worsen and this is considered to be the chronic phase. Using intravital microscopy to examine leukocyte recruitment at these stages of disease in pre-symptomatic mice, an induction of rolling events which peaks

in the acute phase and diminishes in the chronic phase is already seen. Moreover, a very similar pattern is seen for leukocyte adhesion. Interestingly, mice treated with adhesion molecule blocking antibodies against α4-integrin, P-selectin or a combination of both, showed significant reductions in rolling and adhesion events. This is especially important, as anti-α4-integrin is currently in trial in patients with MS with some promising results. It is inferred that the antibody works by preventing leukocyte infiltration into the brain. However, this can not be proven until it is possible to image the process *in vivo*, in real time, in the target organ.

Mr. Kerfoot then introduced some new and exciting work from Dr. Kubes's laboratory. As mentioned above, PTx is used to induce EAE but the mechanism of action is unknown. Dr. Kubes's laboratory now has evidence that suggests PTx may act like environmental factors in influencing disease induction. PTx alone can induce leukocyte rolling and adhesion in the brains of otherwise untreated mice. Interestingly, in Toll-like receptor 4 (TLR4) deficient mice this recruitment was completely eliminated, implying that PTx induced leukocyte recruitment is mediated through TLR4. A major drawback of current studies using intravital microscopy is that the cell type is unknown. This issue could be addressed by studying subset-specific mechanisms of recruitment using purified, fluorescently labeled cells transferred into mice with EAE. A more elegant system could perhaps employ transgenic mice that have subset-specific expression of a fluorescent protein. Importantly, Dr. Kubes's laboratory has learned from looking at various animal models of autoimmunity that it is vital to study the target organ as different mechanisms of leukocyte recruitment predominate in different tissues.

A new technique that is currently in development for use in imaging leukocyte recruitment *in vivo* is magnetic resonance imaging (MRI). MRI is used clinically to identify demyelinating lesions in patients with MS and now a number of small animal facilities are available. In this strategy, leukocytes are labeled with magnetic agents, which would then appear on MRI scans where they accumulate. Significant advantages of this technique include the ability to perform longitudinal studies, and localization of leukocytes throughout the body and to lesions specifically. In his concluding remarks Mr. Kerfoot stated that *in vivo* imaging is a powerful tool to understand leukocyte recruitment by permitting direct observation of the process. Moreover, new technologies will permit subset-specific studies. Ultimately, the goal would be to use our knowledge regarding leukocyte recruitment to aid in design of anti-inflammatory therapies.

Session III: Science and Technology Platforms

Co-Chairs: Dr. Steve Collins and **Dr. Pere Santamaria**

Topic	Presenter
Epidemiological Prognostic Models	Dr. Claire Bombardier and Dr. Sheilah Hogg-Johnson
The Application of Proteomics to the Study of Human Disease	Dr. John Wilkins
Emerging Genomic Tools to Study Autoimmune and other Complex Diseases	Dr. Alexandre Montpetit
Towards an Integrated and Intelligent Molecular Medicine	Dr. Igor Jurisica

Epidemiological Prognostic Models

Dr. Claire Bombardier (in association with Dr. Sheilah Hogg-Johnson), Toronto General Research Institute

As described by Dr. Bombardier, assembling cohorts for study is a challenging task. Population epidemiologists look at healthy population cohorts with the goal of identifying risk factors associated with disease onset, while clinical epidemiologists deal with people who already have disease. The challenge in studying a healthy population is that not many people actually get disease so the denominator is huge. However, once people have the condition the challenge is to design clinical cohorts that will be useful for recognizing prognostic factors. Using the example of rheumatoid arthritis (RA), Dr. Bombardier discussed classic predictors of disease outcome which include the presence of rheumatoid factor (RF) as a prognostic factor; disease activity at presentation; spread in terms of structural damage; functional ability; and variables such as socio-economic status apart from biological factors that have impact on disease outcome. Some of the problems that clinical epidemiologists are faced with involve assembling and maintaining the cohort. In order to test prognostic factors, an inception cohort is needed. This cohort is defined as a group of patients who are recruited at a uniform point in the course of disease and followed from that point onward. Ideally, the point of inception would be the onset of first symptoms. In practice this is not possible as most patients tend to delay a visit to their doctor. Hence, an alternative inception cohort could be followed from the first visit to the doctor. Similarly, another inception cohort could be formed following referral to a specialist, such as a rheumatologist, and finally the point at which the first diagnosis is made could comprise yet another inception point. Most studies will use the point of diagnosis as time zero, so it becomes evident that the cohort looks very different with respect to

length of follow-up. It is important to note the implications with respect to times of follow-up, characteristics of disease, and prognostic factors if an earlier inception cohort was selected, and how different studies could be based on inception point. A common mistake a physician will make when designing a cohort is to see a patient at the time of diagnosis and obtain details on when his or her symptoms first started and use this information to set time zero. It is not a good practice to go backwards because this biases the cohort with patients with chronic disease. In reality, a cohort of patients that is assembled at the onset of first symptoms will not all progress to disease. In order to design more upstream studies, such as at the time of first symptoms, we need a better understanding of the magnitude of these populations.

Dr. Bombardier next discussed the enormous challenges of retaining the cohort, loss to follow-up, and missing data. Dr. Bombardier's colleagues at the Institute for Work and Health modeled the impact of loss to follow-up on the estimate of odds ratio of how strong the factor of interest is related to the outcome. The model plots % of patients loss-to-follow-up versus % confidence interval including true odds ratio (i.e., is the true estimate within the calculated confidence interval?). There are two types of missing data: random missing data and non-random missing data. With random missing data, the true estimate of the odds ratio will commonly be within the confidence interval. This means that with a substantial amount of random missing data, the confidence interval will be very large but the true odds ratio will be within that confidence interval. Conversely, if there is more than 20% non-random missing data, the true odds ratio lies outside the confidence interval and will result in completely biased information. This implies that it is absolutely necessary to have less than 20% loss to follow up, but this is very difficult to achieve. Dr. Bombardier and colleagues are conducting a study across North America of approximately 1000 early RA patients (<1 yr) who will be followed for five years. At the one-year mark there is already 8% missing data. Over a five-year period this could accumulate to 40% missing data, which exemplifies the importance of maintaining both the cohort and the data.

When trying to predict outcomes for the cohort, the challenge is determining what outcome to examine. With respect to RA, one could predict inflammatory disease activity, structural damage, function, quality of life, or mortality. Studies have suggested when looking at long-term effects it is best to measure a variety of outcomes rather than just one. Furthermore, using the appropriate statistical technique to study the cohort presents a great challenge because there are several variables at baseline. The statistical method chosen will really depend on the variable that is being studied.

To summarize, Dr. Bombardier discussed a conceptual framework to classify prognostic studies. First the internal validity of the cohort must be considered: how it was assembled, the follow-up, the quality of the outcome, and the use of appropriate statistical techniques. Secondly, it is important to bear in mind that the findings may be true for patients in the cohort with very severe disease but may not be applicable to all patients. In addition, the current stage of knowledge in the field should be determined. We should identify whether ongoing and previous studies are generating hypotheses from descriptive studies or whether ongoing and previous studies are testing specific theories.

The Application of Proteomics to the Study of Human Disease

Dr. John A. Wilkins, Manitoba Centre for Proteomics

Dr. Wilkins provided three specific examples of proteomics approaches to the study of human diseases. He also discussed issues of patient selection and sample acquisition. First, Dr. Wilkins described an example of 2D analysis as a tool for obtaining compositional information on clinical samples of interest. In this approach samples are separated based on molecular weight and isoelectric point, and the resolved proteins are excised and digested in a gel with trypsin. Subsequently, the peptides are extracted and analyzed by mass spectrometry, generating a peak list that can be subjected to database searches for protein identification. Using synovial fibroblast lysates, Dr. Wilkins's group extracted 390 spots and identified 328 proteins, which included autoantigens, regulatory and novel species of proteins found in patients with rheumatic diseases. A second approach which shows great promise is a proteomics based approach for defining the specificity of autoantibodies. Serum or antibodies from autoimmune individuals are used to select antigens by immunoprecipitation or western blot and the antigens are identified by mass spectrometry. As a cautionary note, it was pointed out that only about 10% to15% of antibodies will actually blot. Using this method for antigen detection, a large subset of potentially physiologically significant autoantibodies may not be detected. Nevertheless, this approach may be useful for tracking autoantibody repertoires during the course of autoimmune development. The third approach that Dr. Wilkins discussed was chip-based surface-enhanced laser desorption ionization (SELDI) analysis. The feature that makes this approach particularly useful and unique is the use of retentate chromatography in conjunction with mass spectrometry. As an illustration of the application of this technique, Dr. Wilkins presented a specific study examining renal transplant patients. The intent was to identify biomarkers associated with acute transplant rejections. The SELDI profiles of urinary proteins fractionated by retentate chromatography were compared between controls and patients with either stable or rejecting transplants. A set of biomarkers were identified which allowed for differentiating between the two patient groups. Those with stable transplants displayed profiles similar to those of non-

transplanted controls. In contrast, those patients with ongoing rejections each had a unique profile. These results indicate that it is feasible to identify biomarker patterns that are associated with acute rejection. This type of marker may be useful to monitor disease progression and predict flares in activity. Identification of these biomarkers may also provide a basis for a better understanding of the pathogenic processes involved in the disease process. Ultimately, this type of approach may be useful in assessing treatment regimens and monitoring a patient's response.

Several issues related to study design and patient selection were presented. These included intra versus inter patient comparisons. Depending on the patient heterogeneity, intra patient comparisons may be more informative. Knowledge of disease stage is critical for comparisons between patients. Unlike the genome, protein expression patterns are dynamic, will change over time, and will be influenced by therapies. The source and accessibility of clinical samples are important considerations, especially if multiple samples are required. Ideally, one would like samples from the affected target organ. In order to establish a sample bank, it is important that the samples are processed and stored in such a way to ensure that their integrity is preserved. Detailed clinical data is an essential component of any medical proteomics initiative, as are data analysis and bioinformatics. The latter are required for data acquisition, protein identification, and analysis.

In his concluding remarks, Dr. Wilkins stated that our proteomic capabilities are rapidly increasing and large/broad scale analysis offers new opportunities. However, the power of the technology also presents new challenges in terms of complexity and quantity of data generated. The take home message from the analyses performed to date is that simple, well-designed studies with the most homogeneous patient populations obtainable are critical. Attention to these parameters offers a reasonable chance of success Achievement of these objectives requires the integrated efforts of clinical and basic scientists. In the context of autoimmune diseases, these issues pose exceptional challenges.

Emerging Genomic Tools to Study Autoimmune and Other Complex Diseases

Dr. Alexandre Montpetit, McGill University and Genome Quebec Innovation Centre

Dr. Montpetit discussed the application of genomic tools to investigate the genetic basis of autoimmune and other complex diseases. The phenotype associated with a given disease and the underlying genetic defect can be studied by linkage analysis or association. However, due to the large size of the human genome, linkage analysis is more appropriate for mapping on a genomic scale. Using SNPs or microsatellite DNA,

linkage analysis can be performed. Dr. Montpetit described the application of a DNA chip based technology using SNPs for performing such analyses that affords many advantages over using microsatellite DNA markers. Similar conclusions can be derived whether using SNPs or microsatellite DNA. Most significantly, the SNP chip analysis allows for very rapid genome scans. The usefulness of performing linkage analysis with an SNP DNA chip in familial studies is complicated in part by the fact that a large cohort of families is required to reliably demonstrate linkage of a given phenotype with a genetic locus. Application of linkage analysis using SNPs was exemplified using inflammatory bowel disease (IBD). In IBD a linkage peak associated with the long arm of human chromosome 5 was identified and the SNPs within this region were characterized. This enabled the identification of an IBD susceptibility haplotype. This study demonstrates the utility of linkage analysis using SNPs for the identification of disease susceptibility loci and is the basis for the Haplotype Project currently being developed (www.hapmap.org). The haplotype project involves the identification characterization of SNPs throughout the genome in European, Asian, and African populations. Currently data on the 145, 554 SNPs has been released on the HapMap web site.

Towards an Integrated and Intelligent Molecular Medicine

Dr. Igor Jurisica, University of Toronto and Queen's University

Dr. Jurisica discussed the computational aspects, challenges and possibilities that high throughput data obtained from microarray and protein array analyses afford in the characterization of complex diseases. The identified genetic markers may vary between separate studies of a given complex disease. The reasons for this discrepancy are that many subtypes of disease may exist, most studies involve differential analysis, and the approaches to data analysis may differ between studies. Dr. Jurisica described a multi-faceted approach to data analysis. First, data is analyzed in an unbiased manner allowing new hypotheses to be put forth that require subsequent validation through experimentation or further statistical analyses. Multiple platforms exist to acquire experimental data; however, very little overlap exists between each platform. This was illustrated using as an example a recent analysis of data obtained for lung carcinoma where multiple large microarray studies were employed. The complexity of many diseases is large and to date no platform exists that encompasses all genes. By using multiple platforms the identification of genetic markers can be addressed systematically. Dr. Jurisica stressed the importance of knowing the differences between what is being compared in each study. Molecular profiling was also introduced as a useful analysis for the characterization of disease. In this capacity the underlying disease processes can be identified without overt clinical diagnosis. Molecular profiling may also be useful for establishing stages of disease progression. However, using this technique, it is difficult to get patient samples which give conclusive results. It is

important to perform analysis without bias in order to obtain some results but obtaining statistically significant results may not be possible. This means new studies must be developed and re-examined. Molecular profiling attempts to take a large screen and to identify a reduced number of disease associated markers that can subsequently be validated. This is a form of data compression and also a process of visualization.

Another approach to analyze gene or protein expression profiles describes these profiles as a two-dimensional table. The data in the table can be clustered and analyzed either unsupervised or with some degree of bias. Dr. Jurisica's group uses two types of analysis: one combines a modified K-means clustering and SOM organizing maps in a complimentary way. SOMs is an approach that combines vector organization and vector quantification. Statistics can be applied after both dimensions of the table have been clustered (i.e., samples and genes or samples and proteins), because clustering ensures that homogeneous groups are compared.

Session IV: US National Institute of Allergy and Infectious Diseases

Chair: Dr. Jack P. Antel

Topic	Presenter
NIAID/NIH Funding and Strategic Planning for Autoimmune Diseases Research	Dr. Daniel Rotrosen

NIAID/NIH Funding and Strategic Planning for Autoimmune Diseases Research

Dr. Daniel Rotrosen, National Institutes of Health

Dr. Rotrosen presented an overview of NIAID/NIH funding and strategic planning as related to autoimmune disease. In the 2003 fiscal year the NIH awarded an estimated $591 million dollars for autoimmunity research, which represents about 2.2% of the $27 billion dollar NIH budget. This percentage is actually slightly lower than what is spent on autoimmunity in Canada. The NIH consists of 27 institutes and centres. The three institutes with the largest expenditures for autoimmunity research are NIAMS, NIAID and NIDDK, each over $100 million. The majority of the NIH budget is awarded to investigator-initiated research project grants, usually to single investigators; but an increasing portion is now being allocated to "large-science" team projects. Approximately 45% of the autoimmunity expenditures are in projects examining pathogenesis and immune dysfunction, while 3% of the funds are allocated to the development of new animal models.

In 1998, Congress required the NIH to convene what is now known as the Autoimmune Disease Coordinating Committee (ADCC). It is comprised of representatives from 22 NIH institutes, as well as from various other federal agencies and private organizations with research programs and advocacy interests that include autoimmunity. Congress called for the committee to develop a strategic plan for coordination of research across NIH and a plan was submitted to Congress in 2002. In addition to the normally appropriated funds, Congress appropriated $150 million dollars a year for type 1 diabetes research that bypasses the normally appropriated NIH budget. These funds are overseen by NIH under the leadership of NIDDK, and the awards are made by a variety of NIH institutes whose missions include prevention or treatment of complications of type 1 diabetes. The ADCC research plan supports and recommends platforms such as the following: support for basic research and clinical trials, expanded support for research resources, registries, repositories, reagent production and distribution, and core facilities. The research plan also proposed increased support for epidemiology and surveillance studies. Interestingly, one of the things that was very clear after assembling this report is that in the United States very little is known about the real prevalence and incidence of autoimmune disease. The plan supports the development and implementation of public awareness and professional education programs.

Another program the NIH expanded in 2003 is the Autoimmunity Centers of Excellence. Under the RFAs soliciting this program, each of the 9 centres is required to bring together physicians and basic scientists representing 3 or 4 medical disciplines spanning autoimmune diseases, for example, neurology, gastroenterology, and rheumatology. By doing so, a very strong network of centres is now capable of conducting multi-site trials in addition to basic research. Approximately 3/4 of the budget for these centres funds basic research, but there is a pilot clinical trials program that is an important component. NIH also supports an accelerated grants program designed to rapidly review and award proposals for mechanistic studies that are performed in conjunction with industry sponsored clinical trials.

The Immune Tolerance Network (ITN) is another NIAID sponsored research consortium that supports clinical trials in autoimmune disease. The ITN supports trials through a national and international network of clinical trial sites and its budget includes resources for state-of-the-art core facilities. These core facilities permit assay centralization for quality control and data accessibility, rapid acquisition and dissemination of data, and central data collection for higher order analyses. The core facilities have both R and D and reagent production/distribution functions. A few of the current ITN core facilities include the following: a tissue sample repository that can handle up to tens of thousands of samples, MHC class I and II tetramer facilities, genomics (microarray and real-time PCR), proteomics, MHC typing, and a variety of

other activities. Sample processing is highly regulated at clinical sites whereby the sample goes through a bar coding process and is immediately linked to protocols in the database. The samples are shipped to a repository and from there they may be sent to one of the core facilities for analysis. From these core labs, the data are deposited in a central data server accessible to both ITN sponsored investigators and, following publication of results, to the general research community to do data mining, analysis and hypothesis generation.

Lastly, Dr. Rotrosen discussed strategic and research planning at the NIH. In order to prepare an RFA, the NIH holds meetings, similar to the current CIHR research symposium, where experts from the academic community and industry are assembled to give their opinions. In general, the entire process takes a year and a half and perhaps even longer to initiate large programs like the ITN. Another important aspect of long-range initiative planning is to enable institutes with shared missions to coordinate activities in order to share costs. For example, many of the programs described above have been co-sponsored by multiple institutes at the NIH. Most of the programs, especially those that involve clinical research, are very heavily dependent on strong partnerships with industry. The ultimate goal of these clinical research programs is to bring new vaccines, immune-based therapies and diagnostics to clinical practice.

Part II: Consultation Report
Supports, Opportunities and Challenges

During the scientific presentations, participants were asked to consider:

a) supports (e.g., infrastructure, capacity building) and opportunities for a Canadian health research agenda with a focus on integrated discovery platforms in autoimmune diseases

b) key challenges and considerations when developing a framework for a Canadian health research agenda with a focus on integrated discovery platforms in autoimmune diseases over the next ten years

Following the presentations, participants worked in small, mixed groups to discuss these two areas with the goal of selecting strategic research directions. Some groups noted overlap between these two areas. The following is a summary of discussions.

Supports and Opportunities

- Many existing agencies and organizations with programs suitable for support of autoimmune research
- Systematic access to discovery technology platforms (PENCE, Genome Quebec, etc.)
- Growing strength in stem cell research (e.g., StemNet NCE) and a more permissive environment in Canada than in US for stem cell research
- Potential for partnering with Voluntary Health Organizations (VHO)
- Opportunities to develop national clinical research consortia in autoimmunity
- Opportunity to attract biostatistician and technology specialists to autoimmunity research
- Opportunity to strengthen clinical trial collaborations with international partners

Challenges and Considerations

- Provide access to high-quality specimens from well-characterized patients in well-managed tissue bank facilities
- Develop registries enabling access to tissue banks
- Streamline and standardize legal, ethical and privacy guidelines

- Design and implement databases for optimal acquisition, management and analysis of diverse datasets
- Implement high throughput computational analysis using readily available centralized database resources
- Develop technologies that enable the translation of new knowledge from data-mining into therapeutic tools
- Develop experimental models to validate genetic discoveries
- Develop access to sophisticated imaging technologies with particular application to animal models
- Overcome barriers to the integration of specialized disciplines, e.g., through creation and development of partnerships
- Enhance networking among basic scientists who study parallel themes
- Develop conduits for interdisciplinary communication
- Acquire programmatic funding for comprehensive autoimmune research
- Identify pre-inflammation patients and those with no symptoms of disease.

Strategic Research Directions

Participants came to an agreement on nine strategic research directions which are listed below in an order that reflects participants' perception of priorities and their enthusiasm in relation to the importance of these directions.

1. Biomarkers
2. Immunopathogenesis
3. Functional Genomics
4. Microbial Autoimmune Pathogenesis
5. Biometrics
6. Tissue Regeneration and Repair
7. Cohort Methodologies
8. Methods for Early Case Findings
9. Clinical Trials

After identifying the above areas, participants were engaged in small group discussion. Each group addressed one of these areas for further exploration and developed a report that described the area, provided examples of new research questions, and suggested supports required to enable implementation of the research.

Given the time available and representation in the symposium, one group focused on three areas: Cohort Methodologies, Biometrics and Methods for Early Case Findings. The report on Biometrics[1] from this combined group reflects the clinical perspective of group members and the fact that those with an interest in computational methods selected other topic areas.[2]

While discussing strategic research directions, participants also identified the following area for cross-CIHR Institute Collaboration: "Development of new animal models for identification of early markers to validate target discoveries across a variety of diseases."

---

1 This area was initially titled "Developing methodology for integrating and analyzing large complex data sets (bioinformatics)."

2 It is important not to lose the initial intention for this strategic direction, which was the need for new computational/data handling methods for large data sets which are not exclusive to clinical cohorts but also include areas such as genomics, proteomics and cell-cell-signal interactions. By focusing on methodology in this way, there is recognition that methods may be common among data sets collected for different reasons.

Methods for Early Case Findings

This strategic research direction addresses the challenge of going upstream with respect to autoimmune diseases. There is a need to

- Understand and describe current patterns of case findings and the relative proportion and nature of patients seen in various situations such as university clinics, research clinics, community specialists and primary care physicians.
- Identify and evaluate different methods of early case findings and their relative value in achieving earlier diagnoses; this includes the value for research in asking early disease questions and the value for patients in terms of diagnosis and care.

Examples of new research questions that could provide significant value in this research area include:

- Benefits and drawbacks of doing direct-to-consumer advertising to generate cases, including analysis of retrieval numbers and false positives
- Value of billing databases in identifying early diagnosis
- Benefits of networks with general practitioners to identify early cases, e.g., through continuing medical education

Supports are required to ensure that the research questions in the previous three sections are addressed. A top priority in terms of capacity development involves the creation of a funded standing group or superstructure that enables integrated approaches among autoimmune disease researchers. Clinical researchers in autoimmune disease face many similar problems across Canada, both within individual diseases and across diseases. The purpose of this standing group would be to identify, clarify and address issues such as information technology, bar codes, privacy, data security, standards for tissue collection and handling, innovative methods for data collection, and access to billing data.

Biometrics

There is a need to include analysis of the determinants of health variables in cohort studies across the autoimmune diseases and across CIHR Institutes (e.g., Institute of Population and Public Health, Institute of Health Services and Policy Research). Currently researchers are collecting the determinants of health differently (e.g., ethnicity, social levels and education), which is causing confusion and potential misinterpretation.

Examples of new research questions that could provide significant value in this research area include:

- Development of a clean, standardized, agreed-upon set of common variables for the determinants of health
- Methods for cohort research, e.g., statistical analysis for innovative data mining of biometrics, patterns of care, patient outcomes
- Innovative study designs, e.g., crossover designs with strategies for selecting control groups
- Common, across-disease, early case definitions and innovative statistical methods for grouping clusters of early disease classifications

Cohort Methodologies

This strategic direction involves cohort research, including methods of assembling and maintaining cohorts.

Examples of new research questions that could provide significant value in this research area include:

- Innovative data collection methods that facilitate participation and retention, e.g., data collection that is integrated into practice, with value added for participating clinicians and applications to community practice
- Research into methods for addressing practical issues related to cohort retention and follow-up, e.g., what to do when patients change physicians or move to another province, incentives for patients to remain involved in data collection processes
- Issues related to methods of targeted sampling, e.g., to achieve community representation or to support standard tissue collection across various sites
- Investigator-initiated research questions, e.g., on courses and prognosis of patients

Tissue Regeneration and Repair

The focus of this strategic research direction is to understand the factors that impede or enhance repair and remodeling as part of the biologic response to tissue damage, and to develop experimental and clinical strategies to regenerate healthy tissue. Research in this area can be organized for both individual and team/program applications.

The following research themes are most relevant to this research direction.

Basic biomedical, e.g., genetic, molecular, cellular, tissue physiology	Applied clinical, e.g., drugs, devices, social intervention	Health systems, health services, e.g., epidemiology, health care quality, cost-effectiveness	Societal, cultural and environmental influences on health and the health of populations
√	√		

In the future, research outcomes in this area should be applied to improve health care delivery and quality of life for patients.

The determinants of health most closely linked to this strategic direction are summarized in the following table.

Income and Social Status		Personal Health Practices and Coping Skills	
Social Support Networks		Healthy Child Development	√
Education		Biology and Genetic Endowment	√
Employment/ Working Conditions		Health Services	
Social Environments		Gender	√
Physical Environments	√	Culture	

Examples of new research questions that could provide significant value in this research area include:

- Mobilization of progenitor cells to enhance repair
- Manipulation of pre-existent cells to promote down regulation of cytopathic receptors, or upregulation of growth receptors
- Molecular response during damage, recovery, repair and remodeling

- The process of tissue response to damage (fibrosis, gliosis), when it ceases to be beneficial and becomes detrimental to repair

Supports required to ensure that these research questions are addressed include:

- Effective collaboration and cohesion among the agendas of hospitals, research institutes, universities, as well as public and private funding agencies
- Coordinated access to relevant tissues to optimize research
- Rational integration of the multiple federal programs in existence to facilitate and optimize hiring practices and initiation of research

Biomarkers

This strategic research direction involves a multidisciplinary approach to the identification, development, validation and implementation of biomarkers. It covers earliest events and ongoing/stage progression. This area includes:

- A need for definitions, e.g., the perspectives from NIH, FDA, etc.
- Identification: predictors of risk, e.g., pre-clinical triggers, markers of activity, prognostics, responses to drugs, markers of responders and non-responders
- Objective measures of categories include: gene expression profile, proteomics, imaging, markers, age-specific immune response at the cellular level, antibodies and serology

The following research themes are most relevant to this research direction.

Basic biomedical, e.g., genetic, molecular, cellular, tissue physiology	Applied clinical, e.g., drugs, devices, social intervention	Health systems, health services, e.g., epidemiology, health care quality, cost-effectiveness	Societal, cultural and environmental influences on health and the health of populations
√	√	√	√

The determinants of health most closely linked to this strategic direction are summarized in the following table.

Income and Social Status	√	Personal Health Practices and Coping Skills	√
Social Support Networks	√	Healthy Child Development	
Education		Biology and Genetic Endowment	√
Employment/ Working Conditions		Health Services	√
Social Environments		Gender	√
Physical Environments		Culture	√

Examples of new research questions that could provide significant value in this research area include:

- Biomarker identification and validation (risk, activity, progression, response to drugs, and disease)

- Development and implementation of biomarkers and bioassays in well-designed clinical trials
- Hyper-accelerated progression of biomarkers in clinical trials
- Tissue- and species-specific biomarkers
- Population-based studies involving the building of new, early cohorts to identify/develop biomarkers
- Interface with chemical genomics – array data (gene) and screen library
- Imaging biomarkers including molecular biomarkers for *in vivo* imaging of target organs
- Development of methodology for dealing with large datasets that are unique to Autoimmune Diseases (AID)

Supports required to ensure that these research questions are addressed include:

- There is a need for infrastructure and core facilities and the development of national consortia to enable integrated approaches to AID that can minimize duplication among the agencies involved.
- Integrated technology platforms in core facilities are required to develop partnerships and collaborations for accessing, developing and standardizing specialized assays.
- Hyper-accelerated programs are needed to support the development and implementation of bioassays into clinical trials of AID.
- Academic and clinical consortia/teams are required to build on Canadian traditions of collaborative projects, e.g., to
  - enable support for clinician buy-in
  - facilitate standardization of bioassays
  - help with the mechanics of getting patient samples, i.e., blood draws, information technology, ethics

Immunopathogenesis

This strategic research direction includes:

- Mechanisms involved in the breakdown of tolerance/homeostasis including central and peripheral mechanisms, regulatory T cells, cytokines
- Target tissues and immune system interactions
- Sex-related differences in immune response
- Interactions between genetic and environmental factors and their impact on the host response
- Immunotherapy/mechanisms to abort the autoimmune response

This area overlaps with tissue regeneration and the role of microbes, cohorts, biomarker and genetic studies. Immunoregulation is the central hub linking these areas.

The following research themes are most relevant to this research direction.

Basic biomedical, e.g., genetic, molecular, cellular, tissue physiology	Applied clinical, e.g., drugs, devices, social intervention	Health systems, health services, e.g., epidemiology, health care quality, cost-effectiveness	Societal, cultural and environmental influences on health and the health of populations
√			

Given the makeup of the group working on this area and the nature of the topic, the basic biomedical pillar is seen to be most relevant. However, it is recognized that the other three themes also affect the basic biomedical area.

The determinants of health most closely linked to this strategic direction are summarized in the following table.

Income and Social Status	4	Personal Health Practices and Coping Skills	3
Social Support Networks		Healthy Child Development	2
Education		Biology and Genetic Endowment	1
Employment/ Working Conditions	6	Health Services	5
Social Environments	6	Gender	2
Physical Environments	6	Culture	

Many of the determinants of health affect immunopathogenesis and vice versa. In addition, the determinants of health interact with and affect each other. The basis of the above ranking reflects the belief that understanding the cause of disease will affect all other determinants of health.

Examples of new research questions that could provide significant value in this research area include:

- Exploration of regulatory pathways for treatment from the genetics to expression and function
- Immunotherapies that alter and cure disease
- Correlation of lessons learned from oncology

Supports required to ensure that these research questions are addressed include:

- Capacity building through training and recruiting
- Exploration of linkages to established immune conference networks

Functional Genomics

This strategic research direction includes the following goals:

- Identify genetic pathways causing susceptibility and severity
- Identify genetic variants with a focus on commonalities and pleiotropy
- Explore "extreme" genetics: early onset, co-morbidity with other autoimmune diseases
- Determine clinical phenotypes of rheumatoid arthritis, irritable bowel disease, lupus
- Explore co-morbidity with vascular disease, cancer, osteoporosis
- Research animal models to identify variants and test as human candidates; develop platforms to test functional impact on human variants, e.g., BACtg, SCRNA; study interactions: gene-gene, gene-environments, gene-therapy (pharmacogenetics)
- Use genetic variants as biomarkers of disease risk and severity, linking to RFA in biomarker development

The following research themes are most relevant to this research direction.

Basic biomedical, e.g., genetic, molecular, cellular, tissue physiology	Applied clinical, e.g., drugs, devices, social intervention	Health systems, health services, e.g., epidemiology, health care quality, cost-effectiveness	Societal, cultural and environmental influences on health and the health of populations
√	√		√

The determinants of health most closely linked to this strategic direction are summarized in the following table.

Income and Social Status		Personal Health Practices and Coping Skills	√
Social Support Networks		Healthy Child Development	√
Education		Biology and Genetic Endowment	√
Employment/ Working Conditions		Health Services	
Social Environments		Gender	√*
Physical Environments	√	Culture	

* The incidence of AID is much higher in females than in males. This is a major unexplored component of autoimmune pathogenesis, with very little research in this area worldwide.

Examples of new research questions that could provide significant value in this research area include:

- How to validate the functional impact of genetic polymorphisms identified in human or animal models
- How to harness outputs of large scale genomic/proteomic data sets to translate to molecular phenotype and pathophysiology of disease
- Genetic regulation of pre-clinical phenotypes (based on biomarkers)

Supports required to implement effective research teams include:

- Organizational infrastructure for a data coordinating centre, including financial administration, communication between research centres, information and ready access to core facilities for genomics, proteomics, imaging
- Sustained funding adequate to allow new teams to organize, establish platforms, produce data and take the risks required for innovation

Without sustained funding for infrastructure and science, researchers can not build capacity for excellence and clinician scientists will not change the existing paradigm of small laboratories, segregation of samples to single hospitals, etc.

Microbial Autoimmune Pathogenesis

This strategic research direction includes:

- The definition of microbials, viruses, bacteria and products
- The four phases of disease, e.g., initiation, perpetuation, exacerbation and therapy
- Epidemiology, e.g., disease clustering/transmission environment

The following research themes are most relevant to this research direction.

Basic biomedical, e.g., genetic, molecular, cellular, tissue physiology	Applied clinical, e.g., drugs, devices, social intervention	Health systems, health services, e.g., epidemiology, health care quality, cost-effectiveness	Societal, cultural and environmental influences on health and the health of populations
√	√		√

The determinants of health most closely linked to this strategic direction are summarized in the following table.

Income and Social Status		Personal Health Practices and Coping Skills	√√
Social Support Networks		Healthy Child Development	√√√√
Education		Biology and Genetic Endowment	√√√
Employment/ Working Conditions		Health Services	
Social Environments	√√√	Gender	√
Physical Environments	√√√	Culture	

Examples of new research questions that could provide significant value in this research area include:

- Construction of new animal models of autoimmune disease (including non-GI) using proscribed infections with well-defined microbial constituents
- Looking at responses to infection and products of replicated fetal/immediate newborn in a gnotobiotic controlled environment
- Determinants of immunoreactivity throughout life
- Translation to human neonatal physiology/biology imprinting

Supports required to ensure that these research questions are addressed are focused on infrastructure:

- Gnotobiotic facilities for experimental animals
- Databases, e.g., mining and construction of appropriate questions
- Cryopreservation of animal models for interprovincial transfer
- Free availability of new animal models
- Viral/microbial bank

Conclusion

Dr. Katherine Siminovitch, symposium co-chair, acknowledged the enthusiastic involvement and commitment of participants throughout the session. Dr. Siminovitch also thanked Dr. Bhagirath Singh, Scientific Director of the CIHR Institute of Infection and Immunity, for initiating the event, and the Organizing Committee, speakers and session chairs for their contributions to achieving the session objectives.

Dr. Diane Finegood, Scientific Director of the Institute of Nutrition, Metabolism and Diabetes (INMD) and a researcher in autoimmune diabetes, expressed her support for the results of the meeting as a foundation for developing new research initiatives on integrated discovery platforms. Dr. Finegood also expressed an interest in exploring the strategic research agenda developed at this meeting as input to the evolving research priorities for INMD over the next few years.

In closing the symposium, Dr. Bhagirath Singh confirmed the cross-cutting nature of autoimmune diseases and the need to have Voluntary Health Organizations (VHO) involved in the development and implementation of research frameworks. He emphasized the benefits of having VHO representatives at the symposium and referred to their remarks on the second afternoon, when VHO participants emphasized the importance of inclusive, collaborative approaches to research that would result in clear health outcomes for both patients and caregivers.

Dr. Singh also commented on the presence of researchers across the four CIHR themes and the importance of following through on new relationships developed at this session. He will be sharing the results of the workshop with the Institute Advisory Board and collaborating with other CIHR Institutes and VHO as partners in following through on the results of this symposium. Dr. Singh will also be holding further discussions with the NIH to follow through on suggestions made regarding possible long-term infrastructure partnerships.

Participants rated the workshop a success: an average of 3.5 on a 4.0 scale. They appreciated the fact that a diverse group of individuals representing different diseases and disciplines were represented at the symposium and that they had an opportunity to develop an agreement on a framework for a Canadian health research agenda in autoimmune diseases.

Appendices


RESEARCH SYMPOSIUM ON INTEGRATING
DISCOVERY PLATFORMS IN AUTOIMMUNE DISEASES

Appendix I

Integrating Discovery Platforms in Autoimmune Diseases Organizing Committee

Dr. Claire Bombardier, Head, Division of Clinical Decision Making and Health Care, Toronto General Research Institute

Dr. Ken Croitoru, Professor, Department of Medicine, McMaster University

Dr. Eleanor Fish, Professor, Department of Immunology, University of Toronto

Dr. Jon Meddings, Professor, Department of Internal Medicine, Foothills Hospital, University of Calgary

Dr. Trevor Owens, Professor, Neuroimmunology Unit, Montreal Neurological Institute

Ms. Ximena Ramos Salas, Project Manager, Planning and Policy, Institute of Nutrition, Metabolism and Diabetes, Canadian Institutes of Health Research

Dr. Katherine A. Siminovitch, Professor, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto

Dr. Bhagirath Singh, Scientific Director, Institute of Infection and Immunity, Canadian Institutes of Health Research

Appendix II

Integrating Discovery Platforms in Autoimmune Diseases Symposium Agenda

Thursday, December 4, 2003

7:30 am Registration/Breakfast

8:30 am Opening Remarks: Dr. Bhagirath Singh, Dr. Katherine Siminovitch

8:40 am **Symposium Overview**: Dorothy Strachan, Facilitator
Introductions, outcomes, key questions

9:00 am **Part I: Autoimmune Diseases: Basic Mechanisms and Commonalities**
Co-Chairs: Dr. Paul Fortin, Dr. Luanne Metz
Presentations: 15 minutes each

- *Multiple Sclerosis: The Neuroimmune Interface,* Dr. Amit Bar-Or
- *The Inflammatory Bowel Diseases: Disorders of the host (self) - microbial (nonself) interface,* Dr. Charles Elson
- *Type 1 Diabetes: Immunogenetic Mechanisms and Prospects for Deconstructing Complex Disease,* Dr. Jayne Danska
- *Immunopathogenesis of Rheumatoid Arthritis,* Dr. Peter Lipsky

Discussion: 20 minutes

10:20 am Break

10:40 am **Part I, cont'd**
Chair: Dr. Hani El-Gabalawy
Presentation: 15 minutes

- *Plans for the Cohort Studies of the Canadian Lifelong Health Initiative,* Dr. John McLaughlin

Discussion: 10 minutes

11:05 am Table discussions and plenary reports

Question #1
What stands out with respect to (a) basic mechanisms leading to the development of autoimmune diseases, and (b) commonalities among these diseases?

12:30 pm Lunch

1:15 pm **Part II: Immunological Principles**
Co-Chairs: Dr. Karen Madsen, Dr. Ken Croitoru
Presentations: 15 minutes each

- *Immunological Principles Underlying the Pathogenesis and Regulation of T Cell-Mediated Autoimmune Disease,* Dr. Steve Miller
- *Compartmentalisation of Immune Responses to Commensal Intestinal Bacteria,* Dr. Andrew Macpherson
- *Trafficking of Leukocytes in the Brain: Learning by Watching Leukocyte Behaviour,* Mr. Steven Kerfoot for Dr. Paul Kubes

Discussion: 20 minutes

2:20 pm Break

2:40 pm **Part III: Science and Technology Platforms**
Co-Chairs: Dr. Steve Collins, Dr. Pere Santamaria
Presentations: 15 minutes each

- *Epidemiological Prognostic Models,* Dr. Claire Bombardier and Dr. Sheilah Hogg-Johnson
- *The Application of Proteomics to the Study of Human Disease,* Dr. John Wilkins
- *Emerging Genomic Tools to Study Autoimmune and Other Complex Diseases,* Dr. Alexandre Montpetit
- *Towards an Integrated and Intelligent Molecular Medicine,* Dr. Igor Jurisica

Discussion: 20 minutes

4:00 pm **Part IV: Exploring Challenges and Opportunities**

Table discussions and plenary reports

Question #2
What key challenges and considerations come to mind when developing a framework for a Canadian health research agenda with a focus on integrated discovery platforms in autoimmune diseases over the next ten years?

Question #3
What supports (e.g., infrastructure, capacity building) and opportunities are you aware of with respect to a Canadian health research agenda with a focus on integrated discovery platforms in autoimmune diseases?

5:25 pm Closing Remarks
5:30 pm Free Time
Meeting of Organizing Committee and Chairs
7:00 pm Group Dinner: Kingbridge Auditorium

Friday, December 5, 2003

7:30 am Breakfast

8:30 am Agenda overview

8:45 am **Part V: US National Institute of Allergy and Infectious Diseases**
Chair: Dr. Jack P. Antel
Presentation: 15 minutes

- *NIAID/NIH Funding and Strategic Planning for Autoimmune Diseases Research*, Dr. Daniel Rotrosen, Director, Division of Allergy, Immunology and Transplantation

Discussion: 10 minutes

9:10 am	**Part VI: Strategic Research Directions and Partnerships** Table discussions, plenary reports, agreement building *Question #4* *What are the top 6 to 8 key research directions (and related questions) that should be included in a Canadian health research agenda with a focus on integrated discovery platforms in autoimmune diseases over the next ten years?*
10:30 am	Break
10:50 am	**Part VI, cont'd**
12:30 pm	Lunch
1:30 pm	*Question #5* *What supports (e.g., infrastructure, capacity building) are required to implement this research agenda?*
2:45 pm	Concluding Remarks
3:00 pm	Closing
3:15 pm	Organizing committee meeting

Appendix III

Integrating Discovery Platforms in Autoimmune Diseases
Abstracts and Biographies of Speakers

Dr. Amit Bar-Or, Assistant Professor, Neurology and Neurosurgery, Montreal Neurological Institute, and Associate, Microbiology and Immunology, McGill University Medical School

Multiple Sclerosis: The Neuroimmune Interface

Abstract

The aim of this brief presentation is to introduce multiple sclerosis (MS) as an immune mediated disease targeting the central nervous system. An overview of the clinical spectrum and immune-mediated pathophysiology will be coupled with emerging themes in the neurobiology of MS. Examining the impact of selected therapies in recent clinical trials will provide a window into the disease process, and identify intriguing contrasts with other autoimmune disease states.

Biography

Dr. Bar-Or completed undergraduate work in biopsychology at McMaster University (1988), and received his medical degree cum laude from McGill's Faculty of Medicine (1993). He pursued Internship and Neurology Residency training at the Massachusetts General Hospital and at Harvard University Medical School where he subsequently completed a Neuroimmunology Research Fellowship and, in a joint program with the Massachusetts Institute of Technology, was awarded an MSc in Translational Research upon completion of the Clinical Investigator Training Program (CITP).

Dr. Bar-Or joined the Montreal Neurological Institute and Hospital in 2000 as a Clinician-Scientist. He is an Assistant Professor and Staff neurologist in the Department of Neurology and Neurosurgery, and an Associate in Microbiology and Immunology at McGill University. Dr. Bar-Or directs a laboratory that uses cellular and molecular immunology research techniques to study autoimmune diseases with a focus on multiple sclerosis (MS).

He is recipient of the MS Society of Canada (MSSC) Career Scientist Award and an FRSQ Chercheur Boursier Clinicien Award. He holds active research grants from the CIHR, the MSSC, the Wadsworth Foundation (USA) and the NIH-supported Immune Tolerance Network (ITN). His laboratory activities involve basic studies of memory B cell and T cell responses, antigen presenting cells and immune-neural interaction. In

addition, Dr. Bar-Or has established a program in Experimental Therapeutics, which aims to develop and incorporate novel immune assays into well-designed clinical trials of MS. This approach provides a unique opportunity to gain insights into disease mechanisms and to develop biomarkers of response to therapy while also evaluating the safety and efficacy of novel therapies in clinically well-characterized patients with MS.

Dr. Claire Bombardier, Head, Division of Clinical Decision Making and Health Care, Toronto General Research Institute (in association with Dr. Sheilah Hogg-Johnson)

Epidemiological Prognostic Models

Abstract

Not available at time of printing.

Biography

Dr. Claire Bombardier is a Professor of Medicine at the University of Toronto, Canada, where she was the founding director of the clinical epidemiology program. In January 2003, Dr. Bombardier was appointed Director of the Division of Rheumatology at the university. She is a senior scientist at the Institute for Work and Health, the mission of which is to research and promote new ways to prevent workplace disability and improve treatment and recovery, and Director of the Clinical Decision Making and Health Care Division, Toronto General Hospital Research Institute, University Health Network. In addition, she is also a rheumatologist at Mount Sinai Hospital.

Dr. Bombardier completed her MD at the University of Montreal and her residencies in internal medicine and rheumatology at McGill and Stanford University. As a Robert Wood Clinical Scholar, she trained in economics at McGill and was subsequently a research fellow at the National Bureau of Economic Research at Stanford. Honours she has received include the University of Toronto's Goldie Price Award (1986), an Arthritis Society Associateship (1979-85), a National Health Research Scholar Award (1986-91) and the University of Toronto, Department of Medicine 2001 Research Award for outstanding research accomplishments. In May 2001, the Endowment of "The Claire Bombardier Award" for the most promising (MSc Clinical Epidemiology) student was created. In April 2002, Dr. Bombardier, was awarded a seven-year Canada Research Chair from the Government of Canada and in June, 2003, received the University of Toronto, Dales Award in Medical Research.

In 2000, Dr. Bombardier became Chair of the Board of Directors of the International Clinical Epidemiology Network (INCLEN), a worldwide program of the Rockefeller Foundation, which promotes research on evidence-based practice. She has been a member of the Quebec Task Force on Spinal Disorders (1983-86), and the Clinical Practice Guidelines Panel of the US Agency for Health Care Policy and Research (1992-1994). She has also chaired the Health Canada Therapeutic Products Directorate, Expert Advisory Committee on Complementary Medicines (1997-2000). Dr. Bombardier is a co-editor of The Cochrane Collaboration Back Review Group.

Dr. Jayne Danska, Senior Scientist, Hospital for Sick Children and Professor, Faculty of Medicine, University of Toronto

Type 1 Diabetes: Immunogenetic Mechanisms and Prospects for Deconstructing Complex Disease

Abstract

Type 1 Diabetes (T1D), an autoimmune disease that affects 0.4 to 0.6% of Canadians, is associated with significant morbidity and mortality. T1D is a prototype of a complex disease caused by allelic variation at multiple loci, few of which have been identified at the molecular level. Conventional approaches to positional cloning have failed to identify genes involved in T1D. This lack of success arises from the high degree of locus heterogeneity in human populations and the complexity of the relationship between genotypes and T1D pathophysiology. Fortunately, T1D is one of the few complex diseases for which spontaneous rodent models recapitulate the pathogenesis of the human disease. The major gene contributing to T1D risk, the major histocompatibility (MHC) class II locus, is shared between these rodent models and humans. Rodent models allow genetic and cellular manipulation to investigate disease pathogenesis, tools that cannot be used in patients. Multidisciplinary efforts in studying the causes of T1D provide a framework for developing effective strategies to confront other autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease and multiple sclerosis. In each of these diseases, early diagnosis and use of specific therapies is limited by our understanding of the genes contributing to the disease, and which biological pathways they control. The immune cell types underlying T1D will be overviewed, with focus on regulatory and natural killer T cells, emerging players in T1D pathogenesis. Our group has identified important early steps in the disease using two rodent models that have allowed us to precisely localize individual genetic regions that control these early steps in the disease. The genes identified through their involvement in the disease pathways of rodent T1D are likely to be associated with T1D in humans, and are being used in association studies in several large T1D family cohorts.

Biography

Dr. Danska is a Senior Scientist at the Hospital for Sick Children and Professor in the Faculty of Medicine, University of Toronto, holding appointments in the Departments of Immunology, Medical Biophysics and the Institute of Medical Sciences. She has made significant contributions in two fields, genetic regulation of Type 1 diabetes immunopathogenesis, and surveillance of DNA damage and maintenance of genome stability in lymphoid cancer. In Type 1 diabetes genetics, her group revealed early steps responsible for the establishment and progression of immune cell inflammation of the pancreas that precede disease onset. They have used these pre-clinical steps in the disease process to map and refine the location of several disease loci in the NOD mouse model using immunological, genomic and bioinformatics approaches to positional cloning and candidate gene analysis. She is the Principal Investigator of a Genome Canada project applying functional genomic analysis of congenic rat and mouse strains to identify gene candidates for human T1D analyzed in three large cohorts of T1D families from Newfoundland, French Quebec and the US with collaborators Andrew Paterson, Stephen Scherer, Philippe Poussier and Constantin Polychronakos. In molecular analysis of lymphoid cancer, her group has developed novel mouse models that have revealed relationships between DNA repair and genome damage surveillance pathways. Recently her group reported the first mouse model of acute lymphoblastic leukemia that disseminates to the central nervous system, a frequent and morbid complication of pediatric ALL. Dr. Danska is primary author of publications in leading journals, chairs and serves on grant panels at the National Cancer Institute of Canada (NCIC), the CIHR, Canadian Diabetes Association, and the National Institutes of Health (US). She also holds leadership positions within the Canadian Genetic Disease Network, and serves on scientific advisory boards of biotechnology companies. She is a recipient of a NCIC Scientist Award, and a Premier's Research Excellence Award.

Dr. Charles Elson, Professor of Medicine and Microbiology, Division of Gastroenterology and Hepatology, University of Alabama at Birmingham

The Inflammatory Bowel Diseases: Disorders of the Host (self)-Microbial (non-self) Interface

Abstract

The talk will discuss the possible role of autoimmunity in IBD, and the current concept of disease pathogenesis, in which disease is due to abnormal immune reactivity to the commensal microbiota in genetically susceptible hosts. The latter can be thought of in general terms as an abnormality of self/non-self discrimination, resulting in an immune-mediated inflammatory disorder.

Biography

Dr. Charles Elson is Professor of Medicine and Microbiology, Division of Gastroenterology and Hepatology, and the first recipient of the Basil I. Hirschowitz Chair in Gastroenterology at the University of Alabama at Birmingham. He is also Vice-Chair of Research for the UAB Department of Medicine. He received his undergraduate degree from the University of Notre Dame and is a graduate of Washington University School of Medicine. He received his internal medicine training at Cornell University and the University of Chicago and received his gastroenterology training at the latter. He furthered his research career by doing a Fellowship at the National Institutes of Health, Bethesda, Maryland. His primary clinical research interests are inflammatory bowel diseases of the intestine, while his basic research focuses on mucosal immunology. He has made substantial contributions to the field of mucosal immunology and within that field to pathogenetic mechanisms in inflammatory bowel disease. He has authored or co-authored approximately 300 book chapters, manuscripts, and abstracts related to this research.

Dr. Elson's expertise has been recognized by invitations to serve on numerous NIH and foundation study sections and advisory panels. He has held and currently holds leadership positions in a number of national and international organizations in his area of expertise, including the Crohn's and Colitis Foundation of America, Inc., the American Association of Immunologists, the American Society for Microbiology, the Clinical Immunology Society, and the Society for Mucosal Immunology, of which he is a co-founder and past-President. He is presently serving as a member of the editorial boards for the *Journal of Clinical Immunology, Inflammatory Bowel Diseases,* and *Clinical Immunology*.

Dr. Igor Jurisica, Assistant Professor, Departments of Computer Science and Medical Biophysics, University of Toronto and Department of Computing and Information Science, Queen's University

Towards an Integrated and Intelligent Molecular Medicine

Abstract

Our goal is to understand diseases such as cancer at the molecular level to develop early detection methods, accurate prognosis and therapies. Addressing these important clinical questions requires systematic knowledge management and analysis of large volumes of information.

We can increase our understanding of the disease origin and tumorigenesis by integrating existing large-scale genomic and proteomic data sets. This requires new analysis methods to combine, consolidate and interpret heterogeneous data. No single database or algorithm will be successful at solving these complex analytical problems. Thus, we need to integrate different tools and approaches, multiple sources of single types of data, and diverse data types.

Biography

Since July 2000 Igor Jurisica has been a Scientist at the Ontario Cancer Institute/Princess Margaret Hospital, Division of Cancer Informatics. He is an Assistant Professor in the Departments of Computer Science and Medical Biophysics, University of Toronto, and Department of Computing and Information Science, Queen's University. He also holds a Visiting Scientist position at the IBM Canada Toronto Laboratory, Centre for Advanced Studies. Prior to joining OCI, he was a tenure track Assistant Professor of Information Systems at University of Toronto for 2.5 years.

Igor Jurisica received a PhD degree in 1997 from the University of Toronto, and MSc degrees in Electrical Engineering from Slovak Technical University and in Computer Science from the University of Toronto in 1991 and 1993 respectively.

His primary research focus is on computational biology, and representation, analysis and visualization of high-dimensional data generated by high-throughput biology experiments. Of particular interest is the use of comparative analysis in the mining of different data set types such as protein-protein interactions, gene and protein expression profiles.

Mr. Steve Kerfoot on behalf of **Dr. Paul Kubes,** Professor, Immunology Research Group, University of Calgary

Trafficking of Leukocytes in the Brain: Learning by Watching Leukocyte Behaviour

Abstract

Leukocyte recruitment is a hallmark feature of autoimmune diseases, including multiple sclerosis. Understanding how different leukocytes get into the brain will potentially help to develop new therapeutic interventions. We have developed a system to visualize leukocyte recruitment into the brain. We will present data on how the cells manage to get into the brain and what may be the most effective mechanism to disrupt their recruitment. We will comment on environmental factors. We will also

compare and contrast our data in brain with the recruitment of leukocytes into other tissues such as liver. Some new strategies to reduce leukocyte recruitment will also be discussed.

Biography

Dr. Kubes and his team have been studying leukocyte/endothelial cell interactions *in vivo* and *in vitro* using intravital microscopy and flow chambers respectively. Their primary focus is to understand the physiology of leukocyte recruitment in various models and in various tissues. They use currently available molecular tools to assess the importance of adhesion molecules and associated proteins including mutant mice missing the gene(s) for certain proteins involved in the recruitment cascade. Migration through interstitium and responses in sepsis, MS, hepatitis and inflammatory bowel diseases are key areas. His team has also initiated a new program trying to understand the role of CD14 and TLR4 in the immune response, and have complemented their *in vivo* work with *in vitro* human studies to understand which adhesion molecules recruit which leukocytes. Dr. Kubes obtained a PhD at Queen's University and then did a fellowship at LSU Medical Center. Presently, he is Professor in the Immunology Research Group, University of Calgary.

Dr. Peter Lipsky, Scientific Director, Intramural Research Program National Institute of Arthritis and Musculoskeletal and Skin Diseases

Immunopathogenesis of Rheumatoid Arthritis

Abstract

Not available at time of printing.

Biography

Dr. Lipsky received his medical degree from the New York University School of Medicine. He performed residency training in Internal Medicine at Strong Memorial Hospital, Rochester, New York, before becoming a Clinical Associate at the NIH studying macrophage-lymphocyte interactions. From 1975 to 1999, Dr. Lipsky was at the University of Texas Southwestern Medical Center at Dallas. He was Director of the Harold C. Simmons Arthritis Research Center and the Rheumatic Diseases Division from 1984 to 1999. He was Co-Director of the Immunology Graduate Program and is the past editor-in-chief of the *Journal of Immunology*. In 1999, he became Scientific Director of the Intramural Research Program at the National Institute of Arthritis and Musculoskeletal and Skin Diseases. His major interest is in B cell biology and generation of the immunoglobulin repertoire as well as alterations in B cell biology in autoimmune diseases.

Dr. Andrew Macpherson, Institute of Experimental Immunology, University of Zürich

Compartmentalisation of Immune Responses to Commensal Intestinal Bacteria

Abstract

The lower intestine of mammals contains an extremely heavy load of commensal intestinal bacteria, with up to 10^{12} organisms/ml of intestinal contents. Despite containing the same surface molecular patterns that are used by the innate immune system to recognize and respond to pathogens, these bacteria are non-pathogenic. Comparisons between germ-free mice (with no intestinal bacteria whatsoever) and colonised animals of the same strain show that there is profound adaptation of the mucosal immune system to the presence of the commensal flora. Yet, normal animals with an intestinal flora but no pathogens are systemically ignorant but not tolerant of their commensal bacterial load. I shall discuss the mechanisms that ensure this geographical separation of the mucosal and systemic immune systems, which are probably critical to avoid superfluous priming reactions to commensal organisms with the possibility of triggering autoimmunity (*1-4*).

1. A.J. Macpherson *et al.*, *Science* 288, 2222-6 (2000).
2. A.J. Macpherson *et al.*, *Nature Immunology* 2, 625-631 (2001).
3. A.J. Macpherson, L. Hunziker, K. McCoy, A. Lamarre, *Microbes Infect* 3, 1021-35. (2001).
4. A.J. Macpherson, M. M. Martinic, N. Harris, *Cellular and Molecular Life Sciences* 59, 2088-96 (2003).

Biography

Dr. Macpherson studied Medicine at the University of Cambridge UK where he carried out an intercalated PhD in the laboratory of Sir Hans Kornberg on the molecular mechanisms of bacterial sugar transport. After postgraduate clinical training in Internal Medicine and Gastroenterology in Cambridge, Leicester and London he joined the Medical Research Council Clinical Research Centre in Harrow. He moved to King's College School of Medicine in 1991 as a Medical Research Council Clinician Scientist where he started his current work on interactions between the commensal intestinal bacterial flora and the immune system in health and disease. He was appointed to the faculty of King's and as a consultant physician at King's College Hospital in 1993. In 1997 he joined the Institute of Experimental Immunology in Zürich, Switzerland, where he now leads the mucosal immunology research group and is a

gastroenterologist in the University Hospital. His research focuses on the mechanisms of induction of mucosal and systemic immune responses, especially IgA, by the commensal intestinal bacteria, and the way in which the immune content of milk protects the neonate during development. Dr. Macpherson has recently been awarded a Canada chair in mucosal immunology, and will move to McMaster University in the fall of 2004.

Dr. John McLaughlin, Leader, Prosserman Centre for Health Research and Associate Professor, Department of Public Health Sciences, University of Toronto

Plans for Cohort Studies of the Canadian Lifelong Health Initiative

Abstract

Dr. McLaughlin will provide an overview of the Cohort Studies of the Canadian Lifelong Health Initiative.

Biography

Dr. John McLaughlin heads the epidemiology program of the Samuel Lunenfeld Research Institute at Mount Sinai Hospital in Toronto, where he is also leader of the Prosserman Centre for Health Research. He is also appointed as a Scientist of the Canadian Institutes of Health Research, an Advisory Board member for CIHR's Institute of Population and Public Health, wherein he has been involved in the planning of the national birth cohort study. He is also a faculty member in the graduate program of the Department of Public Health Sciences at the University of Toronto. His research program aims to identify environmental and genetic factors that cause cancer among adults and children. In his research, advances from basic sciences are applied in population-based and interdisciplinary studies. To study patterns of cancer in the population, Dr. McLaughlin works with collaborators and cancer registries across the country, and supervises the annual publication of Canadian Cancer Statistics.

Dr. Steve Miller, Professor of Microbiology and Immunology, Northwestern University Medical School

Immunological Principles Underlying the Pathogenesis and Regulation of T Cell-Mediated Autoimmune Disease

Abstract

The laboratory employs myelin peptide-induced relapsing-remitting experimental autoimmune encephalomyelitis (R-EAE) models of multiple sclerosis in SJL mice to study approaches to the therapeutic immunoregulation of pre-existing autoimmune disease. Our results over the past decade have indicated that relapses in myelin peptide-induced R-EAE are due to the activation of T cells specific for endogenous myelin epitopes, distinct from that which is used to initiate disease, which are released during the acute phase of disease via a phenomenon termed *epitope spreading*. This phenomenon appears to be a common feature of chronic autoimmunity in both animals and humans. Epitope spreading has important implications for potential treatment of established disease using antigen-specific approaches, such as peptide-specific immune tolerance, since it shows that the specificity of the autoreactive T cells driving pathologic disease changes over time. However, we have shown that multiple approaches targeting T cell receptor/peptide-MHC class II and co-stimulatory molecule interactions are efficacious in treating mice with established EAE (either at the peak of the acute phase of disease or during remission from acute disease) resulting in the prevention of disease relapses. These approaches include peptide-specific tolerance induced with either single or multiple peptides involved in the epitope spreading process, inactivation of pathologic T cells using non-mitogenic forms of an antibody directed at the CD3 signalling complex on activated Th1 cells, and antibodies directed at either the B7/CD28 or the CD40/CD154 co-stimulatory pathways. The efficacy, molecular mechanisms of action and prospects for eventually employing these strategies to treat human autoimmune diseases will be discussed.

Biography

Dr. Miller received his PhD in Immunology in 1975 from Pennsylvania State University and did postdoctoral work in Cellular Immunology from 1975-78 at the University of Colorado Medical School in Denver with Dr. Henry N. Claman. He then assumed a junior faculty position at the University of Colorado from 1978-81 and was appointed Assistant Professor of Microbiology-Immunology at Northwestern University Medical School in June, 1981. Since 1992 he has been a Professor of Microbiology-Immunology and Director of the Interdepartmental Immunobiology Center. Since 1995, he has directed the Immunology and Molecular Pathogenesis Training Program funded by the National Institutes of Health. In November, 2000, Dr. Miller was named

the Congressman John E. Porter Professor of Biomedical Sciences. He currently serves as the Chairman of the Publications Committee of the American Association of Immunologists and on the editorial boards of *Cellular Immunology*, *Viral Immunology*, *Virology,* and the *Journal of Autoimmunity*. He also serves as a member of the Steering Committee for the NIH-funded Immune Tolerance Network and as a member of the US National Multiple Sclerosis Society (NMSS) Panel B Study Section.

Dr. Miller's laboratory investigates the cellular and molecular mechanisms of multiple aspects of the immunopathogenesis and immunoregulation of T cell-mediated autoimmune responses employing two mouse models of multiple sclerosis (MS): Theiler's virus-induced demyelinating disease, a virus-induced model of MS; and Relapsing Experimental Autoimmune Encephalomyelitis (R-EAE), an autoimmune model of MS. The laboratory examines the mechanisms by which epitope spreading (the process whereby self tissue destruction results in activation and recruitment of autoreactive T/B cells specific for endogenous self antigens) and molecular mimicry (the process whereby immune responses to viral epitopes cross-react with self tissue determinants) lead to induction and/or progression of autoimmunity. The laboratory also studies the cellular and molecular mechanisms whereby peptide-specific tolerance and antagonism of lymphocyte co-stimulatory/homing pathways (e.g., B7/CD28, CD40/CD40L, and VCAM-1/VLA-4) can be used to control ongoing autoimmune diseases. His research is currently funded by five separate grants from the US National Institutes of Health and by a grant from the US NMSS.

Dr. Alexandre Montpetit, Postdoctoral Fellow, McGill University and Genome Quebec Innovation Centre

Emerging Genomic Tools to Study Autoimmune and Other Complex Diseases

Abstract

The classical positional cloning approach has had only restricted success for detecting genes associated with autoimmune and other complex diseases. While the mapping of the human genome provides a tremendous tool for genetic research, it is still impractical to test the approximately 10 million common variations to discover their role in complex traits. Recent research, however, suggests that variations on human chromosomes are organized into blocks of DNA, which come in a relatively small number of varieties (called haplotypes) and which are relatively large in size. The knowledge of such a haplotype map, which is being generated by an International Consortium of 8 different centres located in 5 countries, will greatly facilitate the identification of genes causing common genetic diseases by lowering the number of

SNPs needed to study. Also, emerging new genotyping technologies can now perform highly multiplexed (>1000 X) genotyping reactions, making large-scale studies more affordable.

Biography

Dr. Montpetit obtained his PhD in Biochemistry from the University of Montreal in 2002. Working in Dr. Daniel Sinnett's laboratory, his thesis focused on the study of a recurrent deleted region in acute lymphoblastic leukemia and the use of various genomic tools to characterize the genes located in this region and their expression. Dr. Montpetit is now a postdoctoral fellow at McGill University in the laboratory of Dr. Tom Hudson (since March 2002). He is the scientific coordinator for the HapMap project in Montreal. His work also involves the genetic analysis of various complex diseases (asthma, multiple sclerosis, type II diabetes, cardiovascular disease) using dense maps of SNPs. He is supported by a CIHR post-doctoral fellowship.

Dr. Daniel Rotrosen, Director, Division of Allergy, Immunology and Transplantation, US National Institutes of Health

NIAID/NIH Funding and Strategic Planning for Autoimmune Diseases Research

Abstract

Dr. Rotrosen will provide an overview of funding and strategic planning for autoimmune disease research and NIAID/NIH.

Biography

Dr. Rotrosen is Director of the Division of Allergy, Immunology and Transplantation at the National Institute of Allergy and Infectious Diseases. He is a graduate of Boston University School of Medicine, and trained in Internal Medicine and Infectious Diseases at Harbor-UCLA Medical Center in Los Angeles. Since 1984, he has been at the National Institute of Allergy and Infectious Diseases, as a member of the intramural Laboratory of Clinical Investigation and the Laboratory of Host Defenses. Since 1997 he has directed the Division of Allergy, Immunology and Transplantation, one of three extramural divisions of the Institute, and has been a strong proponent of the expansion of NIH programs in clinical immunology. Since 1998 he has served as chair of the NIH Autoimmune Diseases Coordinating Committee.

Dr. John Wilkins, Director, Manitoba Centre for Proteomics

The Application of Proteomics to the Study of Human Disease

Abstract

Proteomics provides the unprecedented potential for broad-scale analysis of the protein expression repertoire of an organism and its component cells and tissues. The presentation will discuss proteomic approaches for the comparative analysis of cells and tissues in health and disease, the selection and identification of biomarkers, and the characterization of pathogenic processes. Discussion will also include limitations of current technologies, and issues of the importance of appropriate patient/sample selection. The intent is to provide a basis for discussing strategies to examine autoimmune diseases and the processes, which are most amenable to current proteomic analysis.

Biography

Dr. Wilkins obtained his PhD in Immunology from the University of Manitoba in 1979 and worked as a post-doctoral fellow in the MRC Group on Immunoregulation, Edmonton, 1978-80. He joined the Rheumatic Diseases Research Laboratory in 1980 and became its Scientific Director in 1997. He is also currently Director of the Manitoba Centre for Proteomics, a Program Leader in the CIHR-funded Biomedical Proteomics Program, and Professor in the Departments of Immunology, Medicine, Biochemistry and Medical Genetics, University of Manitoba.

Appendix IV

Integrating Discovery Platforms in Autoimmune Diseases
Lay Introduction to the Immune System

The immune system and its components are responsible for the collective and coordinated response against foreign substances. An individual's immune system is made up of specialized tissues and cells. The structural organization of lymphoid tissues optimizes intimate contact and short-range interactions between the cell populations that cooperate in the generation of immune responses. The principle cellular constituents are lymphocytes, mononuclear phagocytes, and related accessory cells such as antigen presenting cells (APCs). Lymphocytes are the only immunocompetent cells capable of specific recognition of antigens. They consist of distinct subsets that perform different functions and can be distinguished phenotypically. B lymphocytes are the cells that produce antibodies and are thus the mediators of humoral immune responses. T lymphocytes are the key cells in cell-mediated immunity or cellular immunity. Some T lymphocytes express the CD4 surface marker, and function as helper cells to stimulate antibody production by B cells and to activate macrophages to destroy phagocytosed microbes. Other T lymphocytes express the CD8 marker, and function as cytotoxic cells to kill target cells expressing foreign antigens. Mononuclear phagocytes are critical for host defence in the absence of specific immunity and have also evolved into key participants in the recognition, activation, and effector phases of specific immune responses. Dendritic cells are accessory cells that are involved in the initiation of T lymphocyte responses to protein antigens. They are the immune system's most potent APCs.

Lymphocytes originate in the bone marrow and mature in different generative organs, the bone marrow itself for B cells, and the thymus for T cells. Mature lymphocytes and accessory cells migrate to defined peripheral lymphoid tissues. Lymph nodes are the sites where protein antigens are transported in the lymph and concentrated, and immune responses to these antigens are initiated and develop. The spleen is the organ where immune responses to blood-borne antigens are initiated. In addition, lymphocytes are found either scattered or in aggregates in many tissues, for example, the Peyer's patches of the small intestine, tonsils in the pharynx, and dermal and epidermal Langerhans cells. Lymphoid tissues can also develop at sites of strong immune responses, in rheumatoid arthritis (RA), in which an immune response in the synovium ultimately leads to destruction of the cartilage and bone in joints, synovial tissues develop lymphoid follicles.

Appendix V

Integrating Discovery Platforms in Autoimmune Diseases
Background Document

Foreword

Autoimmunity results from a dysfunction of the immune system in which the body attacks its own organs, tissues, and cells. Immune-mediated diseases such as rheumatoid arthritis, multiple sclerosis, type 1 diabetes, and systemic lupus erythematosus, cause much human suffering and place a major burden on the health care system. Millions of Canadians are affected and increasing numbers urge amelioration in clinical research and health care.

The Canadian Institutes of Health Research (CIHR) Institute of Infection and Immunity (III) supports research to enhance immune-mediated health and to reduce the burden of disease through prevention plans, diagnosis, treatment strategies, support systems, and palliation. To facilitate discoveries and broaden current understanding, the III encourages cross-disciplinary collaborations. As such, a committee has been formed and the research workshop "Integrating Discovery Platforms in Autoimmune Diseases" organized, in order to develop a Canadian health research agenda in autoimmune diseases.

The research workshop objectives are as follows:

- to identify commonalities among autoimmune diseases
- to develop coordinated theme areas and research questions
- to outline strategic directions and mechanisms for translating biomedical research into better health for patients
- to elaborate a framework for collaboration and partnership among stakeholders in the autoimmune diseases community

Partnership programs involving government agencies, private organizations, academic groups, and patient associations will increase capacity in health research and permit the efficient translation into effective clinical care. The goal is to establish priorities and a strategic plan focused on understanding the common mechanisms that cause autoimmune diseases and develop new therapies for their management and prevention. This endeavour will ultimately seek to reduce global burden of immune-based diseases and improve the quality of life.

Dr. Bhagirath Singh, PhD
Scientific Director, CIHR Institute of Infection and Immunity
Scientist, Robarts Research Institute
Professor, The University of Western Ontario

Introduction: Immune Dysfunction and Autoimmunity

The different constituent cell populations of the various compartments of the immune system work together to respond to and eliminate foreign antigens that threaten the host. The dysfunction of the immune system resulting in the mistaken identity of self and consequent tissue damage and even organ failure is termed *autoimmunity*. The safeguards that the immune system naturally possesses to protect from harming self are collectively termed *immune tolerance.* Central tolerance is the process by which potentially autoreactive immune system cells are eliminated before they mature into active cells and enter the circulation. Peripheral tolerance is the process by which cells that have escaped central tolerance are controlled so as not to damage tissues; peripheral tolerance constitutes the major mechanisms to control autoreactive cells. Loss of self-tolerance may result from abnormal selection or regulation of self-reactive lymphocytes, and from abnormalities in the way self-antigens are presented to the immune system. Activation of self-reactive cells requires several factors. If cells are stimulated without co-stimulatory signals, they may die or survive in an unresponsive state, termed *anergy.* Aberrant presentation by APCs may lead to the faulty activation of self-reactive T cells, leading to the breakdown of anergy. T cell anergy may also fail because of defects in the T cells themselves. The elimination of autoreactive T cells depends largely on the activation-induced cell death of mature cells. If the cells can evade this mechanism they will persist and continue the response against self. Lastly, it is believed that there exists a regulatory T cell population that blocks/suppresses the activation of autoreactive cells. There may be a defect in this population in autoimmune diseases.

It has long been appreciated that these disorders have a strong genetic component. Particular genes within the major histocompatibility complex (MHC), a family of genes that regulate immune responses, are associated with susceptibility to type 1 diabetes (T1D), RA, inflammatory bowel disease and others. Importantly, most susceptibility genes may increase the probability of getting a particular disease, but they alone do not determine whether an individual will or will not develop an autoimmune disorder. Various exogenous environmental factors, including infectious agents and chemical toxins, have also been associated with the development of several autoimmune diseases. For example, chronic reactive arthritis (Reiter's syndrome) follows a variety of infections by *Chlamydia trachomatis*, *Salmonella*, or *Shigella*. The mechanism by which infectious agents may trigger the autoimmune process is not clear. Possibilities include polyclonal lymphocyte activation, local tissue inflammation leading to enhanced expression of costimulators, alterations of self-antigens, and tissue injury leading to release of anatomically sequestered antigens. Studies also associate certain lifestyle factors such as exercise, diet and smoking to the development and progression of these diseases.

The Burden of Autoimmune Diseases

Autoimmunity plays a role in more than 80 diseases. Autoimmune diseases represent a heterogeneous family of chronic, disabling diseases with a wide spectrum of clinical manifestations. The majority of these diseases disproportionately affect women. Lupus occurs most often in women of childbearing age (15 to 45). Systemic lupus erythematosis (SLE), characterized by antibody deposits and inflammation of various organs and systems, is 8 to 10 times more prevalent in women. About 90 per cent of those diagnosed with Sjogren's syndrome are women, usually of middle age or older. In this condition, the autoimmune response is mostly confined to the tear ducts, salivary glands and other moisture-producing glands but can also spread to the lungs, brain, joints, kidneys and liver. Women also represent approximately 85 per cent of patients with thyroiditis and scleroderma and 55 to 70 per cent of patients with multiple sclerosis (MS), myasthania gravis, and inflammatory bowel disease. A bias for men exists in a few diseases such as Reiter's syndrome and Berger's disease, and ankylosing spondylitis affects young (15 to 35) white males 3 times more frequently than women. The reasons for these gender-based variations are not known. However, evidence from a variety of studies implicates a role for sex hormones in modulating the course and severity of certain autoimmune diseases.

Some reports suggest differences in the rates of autoimmune diseases among various racial groups, but the impact of racial background varies among individual autoimmune diseases. IgA nephropathy, commonly known as Berger's disease, is an autoimmune kidney disease marked by IgA glomerulonephritis due to the glomerular immune deposits in the kidney. It occurs significantly more often in Native Americans than in any other ethnic group tested. Crohn's disease, an inflammatory disease of the small intestine, affects persons of Jewish descent 3 to 6 times more frequently than others. Further, SLE and scleroderma are more common in African Americans, whereas T1D, MS and Reiter's syndrome are more common in Caucasians. Studies on race and autoimmune disease have focused primarily on genetic differences that may contribute to variations in disease risk, including genes affecting immune response and metabolism. Finally, all ages are affected by autoimmune diseases, with onset in childhood, i.e., TID, juvenile chronic arthritis and juvenile rheumatoid arthritis, to late adulthood, i.e., fibromyalgia, Ménière's disease and polymyositis. Because of their chronicity, overlapping symptoms and rarity, autoimmune diseases are difficult to track. National data on the incidence, prevalence, and medical and economic impact are difficult to compile; however, the following statistics offer a brief overview:

T1D

- affects approximately 200 000 Canadians
- leading cause of adult blindness and non-traumatic limb amputation
- heart disease is 2 to 4 times more common in people with diabetes

RA

- affects approximately 300 000 Canadians
- the World Health Organization states that over 50% of patients stop working within 10 years of onset
- mortality is twice as high as expected in the general population and is associated with clinical severity

MS

- Canada has one of the highest rates in the world with approximately 50 000 Canadians affected
- 70% of patients stop working 5 to10 years after they are diagnosed

Lupus

- affects approximately 15 000 Canadians
- disproportionately affects young women and minorities
- systemic lupus erythematosus is the most common and serious type of lupus

The statistics that are available make clear that the impact of these diseases is significant. The burden imposed by these diseases includes a high cost to society in terms of lost productivity, chronic affliction and disruption of social and family structures. Patients with autoimmune diseases frequently have an impaired quality of life due to loss of function of organs targeted by the disease. For example, patients with RA lose joint mobility due to progressive destruction of joints, and patients with MS lose the ability to walk or control bowel and bladder function due to destruction of the myelin sheath on nerves. These individuals are seen and treated differently at work and in society, and suffer much mental anguish and frustration. Co-morbid mental illness, particularly depression and anxiety, often accompany their affliction.

Recent Advances and Underlying Themes in Autoimmune Disease Research

Various autoimmune diseases appear to share underlying immunologic mechanisms and the potential to respond to treatment with the same, or related, therapeutic agents. Discovering disease function through research is the only route to developing new and better ways to manage and treat these afflictions. Clinical investigations/trials are generally preceded by applied research. As such, with some knowledge of how a disease begins or proceeds, a researcher might examine the best way of remedying that

condition. This approach does not necessarily lead to a specific product or treatment but instead points the way to how such goals can be achieved. Important advances of the past decade include the development of more selective and less toxic immunosuppressive and immunomodulatory agents and the identification of promising approaches for the induction of immune tolerance.

Current Research Investments

The CIHR and other governmental agencies support a large number of investigator initiated research grants studying basic mechanisms of autoimmunity and various autoimmune diseases, including studies of the genetics, immune mechanisms, and role of environmental agents. Studies of human and animal models are supported. Some recent initiatives and ongoing programs are cited below.

Importance of Coordination

The past two decades of research on the immune system have yielded a wealth of new information and extraordinary growth in conceptual understanding. In addition, emerging technologies such as genomics and proteomics offer great potential as platforms to facilitate the translation of research to clinical practice. As a result, opportunities now exist to identify genetic, environmental, and infectious causes of certain autoimmune diseases and to develop novel approaches for their management, treatment and prevention. However, gaps still exist in current knowledge, and new research programs and infrastructures are needed to fully capitalize on existing as well as future opportunities. This meeting will explore how to maximize these opportunities in the context of a cross-disciplinary research approach focused on cross-cutting initiatives to address key aspects of research into autoimmunity.

The National Institutes of Health (NIH) is the federal focal point for medical research in the United States and is uniquely positioned to coordinate research at all levels, from basic discovery research, to translational research, to clinical trials. In 1998, the Autoimmune Diseases Coordinating Committee (ADCC) was established in order to oversee and facilitate collaboration among the NIH institutes, the federal agencies, and private organizations. The ADCC has analyzed a wide range of ongoing and planned research programs and developed a research plan to address key aspects of autoimmunity. The plan is divided into several thematic areas:

- Epidemiology and Burden of Disease
- Etiology of Diseases: Diagnosis, Treatment, and Prevention
- Training, Education, and Information Dissemination

Additional overarching themes that appear throughout the plan and influence progress in each of the above areas include:

- Identification of biomarkers of disease, stage of disease, and response to therapy
- Application of new technologies
- Integration of bioinformatics and advanced computational tools

The recommendations in this research plan require a coordinated approach to establishing priorities and managing research funding and infrastructure. The CIHR endeavor has modeled the American initiative in order to attain similar goals. The research workshop "Integrating Discovery Platforms in Autoimmune Diseases" is focused on establishing high priority areas of research here in Canada and developing a Canadian health research agenda based on (a) commonalities among different autoimmune diseases and (b) the application of existing and emerging technologies as platforms to translate research into the clinical environment.

Concluding Statement

The Organizing Committee recognizes the efforts and appreciates comments from workshop participants. The elaboration and implementation of this initiative will only succeed if researchers, clinicians, physicians, policy makers, and patient groups come together to address these issues. This workshop is undoubtedly the first step of many towards attaining a cohesive research plan that will increase the exchange of information and greater coordination of research activities, and consequentially, the continued progress towards better health for all Canadians.

Holly Young
December 2003

Appendix V-A

Background Document
List of Autoimmune Diseases

Alopecia areata
Antiphospholipid syndrome
Addison's disease
Arthritis
- Ankylosing spondylitis
- Dermatomyositis
- Fibromyalgia-Fibromyositis
- Juvenile arthritis
- Polymyalgia Rheumatica
- Polymyositis
- Raynaud's phenomenon
- Reiter's syndrome
- Rheumatoid arthritis
- Scleroderma
- Sjogren's syndrome

Arteritis
- Polyarteritis nodosa
- Takayasu Arteritis
- Temporal arteritis/Giant Cell arteritis

Autoimmune hemolytic anemia
Autoimmune hepatitis
Behcet's disease
Cardiomyopathy
Celiac Sprue-dermatitis
Chronic Fatigue Immune Dysfunction Syndrome
Chronic Inflammatory Demyelinating Polyneuropathy
Churg-Strauss Syndrome
CREST syndrome
Cold Agglutinin Disease
Crohn's disease
Type 1 diabetes
Essential Mixed Cryoglobulinemia
Glomerulonephritis
Graves' disease
Guillain-Barre syndrome
Idiopathic Pulmonary Fibrosis
Idiopathic Thrombocytopenia Purpura
IgA Nephropathy (Berger's disease)
Inflammatory bowel disease
Lichen Planus
Lupus
- Lupus nephritis
- Systemic lupus erythematosis

Meniere's disease
Mixed connective tissue disease
Multiple sclerosis
Myasthenia gravis
Myocarditis

Pemphigus/pemphigoid
- Bullous pemphigoid
- Cicatricial pemphigoid
- Pemphigus vulgaris

Pernicious anemia
Polychondritis
Polyglandular syndromes
Primary Agamma-globulinemia
Primary biliary cirrhosis
Psoriasis
Retinitis
Rheumatic fever
Sarcoidosis
Stiff-Man syndrome
Thyroiditis
Ulcerative colitis
Uveitis
Vasculitis
Vitiligo
Wegener's granulomatosis

Appendix V-B

Background Document
Glossary

Antibody: a molecule (or immunoglobulin) produced by B cells in response to an antigen. The binding of antibody to antigen leads to the antigen's elimination/destruction.

Antigen: a substance or molecule that is recognized by the immune system. The molecule can be from a foreign material such as a bacterium or virus, or the molecule can be from the same organism (one's own body) and called a self-antigen.

Autoimmune disease: condition in which the immune system mistakenly attacks the body's own organs and tissues.

Cells: the building blocks that make up tissues, organs, and bloodstream of the body. Immune system cells normally move throughout the bloodstream and reside temporarily in the lymph nodes, spleen, and thymus.

Central tolerance: process by which potentially autoreactive immune system cells are eliminated before they can mature and be released to circulate in the body.

Clinical trial: a prospective, scientific evaluation in human volunteers of a treatment regimen, device, or procedure used for the prevention, diagnosis, or treatment of a disease.

Gene: a unit of genetic material that is inherited from a parent. A gene carries the directions that a cell uses to perform a specific function.

Immune tolerance: the safeguards that the immune system naturally possesses to protect from harming self.

Inflammation: a collection of immune system cells and molecules that invade tissues and organs as part of an immune system response.

Lymphocytes: small white blood cells that are critical components of the immune system. There are several types of lymphocytes: B cells are primarily involved in the production of antibodies; T cells release chemicals that activate and direct the movements of other cells to help fight infection or attack foreign matter.

Macrophage: any of the many forms of mononuclear phagocytes found in tissues. They function as patrol cells and engulf and kill foreign infectious invaders.

Major Histocompatibility Complex (MHC): molecules that are found on cell surfaces and display antigen; the antigen-MHC molecules may then interact with a T cell receptor.

Peripheral tolerance: the process by which potentially autoreactive cells are controlled after they reach the bloodstream.

T cell: a type of lymphocyte. T cells have T cell receptors and, sometimes, co-stimulatory molecules on their surfaces. Different types of T cells help to orchestrate the immune response and can issue orders for other cells to make cytokines and chemokines.

Appendix VI

Integrating Discovery Platforms in Autoimmune Diseases
Determinants of Health[3]

KEY DETERMINANTS OF HEALTH	
KEY DETERMINANTS	**UNDERLYING PREMISES**
Income and Social Status	**Health status improves at each step up the income and social hierarchy.** High income determines living conditions such as safe housing and the ability to buy sufficient good food. The healthiest populations are those in societies that are prosperous and have an equitable distribution of wealth.
Social Support Networks	**Support from families, friends and communities is associated with better health.** Having effective responses to stress and having the support of family and friends provide a caring and supportive relationship that seems to act as a buffer against health problems.
Education	**Health status improves with level of education.** Education increases opportunities for income and job security and equips people with a sense of control over life circumstances—key factors that influence health.
Employment/Working Conditions	**Unemployment, underemployment and stressful work are associated with poorer health.** People who have more control over their work circumstances and fewer stress-related demands of the job are healthier and often live longer than people in more stressful or riskier work and activities.
Social Environments	**The array of values and norms of a society influence in varying ways the health and well-being of individuals and populations.** In addition, social stability, recognition of diversity, safety, good working relationships and cohesive communities provide a supportive society that reduces or avoids many potential risks to good health. Studies have shown that low availability of emotional support and low social participation have a negative impact on health and well-being.

[3] The following table is taken from the discussion paper "Towards a Common Understanding: Clarifying the Core Concepts of Population Health for Health Canada" prepared for Health Canada's Working Group on Population Health Strategy.

KEY DETERMINANTS OF HEALTH *(Continued)*

KEY DETERMINANTS	UNDERLYING PREMISES
Personal Health Practices and Coping Skills	**Social environments that enable and support healthy choices and lifestyles, as well as people's knowledge, intentions, behaviours and coping skills for dealing with life in healthy ways, are key influences on health.** Through research in areas such as heart disease and disadvantaged childhood, there is more evidence that powerful biochemical and physiological pathways link the individual socioeconomic experience to vascular conditions and other adverse health events.
Physical Environments	**Physical factors in the natural environment (e.g., air, water quality) are key influences on health.** Factors in the quality human-built environment such as housing, workplace safety, community and road design are also important influences.
Healthy Child Development	**Prenatal and early childhood experiences have powerful effects on subsequent health, well-being, coping skills and competence.** Children born to low-income families are more likely than those born to high-income families to have low birth weights, to eat less nutritious food and to have more difficulty in school.
Biology and Genetic Endowment	**The basic biology and organic make-up of the human body are fundamental determinants of health.** Genetic endowment provides an inherited predisposition to a wide range of individual responses that affect health status. Although socioeconomic and environmental factors are important determinants of overall health, genetic endowment appears to predispose some individuals to particular diseases or health problems.
Health Services	**Health services—particularly those designed to maintain and promote health, to prevent disease, and to restore health and function—contribute to population health.**
Gender	**Gender refers to the array of roles, personality traits, attitudes, behaviours, values, relative power and influence that society ascribes differentially to the two sexes.** "Gendered" norms influence the health system's practices and priorities. Many health issues are a function of gender-based social status or roles. For example, women are more vulnerable to gender-based sexual or physical violence, low income, lone parenthood, and gender-based causes of exposure to health risks and threats (e.g., accidents, STDs, suicide, smoking, substance abuse, prescription drugs, physical inactivity). Measures to address gender inequality and gender bias within and beyond the health system will improve population health.
Culture	**Some people or groups may face additional health risks due to a socioeconomic environment that is largely determined by dominant cultural values that contribute to the perpetuation of conditions such as marginalization, stigmatization, loss or devaluation of language and culture and lack of access to culturally appropriate health care and services.**

Appendix VII

Integrating Discovery Platforms in Autoimmune Diseases Symposium Participants

Dr. Jack P. Antel
Professor
Montreal Neurological Institute
McGill University
3801 University Street
Montreal, QC H3A 2B4
Tel. 514-398-8550
Fax: 514-398-7371
E-mail: jack.antel@mcgill.ca

Dr. Fawzi Aoudjit
Assistant Professor
Rheumatology/Immunology Research Centre,
Laval University
2705 blvd Laurier
CHUL Research Centre, Bloc T1-49
Sainte-Foy, QC G1V 4G2
Tel: 418-656-4141 ext 48071
Fax: 418-654-2765
E-mail: fawzi.aoudjit@crchul.ulaval.ca

Dr. Nathalie Arbour
Senior Postdoctoral Fellow
Montreal Neurological Institute
Neuroimmunology Unit
3801 University Street, Room 111
Montreal, QC H2A 2B4
Tel: 514-398-8535
Fax: 514-398-7371
E-mail: nathalie.arbour@mail.mcgill.ca

Dr. Amit Bar-Or
Montreal Neurological Institute
Neuroimmunology Unit
3801 University Street, Rm. 111
Montreal, QC H2A 2B4
Tel: 514-398-5132
Fax: 514-398-7371
E-mail: amit.bar-or@mcgill.ca

Dr. Tim Behrens
Professor of Medicine
University of Minnesota
6-126 BSBE Building
312 Church Street SE
Minneapolis, MN 55305
USA
Tel: 612-625-4485
Fax: 612-625-2199
E-mail: behre001@umn.edu

Dr. Gilles Boire
Professor
University of Sherbrooke
Rheumatology Division
CHUS-3001
12th Avenue North
Fleurimont, QC W1H 5N4
Tel: 819-564-5261
Fax: 819-564-5265
E-mail: gilles.boire@usherbrooke.ca

Dr. Claire Bombardier
Professor of Medicine
Institute for Work and Health
481 University Avenue, 8th Floor
Toronto, ON M5G 2E9
Tel: 416-927-2027 ext 228
Fax: 416-927-4167
E-mail: claire.bombardier@utoronto.ca;
cheath@iwh.on.ca

Dr. Alison Buchan
Associate Dean, Research
University of British Columbia
Department of Physiology
2146 Health Sciences Mall
Vancouver, BC
Tel: 604-822-0763
Fax: 604-822-6048
E-mail: ambuchan@interchange.ubc.ca

Dr. George Carayannotis
Professor
Memorial University of Newfoundland
Faculty of Medicine
Health Sciences Centre
300 Prince Philip Drive
St. John's, NL A1B 3V6
Tel: 709-777-6967
Fax: 709-777-7010
E-mail: gcarayan@mun.ca

Dr. Bosco Chan
Associate Professor
Robarts Research Institute,
University of Western Ontario
100 Perth Drive
London, ON
Tel: 519-685-8300 ext 34206
Fax: 519-663-3789
E-mail: bosco@robarts.ca

Dr. Stephen M. Collins
Professor
McMaster University/
Crohn's and Colitis Foundation of Canada
McMaster University Medical Centre
Room 4W8
1200 Main Street West
Hamilton, ON L8N 3Z5
Tel: 905-521-2100 ext 75255
Fax: 905-521-4958
E-mail: scollins@mcmaster.ca

Dr. Ken Croitoru
Professor of Medicine
McMaster University Medical Centre
1200 Main Street West, Room 4W8
Hamilton, ON L8N 3Z5
Tel: 905-521-2100 ext 73495
Fax: 905-521-4958
E-mail: croitoru@mcmaster.ca

Ms. Stephanie Crook
Science Officer, Natural Health Products
Research Program
Health Canada
Natural Health Products Directorate
2936 Baseline Road, Tower A, AL 3302D
Ottawa, ON K1A 0K9
Tel: 613-941-5513
Fax: 613-946-1615
E-mail: stephanie_crook@hc-sc.gc.ca

Dr. Jayne Danska
Professor and Senior Scientist
Hospital for Sick Children Research
Institute
555 University Avenue, Elm 8104
Toronto, ON M5G 1X8
Tel: 416-813-8810
Fax: 416-813-8823
E-mail: jayne.danska@sickkids.ca

Dr. Stephen Davies
Assistant Professor
Institute for Biomaterials and Biomedical
Engineering
RS407
2 Taddle Creek Road
Toronto, ON M5S 3G9
Tel: 416-946-7176
Fax: 416-978-4317
E-mail: stephen.davies@utoronto.ca

Dr. Terry L. Delovitch
Professor/Scientist
Robarts Research Institute
Autoimmunity/Diabetes Group
1400 Western Road
London, ON N6G 2V4
Tel: 519-663-3972
Fax: 619-663-3847
E-mail: del@robarts.ca

Dr. Jan Dutz
Associate Professor
University of British Columbia
835 West 10th Avenue
Vancouver, BC V5Z 4E8
Tel: 604-875-4747
Fax: 604-873-9919
E-mail: dutz@interchange.ubc.ca

Dr. Hani El-Gabalawy
Director, Arthritis Centre/Head, Section of Rheumatology/Clinical Director,
Rheumatic Diseases Research Laboratory
University of Manitoba
Arthritis Centre
RR149-800 Sherbrook Street
Winnipeg, MB R3A 1M4
Tel: 204-787-2209
Fax: 204-787-2475
E-mail: elgabal@cc.umanitoba.ca;
mlmackay@hsc.mb.ca

Dr. Charles Elson
Professor of Medicine
University of Alabama
at Birmingham
Division of Gastroenterolgy and Hepatology
UAB Station
Birmingham, AL 35298
USA
Tel: 205-934-6358
Fax: 204-934-8493
E-mail: coelson@uab.edu

Ms. Judi Farrell
Chief Operating Officer
Lupus Canada
18 Crown Steel Drive,
Suite 209
Markham, ON L3R 9X8
Tel: 905-513-0004
Fax: 905-513-9516
E-mail: farrell_j@bellnet.ca

Dr. Lionel G. Filion
Associate Professor
University of Ottawa
Faculty of Medicine
Department of Biochemistry, Microbiology and Immunology
451 Smyth Road
Ottawa, ON K1H 8M5
Tel: 613-562-5800 ext 8308
Fax: 613-562-5450
E-mail: lfilion@uottawa.ca

Dr. Diane Finegood
Scientific Director
CIHR Institute of Nutrition, Metabolism and Diabetes
8888 University Drive, TC 2805
Burnaby, BC V5A 1S6
Tel: 604-268-6707
Fax: 604-291-3055
E-mail: finegood@sfu.ca

Dr. Eleanor Fish
Director, AARC
Toronto General Research Institute
67 College Street, Room 424
Toronto, ON M5G 2M1
Tel: 416-340-5380
Fax: 416-340-3453
E-mail: en.fish@utoronto.ca

Mr. Ron Forbes
President and Chief Executive Officer
Juvenile Diabetes
Research Foundation
7100 Woodbine Avenue
Suite 311
Markham, ON L3R 5J2
Tel: 905-944-8700
Fax: 905-944-0800
E-mail: rforbes@jdrf.ca; jstroz@jdrf.ca

Dr. Paul Fortin
Program Director, Division of Rheumatology, U of T/Director of Clinical Research, Arthritis Centre of Excellence
University of Toronto/
University Health Network
Toronto Western Hospital
399 Bathurst Street, MP10-304
Toronto, ON M5T 2S8
Tel: 416-603-5664
Fax: 416-603-6288
E-mail: paul.fortin@uhn.on.ca

Dr. Sheilah Hogg-Johnson
Senior Biostatistician
Institute for Work and Health
481 University Avenue
Suite 800
Toronto, ON M5G 2E9
Tel: 416-927-2027 ext 2130
Fax: 416-927-4167
E-mail: shoggjohnson@iwh.on.ca

Dr. Marc S. Horwitz
Assistant Professor
University of British Columbia
Department of Microbiology and Immunology
300-6174 University Blvd.
Vancouver, BC V6T 1Z3
Tel: 604-822-6298
Fax: 604-822-6041
E-mail: mhorwiz@interchange.ubc.ca

Dr. Robert Inman
Professor of Medicine and Immunology
Toronto Western Hospital
ECW 8-005
Toronto, ON M5T 2S8
Tel: 416-603-5869
Fax: 416-603-4348
E-mail: robert.inman@uhn.on.ca

Dr. Igor Jurisica
Ontario Cancer Institute
Princess Margaret Hospital
University Health Network,
Division of Cancer Informatics
610 University Avenue, Room 8-413
Toronto Ontario M5G 2M9 CANADA
Tel. 416-946-2374
Fax: 416-946-4619
E-mail: ij@uhnres.utoronto.ca

Dr. Stephen J. Karlik
Professor
University of Western Ontario
London Health Sciences Centre
Diagnostic Imaging, 2MR21
339 Windermere Road
London, ON N6A 5A5
Tel: 519-663-3648
Fax: 519-663-3544
E-mail: skarlik@uwo.ca

Dr. Azad Kumar Kaushik
Associate Professor
University of Guelph
Department of Microbiology
Guelph, ON N1G 2W1
Tel: 519-824-4120 ext 54389
Fax: 519-837-1802
E-mail: akaushik@uoguelph.ca

Ms. Julia Kennedy
Research Coordinator
The Hospital for Sick Children
555 University Avenue
Toronto, ON M5G 1X8
Tel: 416-813-7654 ext 1317
Fax: 416-813-6334
E-mail: julia.kennedy@sickkids.ca

Mr. Steven Kerfoot
University of Calgary
Department of Physiology and Biophysics
3330 Hospital Drive NW
Calgary, AB T2N 4N1
Tel: 403-220-3012
Fax: 403-283-1267
E-mail: skerfoot@ucalgary.ca

Dr. Ilana Kogan Gombos
Assistant Director
CIHR Institute of Gender and Health
700 University Extension Centre
8303-112th Street
Edmonton, AB T6G 2T4
Tel: 780-492-3656
Fax: 780-492-3689
E-mail: ikg@ualberta.ca

Dr. Lakshmi Kotra
Assistant Professor
Molecular Design and Information Technology Centre
University of Toronto
Leslie Dan Faculty of Pharmacy and
Department of Chemistry
19 Russell Street
Toronto, ON M5S 2S2
Tel: 416-978-2882
Fax: 416-978-8511
E-mail: p.kotra@utoronto.ca

Dr. Sylvie Lesage
Senior Research Fellow
Hôpital Notre-Dame/
Centre de recherce du CHUM
Labratoire Immunorégulation H4211K
1560 rue Sherbrooke Est
Montreal, QC H2L 4M1
Tel: 514-890-8000 ext 25820
Fax: 514-412-7652
E-mail: sylvie.lesage@umontreal.ca

Dr. Peter Lipsky
Scientific Director
National Insitute of Arthritis and Musculoskeletal and Skin Diseases
National Institutes of Health
9000 Rockville Pike
Building 10, Room 9N228
Bethesda, MD 20892
USA
Tel: 301-496-2612
Fax: 301-402-0012
E-mail: lipskyp@mail.nih.gov

Dr. Clara Lopez-Amaya
MS Clinic Coordinator
The Hospital for Sick Children
Department of Neurology
555 University Avenue
Toronto, ON M5G 1X8
Tel: 416-813-7654 ext 1738
Fax: 416-813-6134
E-mail: clara.lopez.amaya@sickkids.ca

Dr. Samuel K. Ludwin
Vice President, Research, Kingston General Hospital/Associate Dean, Research, Queen's University
Kingston General Hospital/
Queen's University
76 Stuart Street
Kingston, ON K7L 2V6
Tel: 613-549-6666 ext 3344
Fax: 613-548-6042
E-mail: ludwins@kgh.kari.net

Dr. Andrew J. S. Macpherson
Institute of Experimental Immunology
Unversitatsspital
Schmelzbergstrasse 12, CH 8091
Zürich, Switzerland
E-mail: amacpher@pathol.unizh.ch

Dr. Joaquin Madrenas
Canada Research Chair in Transplantation and Immunology
Robarts Research Institute
FOCIS Centre for Clinical Immunology and Immunotherapeutics
University of Western Ontario
100 Perth Drive
London, ON
Tel: 519-685-8300 ext 34242
Fax: 519-663-3789
E-mail: madrenas@robarts.ca

Dr. Karen Madsen
Associate Professor
University of Alberta
6146 Dentistry Pharmacy
Edmonton, AB T6G 2N8
Tel: 780-492-5257
Fax: 780-492-7593
E-mail: karen.madsen@ualberta.ca

Dr. Fabrizio Mastronardi
Research Scientist
The Hospital for Sick Children
Department of Structural Biology and Biochemistry
555 University Avenue
Toronto, ON M5G 1X8
Tel: 416-813-6850
Fax: 416-813-5022
E-mail: fabrizio@sickkids.ca

Dr. William J. McIlroy
National Medical Advisor
Multiple Sclerosis Society of Canada
250 Bloor Street East, Suite 1000
Toronto, ON M4W 3P9
Tel: 416-967-3040
Fax: 416-967-3040

Dr. John McLaughlin
Leader,
Prosserman Centre for Health Research
Joseph and Wolf Lebovic Building
Mount Sinai Hospital
Associate Professor, Department of Public Health Sciences,
University of Toronto
600 University Avenue
Toronto, ON M5G 1X5
E-mail: jmclaugh@mshri.on.ca

Dr. Jon Meddings
Professor of Medicine
Head Division of Gastroenterology
University of Calgary
Calgary, AB T2N 1N4
Tel. 403-210-9356
E-mail: meddings@ucalgary.ca

Dr. Luanne Metz
Associate Professor and MS Clinic
Director and Chair, Alberta MS Drug Program
University of Calgary
Clinical Neurosciences, Foothills Medical Centre
1403-29th Street NW, 12th Floor
Calgary, AB T2N 2T9
Tel: 403-944-4241
Fax: 403-283-2270
E-mail: lmetz@ucalgary.ca

Dr. Stephen D. Miller
Professor of Microbiology and Immunology
Northwestern University Medical School
Department of Microbiology-Immunology
303 East Chicago Avenue
Chicago, IL 60611
USA
Tel: 312-503-7674
Fax: 312-503-1154
E-mail: s-d-miller@northwestern.edu

Dr. Alexandre Montpetit
Postdoctoral Fellow
McGill University/
Genome Quebec Innovation Centre
740 Dr. Penfield Drive
Montreal, QC H3A 1A4
Tel: 514-398-3311 ext 00913
Fax: 514-398-1795
E-mail:
alexandre.montpetit@mail.mcgill.ca

Dr. Walid Mourad
Professor
CRRI
CHQ
Pavillon CHUL
2705 boul. Laurier
Sainte-Foy, QC G1V 4G2
Tel: 418-654-2772
Fax: 418-654-2765
E-mail: walid.mourad@crchul.ulaval.ca

Mr. Chris Nelson
President
Canadian Arthritis Network
250 Dundas Street West, Suite 402
Toronto, ON H5T 2Z5
Tel: 416-586-4770
Fax: 416-586-8395
E-mail: chris_nelson@sympatico.ca

Dr. Trevor Owens
Professor
Montreal Neurological Institute
3801 University Street
Montreal, QC H3A 2B4
Tel: 514-398-5036
Fax: 514-398-7371
E-mail: trevor.owens@mcgill.ca

Dr. Andrew Paterson
Assistant Professor and Scientist
Hospital for Sick Children
Research Institute/University of Toronto
555 University Avenue
Rm 11101
Toronto, ON M5G 1X8
Tel: 416-813-6994
Fax: 416-813-2150
E-mail: andrew.paterson@utoronto.ca

Dr. Philippe Poussier
Associate Professor and Senior Scientist
University of Toronto
Sunnybrook and Women's College Health Sciences Centre
2075 Bayview Avenue, Room A3.38
Toronto, ON M4N 3M5
Tel: 416-480-6136
Fax: 416-480-4375
E-mail:
ppoussie@sten.sunnybrook.utoronto.ca

Dr. Daniel Rotrosen
Division Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
6610 Rockledge Drive, Room 3111
Bethesda, MD 20892
Tel: 301-496-1886
Fax: 301-402-0175
E-mail: drotrosen@niaid.nih.gov

Dr. Robert Rottapel
Associate Professor
Ontario Cancer Institute
St. Michael's Hospital
University of Toronto, Rm 10-116
610 University Avenue
Toronto, ON M5G 2M9
Tel: 416-946-2233
Fax: 416-946-2984
E-mail: rottapel@oci.utoronto.ca

Dr. Pere Santamaria
Professor
University of Calgary
Faculty of Medicine
3330 Hospital Drive NW
Calgary, AB
Tel: 403-220-8735
Fax: 403-270-8520
E-mail: psantama@ucalgary.ca

Dr. Ernest Seidman
Professor
Université de Montréal
Service de gastroenterologie et nutrition
Hôpital Ste-Justine
3175, Côte Sainte-Catherine
Montreal, QC H3T 1C5
Tel: 514-345-4626
Fax: 514-345-4999
E-mail: seidmane.msn@attcanada.net

Dr. Jean Sévigny
Assistant Professor
Université de Laval
2705 blvd Laurier
CHUL Research Centre
Bloc T1-49
Sainte-Foy, QC G1V 4G2
Tel: 418-656-4141 ext 46319
Fax: 418-654-2765
E-mail: jean.sevigny@crchul.ulaval.ca

Dr. Philip Sherman
President
Canadian Association
of Gastroenterology
Pharmacology and Therapeutics
University of Calgary
3330 Hospital Drive
Calgary, AB T2N 4W1
Tel: 403-220-7370
Fax: 403-210-9752
E-mail: sherman@ucalgary.ca

Dr. Katherine Siminovitch
Professor
Mount Sinai Hospital
600 University Avenue, Suite 656A
Toronto, ON M5G 1X5
Tel: 416-586-8723
Fax: 416-586-8731
E-mail: ksimino@mshri.on.ca

Dr. Bhagirath Singh
Scientific Director
CIHR Institute of Infection and Immunity
Siebens-Drake Research Institute
The University of Western Ontario
1400 Western Road, Suite 214
London, ON N6G 2V4
Tel: 519-661-3228
Fax: 519-661-4226
E-mail: bsingh@uwo.ca

Dr. A. Hillary Steinhart
Division Head, Gastroenterology
Mt. Sinai Hospital/
University Health Network
600 University Avenue
Rm 445
Toronto, ON M5G 1X5
Tel: 416-586-5121
Fax: 416-586-3174
E-mail: hsteinhart@mtsinai.on.ca

Dr. John A. Wilkins
Director
Manitoba Centre for Proteomics
Rheumatic Diseases Research Laboratory
John Buhler Research Centre, Room 805
715 McDermot Avenue
Winnipeg, MB R3E 3P4
Tel: 204-789-3835
Fax: 204-789-3987
E-mail: jwilkin@cc.umanitoba.ca;
jawilkins@shaw.ca

Dr. Joan Wither
Associate Professor
University of Toronto/
University Health Network
Toronto Western Hospital
399 Bathurst Street, EC8-016A
Toronto, ON M5T 2S8
Tel: 416-603-5048
Fax: 416-603-6288
E-mail: jwither@uhnres.utoronto.ca

Dr. Rae S. M. Yeung
Associate Professor of Pediatrics/Scientiss,
HSCRI
Hospital for Sick Children
Research Institute/University of Toronto
555 University Avenue
Toronto, ON M5G 1X8
Tel: 416-813-8833
Fax: 416-813-8883
E-mail: rae.yeung@sickkids.ca

Dr. Pollen K. F. Yeung
Professor
Dalhousie University
College of Pharmacy
5968 College Street
Halifax, NS
Tel: 902-494-3845
Fax: 902-494-1396
E-mail: pollen.yeung@dal.ca

Dr. Ji-Won Yoon
Professor
University of Calgary
3330 Hospital Drive NW
Calgary, AB T2N 4N1
Tel: 403-220-4569
Fax: 403-220-7526
E-mail: yoon@ucalgary.ca

Support

Dr. Judy Bray
Assistant Director, Special Projects
CIHR Institute of Infection and Immunity
160 Elgin Street
Postal Locator 4809A
Ottawa, ON K1A 0W9
Tel.: 613-954-7223
Fax: 613-941-1040
E-mail: jbray@cihr-irsc.gc.ca

Mr. Patrick Haag
Project and Communications Officer
CIHR Institute of Infection and Immunity
160 Elgin Street
Postal Locator 4809A
Ottawa, ON K1A 0W9
Tel. 613-946-1270
Fax: 613-941-1040
E-mail: phaag@cihr.ca

Mr. Bruce Moor
Assistant Director
CIHR Institute of Infection and Immunity
Siebens-Drake Research Institute
The University of Western Ontario
1400 Western Road, Suite 214
London, ON N6G 2V4
Tel. 519-661-3228
Fax: 519-661-4226
E-mail: bmoor@uwo.ca

Ms. Carol Richardson
Manager, Programs and Evaluation
CIHR Institute of Infection and Immunity
Siebens-Drake Research Institute
The University of Western Ontario
1400 Western Road, Suite 214
London, ON N6G 2V4
Tel. 519-661-3228
Fax: 519-661-4226
E-mail: carol.richardson@fmd.uwo.ca

Ms. Tracey Stephens
Communications Assistant
CIHR Institute of Infection and Immunity
Siebens-Drake Research Institute
The University of Western Ontario
1400 Western Road, Suite 214
London, ON N6G 2V4
E-mail: tstephen@uwo.ca

Consultants

Strachan•Tomlinson and Associates
Process Design and Facilitation:
Ms. Dorothy Strachan
Project Management: Peter Ashley
Strachan•Tomlinson and Associates
31 Euclid Avenue
Ottawa, ON K1S 2W2
Tel. 613-730-1000
Fax: 613-730-0014
E-mail: stractom@cyberus.ca