



Written by: Judith Bray, PhD, Assistant Director, III

Creative Design by: David Hartell, Associate, Institute Strategic Initiative, III  
and Diane Christin, Project Officer, III

Cover image by: Giuseppe Melchiori, The Microsoft Research - University of Trento Centre for Computational  
and Systems Biology - [www.cosbi.eu](http://www.cosbi.eu)

Canadian Institutes of Health Research  
160 Elgin Street, Room 97  
Address Locator 4809A  
Ottawa, ON K1A 0W9

CIHR Institute of Infection and Immunity  
Suite 214, Siebens-Drake Research Institute  
1400 Western Road  
London, ON N6G 2V4  
Phone: 519.661.3228  
Fax: 519.661.4226  
[iii@uwo.ca](mailto:iii@uwo.ca)  
[www.cihr.gc.ca/iii.html](http://www.cihr.gc.ca/iii.html)

© Her Majesty the Queen in Right of Canada (2008)

Cat. No.: MR21-92/2008E-PDF

ISBN: 978-0-662-48235-2

## *Table of Contents*

Workshop Executive Summary .....	1
Background .....	3
Introduction .....	3
Workshop Goals and Objectives .....	4
Keynote Speakers .....	4
Breakout Session 1 - Theme Specific .....	8
Breakout Session 2 - Multidisciplinary .....	11
Summary .....	13
Next Steps .....	14
Appendix One - Participant List .....	15
Appendix Two - Workshop Agenda .....	25
Appendix Three - Breakout Session Groups .....	27
Appendix Four - Breakout Group Questions .....	29

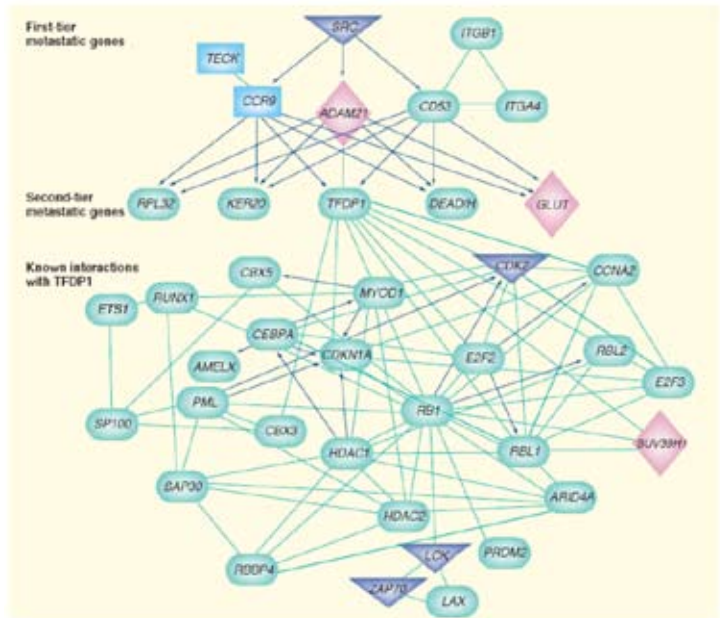




# SYSTEMS BIOLOGY APPROACHES TO IMMUNE MODULATION AND INFLAMMATION

## Workshop Executive Summary

On January 22nd and 23rd, 2008 the Canadian Institutes of Health Research (CIHR) Institute of Infection and Immunity (III) hosted a one and a half day invitational workshop in Montreal to explore the possibility of applying a systems biology approach to the study of immunotherapy, inflammation and immune-based diseases. Recent advances in the application of molecular technologies in biological research have generated vast amounts of data and created extensive databases containing information vital to our understanding of both normal systems and disease processes. However, in order to successfully mine these databases and apply the information they contain to improve the prevention, diagnosis, management and treatment of immunological diseases it is imperative to find ways to facilitate the integration of mathematical, engineering and computational skills into traditional biological research. It is increasingly recognised that a systems approach to research, in which whole systems can be observed and modified, offers advantages over the historical, reductionist approach of examining individual components of systems in isolation from each other. To date, there are few centres in Canada with a robust systems biology focus and even less that are focusing on immune-modulated diseases or therapies.



The workshop brought together systems biologists, immunologists and clinical immunologists to assess the current status of systems biology research in Canada and abroad, and to advise III on the best course of action to encourage the application of systems biology approaches to research on immune modulation and inflammation. It is hoped that the application of these new technologies will improve our understanding of why many traditional immunostimulatory or immunosuppressive therapies are either only partially effective or have adverse side effects.

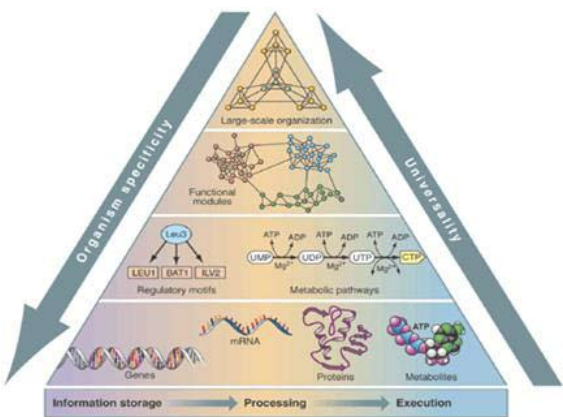
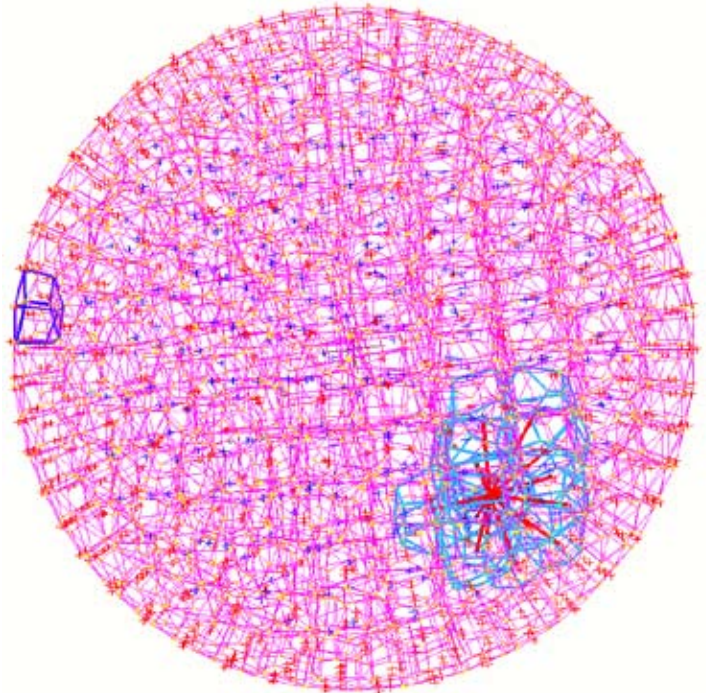


image from: Oltvai ZN, Barabási AL "Systems biology. Life's complexity pyramid." *Science*. 2002 Oct 25;298(5594):763-4.



Following a series of plenary talks by keynote speakers, workshop participants considered the existing 'state of the art' in systems biology and immunotherapy and potential mechanisms for combining multiple fields of expertise. Both immunologists and systems biologists expressed enthusiasm for collaborations that would facilitate the integration of whole systems approaches to the study of immune-mediated diseases and immunotherapy and both groups recognised the advantages of such an approach in clinical research.

From the outset, it was apparent that one of the greatest challenges would be creating effective avenues of communication between the groups and establishing a common language to enable biologists and natural scientists (mathematicians, engineers, computational experts) to work together. It was noted that the regular operating grant system is not ideal for supporting these required cross-linkages and providing multidisciplinary training opportunities. It was also evident that a significant investment of new funds and multiple partnerships would be required to support large multidisciplinary centres capable of moving the field forward at a rapid pace. Although in favour of a bold new initiative with unique components, workshop participants also recognised that incremental, strategic investment would be key to building sustainable capacity and establishing long-term collaborations. Several existing CIHR programs offer promise in this regard, such as the Strategic Training Program in Health Research (STIHR) and the Collaborative Health Research Projects (CHRP) partnership between CIHR and the Natural Science and Engineering Research Council (NSERC). Both these competitions have upcoming application deadlines. There is also a need to make links between relevant initiatives funded by III and other national and international opportunities in the area of systems biology. III staff, in consultation with Institute Advisory Board members, will explore potential partnership opportunities to enable the launch of a large-scale research initiative.



*III is committed to making the integration of systems biology into health research a reality through the promotion of this approach in research on immune-mediated diseases and immunotherapy.*



## *Background*



The Canadian Institutes of Health Research (CIHR) Institute of Infection and Immunity (III), in its 2007-2012 Strategic Plan, identified five strategic research priorities, one of which was “Immunotherapy: New approaches through systems biology”. As a first step towards developing a research agenda to address this priority, a workshop was convened to bring together researchers from the systems biology, basic immunology and clinical immunology communities to initiate a dialogue between these diverse groups. On January 22nd and 23rd, 2008 more than 50 invited participants, including representatives from several potential partner organizations and other CIHR Institutes, came together for a day and a half to explore research opportunities of mutual interest. The supporting

documentation, including the participant list, workshop agenda, and breakout session questions is provided in Appendices 1-4.

## *Introduction*

Modern medicine has evolved to have a predominant emphasis on reductionist science, in which researchers focus on individual components in isolation from the system as a whole. For many diseases this separation of the whole into multiple parts ignores the interactions between these parts and their combined influence in disease pathogenesis. Rarely is an immune or infectious disease process caused by a single modality or failure, but rather by multiple factors acting on many components, either in sequence or simultaneously, to bring about changes in system-wide behaviour. This is particularly evident for most chronic diseases, including autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and Type 1 diabetes.

Systems biology approaches involve a coordinated study of biological systems (from molecules to whole organisms) by: investigating the components of cellular networks and their interactions; applying experimental high-throughput and whole genome techniques; and integrating computational methods with experimental efforts. Immunotherapy is a broad discipline that includes an array of strategies based on the modulation of the immune system to achieve a prophylactic and/or therapeutic goal. Examples of immunotherapy approaches include vaccines, immunosuppressive/stimulatory drugs, biological therapies (e.g. monoclonal antibodies, cytokines) and cell based therapies (e.g. stem cells, dendritic cells, T and B cells).

By applying a systems biology lens to immune modulation it is hoped that the treatment of immune-based diseases can be enhanced through the development of individualized and/or synergistic treatments, minimized interventions, multidimensional uses of medications, time and space sensitive treatments and predictive medicine. The application and integration of systems biology approaches to traditional medicine through a focus on immune modulation is likely to enhance our understanding of many normal biological functions and disease conditions.



## *Workshop Goals and Objectives*



The primary goal of the workshop was to create effective communication channels between systems biology and immunology researchers with the objective of learning how to use systems biology techniques to enhance our understanding of the processes involved in immune modulation, immunotherapy and inflammation. The workshop provided an opportunity for participants to learn about the state of the art in systems biology and immunotherapy from the four keynote speakers and engage in theme specific discussions, in which participants were broadly grouped according to area of expertise. Finally, participants were divided into multidisciplinary groups and tasked with developing a 'mock' research proposal in a process that would encourage them to identify and address the challenges in applying systems biology techniques to solve immunological problems. The overarching workshop objective was to promote partnerships, create opportunities for the sharing of technology platforms around clinical immunology networks, and to provide ILL with advice on how to encourage the integration of systems biology into studies on immune modulation.

## *Keynote Speakers*

Keynote Speakers were invited as experts in their respective fields and asked to provide workshop participants with a broad overview of their particular scientific discipline and also act as a valuable resource during the later breakout sessions. All four speakers identified some of the potential challenges that might be faced in integrating the two approaches, along with examples of situations or programs in which these challenges have been successfully overcome. What follows is a brief synopsis of the most salient points of the presentations. Many of the presentations are available in whole, or in part, through the speakers' host institution websites.

**“Bioinformatics and Systems Biology: Partners for life” – Dr. Francis Ouellette,  
Associate Director of Informatics and Biocomputing,  
Ontario Institute of Cancer Research, Toronto**



This presentation focused on the interdependency between bioinformatics and systems biology; the challenges facing the research community in integrating different technologies and applying them to complex health issues; and the importance of open access to information and resources in moving the science forward. Emerging as new disciplines in the early 1990s, informatics and biocomputing are now central to all biomedical research, driven by the escalating data generation of modern biological technologies such as DNA microarrays and high-throughput genotyping. Bioinformatics serves to turn large-scale data generation into data analysis quickly and accurately, providing new insights into complex biological processes. Systems biology involves the integration of existing diverse and multivariate experimental data using computer tools and biological databases to generate new knowledge about whole systems. Whereas bioinformatics is effective in generating analyses of the parts of a system, systems biology focuses on stringing these parts together to



*Whereas bioinformatics is effective in generating analyses of the parts of a system, systems biology focuses on stringing these parts together to build whole systems and gain an understanding of what happens when things malfunction, such as in disease.*

build whole systems and gain an understanding of what happens when things malfunction, such as in disease. The continuum from bioinformatics to systems biology moves through small molecules, metabolites, proteins, DNA/RNA, genes, genotypes to

whole organisms, populations and ecosystems. An appropriate analogy would be do-it-yourself construction kits such as those popularised by IKEA. Bioinformatics and biocomputing would generate all the necessary knowledge to produce the parts and systems biology would provide the manual for putting the parts together to construct the item. Many of the necessary “parts” or resources are already available in the form of extensive biological clones/reagents/libraries, software applications, multiple databases and open access websites and journals. What is required now is adequate funding to maintain and link these resources and to bring biologists, bioinformaticians and system biologists together in integrated networks underpinned by strong training programs and supplemented by short-term workshops. The presentation was followed by a brief discussion during which the bioinformaticians and statisticians present expressed a willingness to participate in “biologically-orientated” research, particularly if they were engaged in projects from the first stages as an integral part of a multidisciplinary research team.

### “Restoring Tolerance in Autoimmunity” – Dr. Michael Ehrenstein, Centre for Rheumatology, University College, London, UK



Autoimmune diseases are a consequence of perturbations in the normal immune response leading to a breakdown in immune tolerance, manifested as an immunological attack on the body’s normal tissues. Examples of some of the more common autoimmune diseases include rheumatoid arthritis (RA), multiple sclerosis (MS), lupus erythematosus (SLE), inflammatory bowel disease (IBD), and Type 1 diabetes. Historically, treatment for these diseases has relied on non-specific immunosuppression using a variety of drugs (e.g. Corticosteroids, Gold and Methotrexate) with partial effectiveness and often serious side effects. There are also cases where drugs developed for other clinical uses, such as statins

for serum cholesterol reduction, have been shown to be effective in the treatment of certain autoimmune diseases, presumably through known immunomodulatory effects. In the last decade, however, new biological therapies have become available which appear to be far superior to previous treatment options. This presentation provided thought provoking information on how these new treatments might be working and the pitfalls in extrapolating data from animal models into clinical situations. New biologic agents offer improved specificity

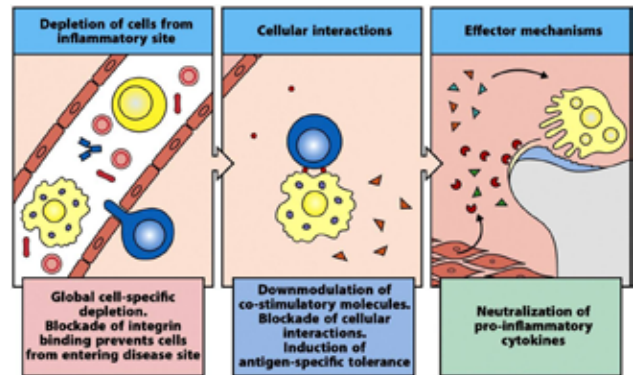


Figure 15-6 Immunobiology, 7ed. © Garland Science 2008

Current/potential therapeutic targets in autoimmunity/inflammation



against the traditional therapeutic targets, which include depletion of cells from the inflammatory site, inhibition of abnormal cellular interactions and regulation of effector mechanisms such as cytokine neutralization. However, the use of different agents that target the same molecule can have very different therapeutic effects. For example, of two drugs (infliximab and etanercept) targeting the same cytokine, tumour necrosis factor (TNF $\alpha$ ), only infliximab is effective in the treatment of Crohn's disease, whereas both drugs are effective treatments for RA patients. In the case of RA, it appears that infliximab acts by modulating the effector function of the defective regulatory T-cells (Tregs) found in RA patients, but it does so through a different mechanism than the drug etanercept. The evidence presented on the complex interactions between TNF, regulatory T cells and anti-TNF agents suggests that these new biological therapies are highly effective treatments and offer the hope of long term remission in autoimmune disease. From the experimental data presented, it is clear that we have a wealth of information on the mechanism of one drug, infliximab, on Treg populations both in vitro and in vivo. However, an even deeper understanding is needed to predict which patients will respond to which drugs, and what the potential side effects might be in different populations. This information will be needed if we are to advance to personalized medicine. Many valuable insights have been gained from the use of experimental models as predictors of human disease. However, there are also instances in which experimental data has not translated into clinical benefits. For example, the use of anti-TNF agents in MS provided encouraging data in a mouse model system but in fact worsened the disease in MS patients. Such cases highlight the importance of research in human systems and the value of clinical research. The integration of systems biology into clinical research might be one approach for advancing our understanding of disease pathogenesis resulting in improved prevention and treatment modalities.

*The integration of systems biology into clinical research might be one approach to advancing our understanding of disease pathogenesis resulting in improved prevention and treatment modalities.*

**“How to Develop a Systems Biology Program useful to Biologists (including immunologists)” – Dr. Ron Germain, Laboratory of Immunology and Program in Systems Immunology and Infectious Disease Modeling, NIAD, NIH, US**



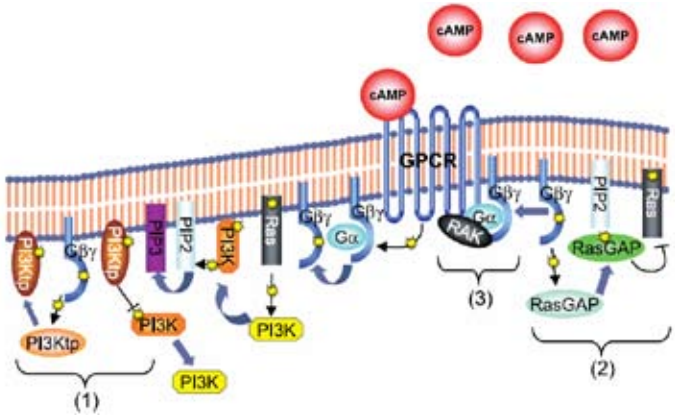
The goal of this presentation was to provide linkages between systems biology and immunology and to set the stage for later discussions on potential systems biology approaches to immune modulation. Biological systems are extremely complex and although a great deal of information is already known about the multiple components of the inflammatory response there is still a gap in our understanding of how these components actually interact or may be used in a predictive capacity to simulate biological behaviours. A systems biology approach builds on genome sequence data, expression profiling, proteomic analysis, imaging datasets, nanostate analysis, global RNAi and chemical library screening to produce network organization of cell components, engineering diagrams of differentiation pathways and models for



*Systems biology requires a multi-component integrated program that brings all the necessary areas of expertise together ... and encourages cross-discipline collaboration.*

simulation and prediction. Through a series of multi-media simulations, the presentation demonstrated the remarkable capabilities of a systems biology approach that integrates computer, mathematical and biological technologies. The capabilities of such

an approach far exceed the traditional “cartoon style” custom model building when applied, for example, to TCR recognition and the early signalling events in T cell activation. For biologists to take advantage of these cutting edge modelling tools, however, the gap must be bridged between computer science, mathematics and biology. The program in Systems Biology and Infectious Disease Modelling (PSIIM) at NIAID has succeeded in doing this through a computer program called Simmune that allows a biologist to construct and run complex models with all the necessary mathematics handled “in the background”. Simmune supports computational models from molecular interactions to multi-cellular systems, as demonstrated in an impressive series of simulations. Using systems such as Simmune, a permanent detailed repository of a biologist’s knowledge is created that others can access and use through linkages to public and private databases and search engines. Systems biology requires a multi-component integrated program that brings all the necessary areas of expertise together, as exists at PSIIM, and encourages cross-discipline collaboration. Through this mechanism, hypotheses can be tested, refined and retested, creating new pathways for biomedical discovery. The presentation was followed by a discussion on the pros and cons of a centralized model in which systems biology capacity is incorporated within individual institutions vs. a “distributed” model across multiple institutions. Many of the systems biology researchers expressed a reluctance to be seen as an external resource to be tapped into “as needed” and would prefer a more integrated model in which research teams included systems biology expertise as part of the core group.



The PI3K Pathway with Local Adaptive Regulation

**“The Ottawa Institute of Systems Biology: Bridging systems biology and diseases”  
– Dr Daniel Figey, Ottawa Institute of Systems Biology, Ottawa**



The final presentation described one example of a Canadian group currently engaged in systems biology research. The Ottawa Institute of Systems Biology, located within the Department of Medicine at the University of Ottawa, has a mandate to create a systems biology group focused on human disease that includes training and education. The Institute takes the technological view of systems biology, as defined by Leroy Hood, as integrating technology, biology and computation. The institute intends to:



- i) *develop a systems biology program aimed at the understanding of human diseases*
- ii) *develop robust platform technologies for high-throughput experiments for systems biology studies and for other projects*
- iii) *develop innovative high-throughput technologies to probe increasing numbers of biomolecules from cells to tissues and develop novel bioinformatics tools and mathematical modeling approaches for systems biology*

The Institute is actively recruiting faculty (several of whom were workshop participants) with a variety of research interests such as biology, biochemistry, biostatistics, biomathematics, x-ray crystallography, neurosciences, and computational modelling. However the long term goal is to collaborate as much as possible across the different disciplines rather than try and recruit from each one. For example, links have already been established with researchers working on Alzheimer disease and stroke, two areas where initial projects will focus. Projects will integrate genomics, proteomics and lipidomics with imaging to provide a novel view of the brain in cerebrovascular, Parkinsons and Alzheimer disease. It is unlikely that success will come overnight as there are many different solutions to apparently simple problems (e.g. ways to boil water) requiring a combination approach and an acceptance that there may be early failures. There are also challenges in recruiting multidisciplinary teams and forging productive and long term collaborations across fields and between institutions. In terms of the application of systems biology approaches to immune modulation, the need to determine the “low hanging fruit” was identified, preferably in an area where a good animal model exists and tissue samples are available.



## *Breakout Session 1 – Theme specific*

Workshop participants were divided into three groups, broadly based on area of expertise, to discuss the state of the art in their respective research areas and to consider approaches to integrating systems biology into the study of immunotherapy/inflammation research. Each group was provided with a series of questions (Appendix 4) to help guide the discussions. The main points discussed and the conclusions reached are described briefly below.

### Group 1 - Systems Biology

Group 1 defined systems biology as a focus on molecular systems and cell-cell interactions and immunotherapy as a two pronged approach – using the immune system to treat disease (e.g. vaccines, cancer) and treating diseases of the immune system (e.g. autoimmune diseases).



*The challenges facing systems biologist and immunologists include finding both a common language with which to communicate effectively and better ways to sort through the huge amounts of existing data to select the few things that can be successfully studied in the laboratory.*

As described in the earlier presentations, the group agreed that the key to success rests on the ability to integrate genome-scale information (genomics, proteomics) in a biological context (pathways, networks) in a way that enables examination of system level properties like signal

propagation, robustness and processes over time. Emergent behaviour is difficult to predict from an examination of the parts in isolation, rather it is necessary to gather all the required information to predict function and outcomes using an iterative approach. A good example of this system in action is the innateDB project in British Columbia, which aims to provide a knowledge base of the genes, interactions and signalling responses in the innate immune responses of humans and mice to microbial infections.

The challenges facing systems biologists and immunologists include finding both a common language with which to communicate effectively and better ways to sort through the huge amounts of existing data to select the few things that can be successfully studied in the laboratory. The existing funding mechanisms are not necessarily supportive of researchers moving between fields and grant applications that combine research disciplines are often difficult to review under the current, predominantly discipline-specific, peer review system. In addition there are scarce resources available to maintain and support existing databases and software. To address these challenges the group suggested that the CIHR resource support grants be re-introduced and that the integration of systems biology approaches to the study of immune modulation be a staged process that includes project support, catalyst grants and extensive cross-training opportunities. Specifically, the group recommended that even with scarce new funding, the communication process could be facilitated through student exchange between laboratories, catalyst/seed grants, co-supervisors from different fields for students, multidisciplinary workshops, short-term (2-3 days) training programs and dual supervision of students. If modest new funding became available the recommendation was for larger scale training programs, perhaps as part of the CIHR strategic training initiative and programs such as Emerging Team grants and specific Requests for Applications (RFAs). There was a broad consensus that if systems biology approaches are to succeed, a long term commitment must be made to support the integration required and that ideally a large sum of money, in the region of \$500 million, would be necessary to establish and maintain this new approach to health research. Such a commitment would require multiple partnerships and considerable new financial investment.

## Group 2 – Clinical Autoimmunity

Members of this breakout group included representatives from five of the six clinical autoimmunity teams recently funded by III and partners under the Clinical Autoimmunity Team Grant initiative. This initiative was launched to support collaborative, multidisciplinary teams engaged in autoimmune research in a clinical setting. Funded projects focused on several different autoimmune conditions including IBD, pediatric disease, psoriasis and psoriatic arthritis, inflammatory arthritis, SLE and multiple sclerosis.



The group agreed with earlier definitions of systems biology as integration of technology (large data sets), biology and the clinical information to model both normal and abnormal biologic processes and also for the need for valid substantive questions to which these technologies can be applied. Given the inherent bias of the group it was agreed that the focus should be disease specific rather than normal functions and focus on the integration of different components of a single disease, e.g. Crohn's disease, using a systems biology approach. Biomarker development was identified as one area that would benefit from an integrated approach and could also make use of existing resources such as the Manitoba prospective cohort study of patients with Crohn's disease.

*It was agreed that all the clinical autoimmunity teams could benefit from systems biology expertise and if it were available from a core consultative resource they would definitely take advantage of it, by recruiting experts/consultants for each team.*

It was agreed that all the clinical autoimmunity teams could benefit from systems biology expertise and if it were available from a core consultative resource they would definitely take advantage of it by recruiting experts/consultants for each team. This generated a debate on the dichotomy between a “user” and a “producer” approach. Rather than establish a central core of systems biology expertise, some researchers felt strongly that systems biology is an experimental science, still in need of development in most areas. An integrated team approach, therefore, would be most beneficial, where systems biologists and immunologists work together from the outset in tackling defined research questions.



In a situation of limited financial resources, the group felt that the development of a shared network of information from ongoing studies, (e.g. creation of a website) between teams and among other chronic disease groups would be valuable. With increased funding, the group favoured support of training programs and multidisciplinary team grants, and with substantial funding the group favoured the creation of a central bioinformatics core to address select projects through competition.

There was broad agreement that partnerships would be key, including industry partnerships with pharmaceutical companies and perhaps computer companies. It was also recommended that projects focus on one clinical problem initially, with a long term funding commitment to ensure growth and sustainability.

### Group 3 – Immunology

Group 3 agreed with previous definitions of systems biology and identified vaccines, tolerance vs. non-tolerance, host pathogen interactions and chronic inflammatory/allergic disease as areas where a systems biology approach would be most beneficial. This group felt strongly that in addition to the challenges described by the other two groups, funding was perhaps the major challenge and that unless sufficient funds become available it might be better to do nothing at all rather than invest in small, insignificant projects. Emphasis was placed on the generation of meaningful partnerships



between, for example, CIHR Institutes, Genome Canada, NRC, NSERC and industry. It was recommended that with sufficient funds (approximately \$5 million per year) one or two major nodes could be established which would serve, to some extent at least, to overcome the geographical barriers Canadians experience in trying to create effective collaborations. It was also recognised that much could be learnt from the experiences of other countries, such as the US, Europe and Japan with respect to the kind of funding models best suited for a systems approach. Open access to datasets and other resources was also identified as a high priority.

## *Breakout Session 2 – Multidisciplinary*

In this breakout session, participants were asked to put into practice what they had learnt during the presentations and discussions on the first day and design a research project that would integrate systems biology approaches with traditional immune modulation/inflammation research. Some key questions and suggested criteria were provided as a guide (Appendix 4). At the end of the breakout session, each group, presented their proposal to the entire group, which then voted (by show of hands) for the “best” proposal.

### Group 1 – A Network Approach to Inflammatory Bowel Disease

*The proposed project would aim to identify predictors of risk, disease progression, patient subsets and outcome.*

Group 1 chose to focus on a single disease, IBD, because there is already an active research community, including teams funded under the III clinical autoimmunity initiative, there are existing cohorts (e.g. the Manitoba cohort), there is existing risk factor/genetic information, there are good animal models, and potential partners can easily be identified e.g. NGOs and industry.

The proposed project would aim to identify predictors of risk, onset, disease progression, patient subsets and outcome. The goal would be to identify new targets that could guide the use of existing therapies or lead to the development of new ones. The project would also study host-pathogen interactions in both normal individuals and patient sub sets (responders vs. non-responders).

The project would require the development of strong partnerships and a team environment that would bring together systems biologists, biologists and clinicians as equal partners to investigate a core problem. Training would by necessity be an integral part of the program and recruitment of a strong academic champion who could dedicate their time to leading and coordinating the project would be essential.



Experimentally, the project would require repeated cycles of proteomic, genetic and other analyses, development of models and testing relative to clinical data and mouse models in an iterative process. The project would build on existing national and international data and link appropriately. The project was envisaged as a large multi-centre team requiring in the range of \$3-5 million per year for operation.

## Group 2- Canadian Human Immunology and Systems Biology Initiative (CHISI)

Rather than an individual project, Group 2 designed an initiative to which research teams could apply through a competitive process based on either a centralized or distributed model. The initiative aligns with an NCE/Large Team grant model and requires a strong training component in which investigators could potentially have a 50% commitment to common shared projects and 50% to individual projects.

*Develop an initiative able to generate and share new tools and resources in a systems biology approach to health research.*

Successful applications would avoid redundancy and incorporate existing infrastructure and would have to include units in basic and clinical science, genomics, proteomics, computational biology, imaging, and technology development, etc. The end result would be one or more centralized or “virtual” institutes that would attract a new cadre of researchers and establish research teams able to generate and share new tools and resources in a systems biology approach to health research.

Again, partnership would be a key feature of the initiative with suggested partners including Genome Canada, CFI, the Provinces, charitable organizations, the NIH and the Canadian Microbiome Initiative. Funding in the region of \$2-5 million would be required to establish and maintain each centre. Success would be measured by the generation of new knowledge, the forging of new alliances, an increase in the number of researchers taking a systems biology approach to health research, and knowledge transfer through technology development and commercialization.

## Group 3 – A Systems Approach to Understanding the pathogenesis and developing treatment Options for Autoimmune Disease

Group 3's proposal followed an in depth discussion between the systems biologists and the immunologist/immunotherapists in the group and a comparison of the relative skills, expertise and approaches in both disciplines. The immunologists explained the complexity of disease pathogenesis and the fact that different autoimmune diseases don't necessarily share the same mechanisms, although it is hoped that commonalities can be found. From the biological perspective it is possible to collect data from blood and, in some cases, tissue samples, but it was not immediately clear how a systems biology approach could be integrated. From the systems biology perspective it is possible to obtain array studies in

*By working together, it should be possible to match gene expression and protein interactions with disease processes and predict therapeutic outcomes.*



lymphocytes to get patterns of genes. If the assumption is made that it is the interaction networks in a cell that govern what happens and lead to genetic change, then by looking at gene expression data and hubs using algorithms, it is possible to make correlations to disease. Proteomic profiling is also possible and in animal models protein interactions can be mapped and localized. By working together it should be possible to match gene expression and protein interactions with disease processes and predict therapeutic outcomes. Outcomes in one autoimmune disease could then be studied in multiple diseases.

The group, therefore, proposed a partnership between systems biologists and immunologists that would build on research currently funded by CIHR (e.g. the clinical autoimmunity teams) and integrate expertise from other fields (e.g. economists, ethicists, epidemiologists). One of the outcomes would be the recruitment of patients into cohort studies to enable long term research projects. Suggested partners included industry, NGOs and the Immune Tolerance Network in the US. The project would be in the form of a large team grant, able to integrate different disciplines to enhance our understanding of disease pathogenesis. Funding levels and infrastructure requirements were not defined.

## Summary

*There was little doubt that a systems biology approach to immune modulation could be highly beneficial to the fields of immunotherapy and inflammation and would likely lead to advances in our understanding of disease pathogenesis.*

The workshop was successful in bringing immunologists, clinicians and systems biologists together, in an environment where they were encouraged to network and open the channels of communication that are essential to future collaboration. All groups reported having learnt from each other and there appeared to be a genuine interest in pursuing collaborative opportunities. By the end of the workshop there was little doubt that a systems biology approach to immune modulation could be highly beneficial to the fields of immunotherapy and inflammation and would likely lead to advances in our understanding of disease pathogenesis. All the representatives of the Clinical Autoimmunity teams showed a keen interest in working with systems biologists to advance their research. It was also clear, however, that integration of the two sciences would not happen overnight as the communication challenges are not insignificant.

Workshop participants proposed several mechanisms to facilitate the creation of effective collaborations, including a variety of potential training models, staged investment in capacity building e.g. through catalyst grants or career transition awards, and the creation of integrated teams which could be either centralized or dispersed (if dispersed frequent face-to-face meetings were highly recommended).



It was recommended that any systems biology initiative be long term and sustainable. As a result, any program created is likely to be resource intensive, e.g. \$5 million per. year, as a minimum investment. Partnerships would be essential to support such an expensive initiative. One partnership model could be a multi-Institute approach in which several CIHR Institutes combine funds to launch an initiative to support the integration of systems biology with health research but with clearly identified research areas corresponding to the Institutes' mandates. Another approach could be to seek partnerships with ongoing initiatives in the US, such as the Immune Tolerance Network or the systems biology initiatives, described by Dr. Germain, that exist within the NIH, or with other organizations such as NGOs.

### *Next Steps*

One of the consistent messages from the workshop was to be bold and innovative and to “think big”. Participants were strongly in favour of a bold new initiative with unique features. However the structure of such an initiative was not clearly defined in the short time available at the meeting. As a first step, the workshop was successful in establishing constructive dialogue between diverse research groups and promoting the concept of collaborations. More discussion will be necessary to identify a specific research program or vehicle that will successfully integrate systems biology approaches into biologically-orientated research such as immunotherapy and inflammation.






There are already existing CIHR programs, described to participants during the workshop, which might be appropriate first steps for collaborative projects and that are open to applicants immediately. These include the CIHR Strategic Training in Health Research Program – LOI April 1, Operating Grants – Registration August 1 and March 15, and the Collaborative Health Research Program (a partnership between CIHR and NSERC) – LOI May 1. Workshop support is also available on a competitive basis, with intake of applications in February, June and October.


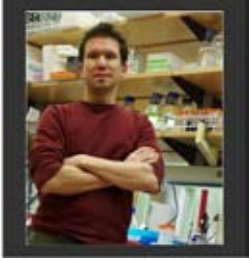
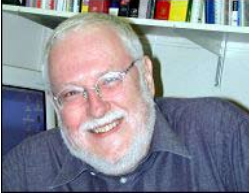


In terms of a specific Request for Applications launched by III or multiple CIHR Institutes, this will be the topic of discussion for the III Institute Advisory Board, and the Research and Knowledge Translation Committee at CIHR which brings together all 13 Institute Scientific Directors with senior management to discuss research planning and priorities. Certainly III remains committed to taking the lead in facilitating the integration of systems biology approaches into traditional health research and will actively pursue avenues likely to make this a reality.






*III remains committed to taking the lead in facilitating the integration of systems biology approaches into traditional health research and will actively pursue avenues likely to make this a reality.*


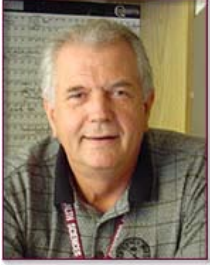



## APPENDIX ONE





### **Participants List**

NAME	CONTACT INFORMATION	AREA OF RESEARCH
<p><b>Jane Aubin</b></p> 	<p>Scientific Director, CIHR Institute of Musculoskeletal health and Arthritis (IMHA)</p> <p><u>University of Toronto</u>            Department of Medical Biophysics            Ontario Cancer Institute, Princess Margaret Hospital            610 University Avenue            Room 7-411            Toronto, ON M5G 2M9            416-978-4220  <a href="mailto:jane.aubin@utoronto.ca">jane.aubin@utoronto.ca</a></p>	<p>IMHA supports research to enhance active living, mobility and movement, and oral health; and addresses causes, prevention, screening, diagnosis, treatment, support systems, and palliation for a wide range of conditions related to bones, joints, muscles, connective tissue, skin and teeth.</p>
<p><b>Gary Bader</b></p> 	<p><u>University of Toronto</u>            160 College Street, Room 602            Terrence Donnelly Centre for Cellular and Biomolecular Research            Toronto, ON M5S 3E1            416-978-3935  <a href="mailto:gary.bader@utoronto.ca">gary.bader@utoronto.ca</a></p>	<p>Organization and evolution of biological systems; computational biology and bioinformatics techniques; molecular interactions in eukaryotic cell signaling systems using comprehensive genomics data like genome sequence and transcript profiles; cellular network evolution; detection of cell type and stage active biological processes using molecular profiles; biological pathway and network databases and analysis tools.</p>
<p><b>Amit Bar-Or</b></p> 	<p><u>McGill University</u>            Neuroimmunology Unit            3801 University Street, Room # 111            Montreal, QC H3A 2B4            514-398-5950  <a href="mailto:amit.bar-or@mcgill.ca">amit.bar-or@mcgill.ca</a></p>	<p>Mechanisms of autoimmune dysregulation; immune-neural interaction and neuro-immunological disease; assessing disease relevant mode of action of novel therapeutics, and biomarker development, for human autoimmune diseases; biology of pediatric inflammatory demyelination and post-ablative immune reconstitution.</p>
<p><b>Paul Bélanger</b></p> 	<p>Assistant Director, CIHR Institute of Nutrition, Metabolism and Diabetes (INMD)</p> <p><u>CIHR</u>            Room 97, 160 Elgin Street            Address locator: 4809A            Ottawa, ON K1A 0W9            613-941-6465  <a href="mailto:pbelanger@cihr-irsc.gc.ca">pbelanger@cihr-irsc.gc.ca</a></p>	<p>INMD supports research to enhance health in relation to diet, digestion, excretion, and metabolism; and to address causes, prevention, screening, diagnosis, treatment, support systems, and palliation for a wide range of conditions and problems associated with hormone, digestive system, kidney, and liver function.</p>
<p><b>Charles Bernstein</b></p> 	<p><u>University of Manitoba</u>            804F-715 McDermot Avenue            Bannatyne Campus            Winnipeg, MB R3E3P4            204-789-3369  <a href="mailto:cbernst@cc.umanitoba.ca">cbernst@cc.umanitoba.ca</a></p>	<p>Epidemiological, outcomes and etiological research in inflammatory bowel diseases including Crohn's disease and ulcerative colitis.</p>






NAME	CONTACT INFORMATION	AREA OF RESEARCH
<p><b>David Bickel</b></p> 	<p><u>University of Ottawa</u>  Ottawa Institute of Systems  Biology  BMI Dept.,  451 Smyth Road  Roger Guindon Hall  Room 1317  Ottawa, ON K1H 8M5  613-562-5800 ext. 8670  <a href="mailto:dbickel@uottawa.ca">dbickel@uottawa.ca</a></p>	<p>Statistical bioinformatics research; gene expression data analysis, molecular network reconstruction, model validation methodology, Bayesian and empirical Bayes inference, machine learning algorithms, and Monte Carlo simulation.</p>
<p><b>Alexandre Blais</b></p> 	<p><u>University of Ottawa</u>  Ottawa Institute of Systems  Biology  Roger Guindon Hall, Room 2539  451 Smyth Road  Ottawa, ON K1H 8M5  613-562-5800 ext 8463  <a href="mailto:Alexandre.Blais@uOttawa.ca">Alexandre.Blais@uOttawa.ca</a></p>	<p>Transcription factors; muscle development; skeletal myogenesis, such as Myogenin and the other myogenic regulatory factors (MRFs); functional genomics e.g. ChIP-on-chip; RNA interference and expression profiling.</p>
<p><b>Philip Branton</b></p> 	<p>Scientific Director, CIHR Institute of Cancer Research (ICR)</p> <p><u>McGill University</u>  Room 706  3655 Promenade Sir-William-Osler  Montreal, QC H3G 1Y6  514-398-8350  <a href="mailto:branton@mcgill.ca">branton@mcgill.ca</a></p>	<p>ICR is dedicated to supporting research that reduces the burden of cancer on individuals and families through prevention strategies, screening, diagnosis, effective treatment, psycho-social support systems, and palliation.</p>
<p><b>Judy Bray</b></p> 	<p>Assistant Director - CIHR Institute of Infection and Immunity (III)</p> <p><u>CIHR</u>  Room 97, 160 Elgin Street  Address Locator: 4809A  Ottawa, ON K1A 0W9  613-954-7223  <a href="mailto:jbray@cihr-irsc.gc.ca">jbray@cihr-irsc.gc.ca</a></p>	<p>The CIHR Institute of Infection and Immunity (III) supports research and helps to build research capacity in the areas of infectious disease and the body's immune system. Through the Institute's programs, researchers address a wide range of health concerns related to infection and immunity including disease mechanisms, disease prevention and treatment, and health promotion through public policy.</p>
<p><b>Earl G. Brown</b></p> 	<p><u>University of Ottawa</u>  Roger-Guindon Hall  451 Smyth Road  Room 4109  Ottawa, ON K1H 8M5  613-562-5800 ext 8310  <a href="mailto:ebrown@uOttawa.ca">ebrown@uOttawa.ca</a></p>	<p>Analysis of viral evolution with respect to pathogenesis of various viruses including mumps virus, vesicular stomatitis virus, reovirus, HCV, influenza A viruses; genomic analyses of influenza virus evolution to high virulence in a new host; evasion of the host immune system by the hepatitis C virus (HCV); studies on HCV protein coat; HCV vaccine development.</p>

NAME	CONTACT INFORMATION	AREA OF RESEARCH
<p><b>Dale Dempsey</b></p> 	<p>Deputy Director – CIHR Knowledge Creation Programs Research Portfolio</p> <p><u>CIHR</u> 160 Elgin Street, Rm 97 Address Locator: 4809A Ottawa, Ontario, K1A 0W9 613-954-5320 <a href="mailto:ddempsey@cihr-irsc.gc.ca">ddempsey@cihr-irsc.gc.ca</a></p>	
<p><b>Michael Ehrenstein</b></p> 	<p><u>University College London</u> Centre for Rheumatology Department of Medicine UCL Windeyer Building, room 319 46 Cleveland Street London, UK W1T 4JF 020 7679 9708 or 020 7380 9281 <a href="mailto:m.ehrenstein@ucl.ac.uk">m.ehrenstein@ucl.ac.uk</a></p>	<p>Regulatory T cell biology in rheumatoid arthritis and systemic lupus erythematosus; effects of biological therapy on immunoregulation in autoimmune rheumatic disease.</p>
<p><b>John Ficele</b></p> 	<p><u>Sigma-Aldrich</u> Marketing Manager Sigma-Genosys Canada 2149 Winston Park Dr Oakville, ON L6H 6J8 <a href="mailto:John.Ficele@sial.com">John.Ficele@sial.com</a></p>	<p>Sigma-Aldrich is a leading Life Science and High Technology company, whose biochemical and organic chemical products and kits are used in scientific and genomic research, biotechnology, pharmaceutical development, the diagnosis of disease and as key components in pharmaceutical and other high technology manufacturing. Sigma-Aldrich operates in 35 countries and has over 6,800 employees providing excellent service worldwide.</p>
<p><b>Daniel Figeys</b></p> 	<p><u>University of Ottawa</u> Ottawa Institute of Systems Biology Health Sciences Campus 451 Smyth Road Roger Guindon Hall Room 4204 Ottawa, ON K1H 8M5 613-562-5800 ext 8674 <a href="mailto:dfigeys@uottawa.ca">dfigeys@uottawa.ca</a></p>	<p>Systems biology; mapping protein-protein interactions of proteins relevant to human diseases; validating the roles that some of these proteins play in human diseases; the development of novel proteomic approaches to study diseases.</p>
<p><b>Eleanor Fish</b></p> 	<p><u>Toronto General Hospital</u> Canadian Blood Services 4th Floor Rm. 424 67 College St Toronto, ON M5G 2M1 416-340-4800 x5380 <a href="mailto:en.fish@utoronto.ca">en.fish@utoronto.ca</a></p>	<p>Interactions of cytokines, and specifically interferons and chemokines, with their receptors at the conformational level, biological responses to these molecules and changes in expression of these molecules in diseased tissue; dysregulation of cytokine and chemokine expression; inflammation; genomic and proteomic investigations in rheumatoid arthritis.</p>






NAME	CONTACT INFORMATION	AREA OF RESEARCH
<p><b>Jennifer Gardy</b></p> 	<p><u>University of British Columbia</u>            CMDR, Room 222A            2259 Lower Mall            Vancouver, BC V6T 1Z4            604-827-4005  <a href="mailto:jennifer@cmdr.ubc.ca">jennifer@cmdr.ubc.ca</a></p>	<p>Pathogenesis of innate immunity; host defence peptides; database creation – key genes, proteins and interactions; systems biology; computational modelling, perturbations of innate immune networks; information visualization.</p>
<p><b>Jack Gauldie</b></p> 	<p><u>McMaster University</u>            MDCL 4016            1200 Main St West            Hamilton, ON L8N 3Z5            905-525-9140 ext 22610  <a href="mailto:gauldie@mcmaster.ca">gauldie@mcmaster.ca</a></p>	<p>Molecular regulation of the acute phase inflammatory response; cytokine biology and the molecular regulation of inflammation and immunity; vaccine development.</p>
<p><b>Ron Germain</b></p> 	<p><u>National Institute of Allergy and Infectious Diseases, NIH</u>            National Institutes of Health, DHHS            Bldg. 10, Rm. 11N311            10 Center Dr., MSC-1892            Bethesda, MD 20892-1892            301-496-1904  <a href="mailto:rgermain@nih.gov">rgermain@nih.gov</a></p>	<p>T cell; antigen recognition; computer modeling.</p>
<p><b>Jack Greenblatt</b></p> 	<p><u>University of Toronto</u>            9th Floor, Terrence Donnelly            Centre for Cellular &amp; Biomolecular            Research (Donnelly CCBR)            160 College Street, Room 906            Toronto, ON M5S 3E1            416-978-5863  <a href="mailto:jack.greenblatt@utoronto.ca">jack.greenblatt@utoronto.ca</a></p>	<p>Transcriptional regulation; bacterial proteomics; mammalian protein interactions; yeast proteomics; genetic interactions in yeast and <i>E. coli</i>; As part of the Proteomics Research Center &lt;<a href="http://www.utoronto.ca/proteomics_center/">http://www.utoronto.ca/proteomics_center/</a>&gt;, we are using technologies such as mass spectrometry and microarray analyses to interrogate cellular biology. Our most recent focus is on how proteins change their interaction partners in different types of cells and tissues from embryonic stem cells to live mice.</p>
<p><b>Phil Hieter</b></p> 	<p><u>University of British Columbia</u>            2185 East Mall            Vancouver, BC V6T 1Z4            604-827-3912  <a href="mailto:hieter@msl.ubc.ca">hieter@msl.ubc.ca</a></p>	<p>Molecular biology of eukaryotic chromosome transmission segregation of chromosomes in the yeast <i>Saccharomyces cerevisiae</i>; mitotic cell division and the chromosome transmission cycle; analysis of a large reference collection of mutants that are defective in chromosome segregation and that define genes required for kinetochore function, sister chromatid cohesion, chromosome structure, and control of cell cycle progression at mitosis; Anaphase Promoting Complex (APC).</p>





NAME	CONTACT INFORMATION	AREA OF RESEARCH
<p><b>Mads Kaern</b></p> 	<p><u>University of Ottawa</u>  Roger Guindon Hall  #3215  451 Smyth Road  Ottawa, ON K1H 8M5  613-562-5800 ext. 8691  <a href="mailto:mkaern@uottawa.ca">mkaern@uottawa.ca</a></p>	<p>Biological control systems with emphasis on gene regulatory networks; design principles of genetic circuits; stochasticity in gene expression; reverse-engineering of complex networks; genome-scale systematic screening; predictive modeling of cellular dynamics; genetic network engineering</p>
<p><b>Paul Kubes</b></p> 	<p><u>University of Calgary</u>  2500 University Drive NW  Room HS1867 &amp; HS1877  Calgary, AB T2N 1N4  403-220-3012  <a href="mailto:pkubes@ucalgary.ca">pkubes@ucalgary.ca</a></p>	<p>Interested in how white cells get to sites of infection and inflammation; adhesion molecules that are used in different organs; imaging of the innate immune system in health and disease; understanding the role of TLRs in innate immunity; chemotaxis and cells recruitment.</p>
<p><b>Quim Madrenas</b></p> 	<p><u>University of Western Ontario</u>  Room 2.05, P.O. Box 5015  100 Perth Drive  London, ON N6A 5K8  519-663-5777 ext. 34242  <a href="mailto:madrenas@robarts.ca">madrenas@robarts.ca</a></p>	<p>Regulation of T cell activation; transplantation, immunology, renal medicine.</p>
<p><b>Jacek Majewski</b></p> 	<p><u>McGill University and Genome Québec,</u>  Department of Human Genetics  Innovation Centre  740 Docteur Penfield Avenue,  Room 7210  Montreal, QC H3A 1A4  514-398-3600  <a href="mailto:jacek.majewski@mcgill.ca">jacek.majewski@mcgill.ca</a></p>	<p>Differential pre-mRNA splicing; mechanisms regulating gene expression; bioinformatics; use of a new microarray design (Affymetrix HuEx chip) to identify exons that are alternatively spliced across different tissues and individuals; identification of sequence motifs and RNA secondary structures that are over-represented in the vicinity of alternative splicing events; evolutionary issues such as determination of mutation rates, recombination rates and detection of selective pressures in eukaryotic genomes.</p>
<p><b>Jean Marshall</b></p> 	<p><u>Dalhousie University</u>  Sir Charles Tupper Medical Building,  Halifax, NS B3H 1X5  902-494-3587  <a href="mailto:Jean.Marshall@Dal.Ca">Jean.Marshall@Dal.Ca</a></p>	<p>Immunology - the role and regulation of mast cells in host defence against tumors and infection; regulation of cytokines in asthma and other inflammatory diseases; microbial and molecular genetics; cancer biology.</p>

NAME	CONTACT INFORMATION	AREA OF RESEARCH
<p><b>Pamela Ohashi</b></p> 	<p><u>University of Toronto</u>            Departments of Medical            Biophysics and Immunology            Division of Signaling Biology            Ontario Cancer Institute/Princess            Margaret Hospital            The Campbell Family Institute for            Breast Cancer Research            University Health Network            610 University Avenue,            Toronto, ON M5G 2M9            416-946-2357  <a href="mailto:pohashi@uhnresearch.ca">pohashi@uhnresearch.ca</a></p>	<p>Mechanisms that maintain tolerance or promote T cell activation, leading to the induction of immunity, autoimmunity or potentially tumor immunity; transgenic models; gene deficient mice; the induction of T cell tolerance or activation; the role of survival versus apoptosis on tolerance and autoimmunity; signaling pathways that control T cell tolerance, activation, immunity, autoimmunity or tumor immunity; immune surveillance and tumor immune therapy.</p>
<p><b>Francis Ouellette</b></p> 	<p><u>Ontario Institute for Cancer            Research</u>            MaRS Centre, South Tower            101 College Street,            Suite 800            Toronto, ON M5G 0A8            416-673-8511  <a href="mailto:francis@oicr.on.ca">francis@oicr.on.ca</a></p>	<p>Informatics and biocomputing; scientific approach to understanding and analyzing data; construction of software and databases.</p>
<p><b>Dave Parrish</b></p> 	<p><u>Immune Tolerance Network (ITN)</u>            ITN Pittsburgh Office            2585 Freeport Road            Pittsburgh, PA 15238, USA            412-820-8807 ext 2310  <a href="mailto:dparrish@immunetolerance.org">dparrish@immunetolerance.org</a></p>	<p>ITN's data management infrastructure; information systems relating data derived from clinical trials, tolerance assay studies and core facilities; laboratory information and knowledge discovery systems.</p>
<p><b>Theodore Perkins</b></p> 	<p><u>McGill University</u>            McGill Centre for Bioinformatics            3775 University Street            Montreal, QC H3A 2B4            514-398-5018  <a href="mailto:perkins@mcb.mcgill.ca">perkins@mcb.mcgill.ca</a></p>	<p>Modeling dynamics and information processing in biochemical networks; using the principles from probability theory, information theory, and control theory to identify and explain the structure and function of biochemical networks; development of efficient algorithms for fitting differential equation models of time-series data; the development and application of machine learning and data mining algorithms for biological data sets.</p>
<p><b>Claude Perreault</b></p> 	<p><u>University of Montreal</u>            Institute for Research in            Immunology and Cancer,            P.O. Box 6128,            Station Centre-Ville,            Montreal, QC H3C 3J7            514-343-6126  <a href="mailto:claudio.perreault@umontreal.ca">claudio.perreault@umontreal.ca</a></p>	<p>Histocompatibility antigens, bone marrow transplantation; T and B cell recognition of abnormal cells; mechanisms responsible for the development of T-lymphocytes; means by which T-lymphocytes distinguish normal cells from abnormal ones; the potential of lymphocytes be tapped into to fight cancer; autoimmune diseases; cancer.</p>

NAME	CONTACT INFORMATION	AREA OF RESEARCH
<p><b>Andrew Potter</b></p> 	<p><u>University of Saskatchewan</u>  Vaccine &amp; Infectious Disease  Organization/InterVac  120 Veterinary Road  Saskatoon, SK S7N 5E3  306-966-7484  <a href="mailto:andrew.potter@usask.ca">andrew.potter@usask.ca</a></p>	<p>Vaccine development and therapeutics; vaccine for E.Coli 0157; respiratory disease in animals; genomics in animal health; mediators of innate immunity; immune enhancing modulators; peptides and immune activation.</p>
<p><b>Chris Power</b></p> 	<p><u>University of Alberta</u>  6-11 Heritage Medical Research  Building  University of Alberta  Edmonton, AB T6G 2S2  780-407-1938  <a href="mailto:chris.power@ualberta.ca">chris.power@ualberta.ca</a></p>	<p>Neurovirology; neuroimmunology; neurodegeneration, retrovirology; Multiple Sclerosis and Neuro-AIDS.</p>
<p><b>Jim Richards</b></p> 	<p><u>Director General, NRC - IBS</u>  (Institute of Biological Sciences)  Room 136 Build M-54  1200 Montreal Road  Ottawa, ON K1A 0R6  613-993-7506  <a href="mailto:James.Richards@nrc-cnrc.gc.ca">James.Richards@nrc-cnrc.gc.ca</a></p>	<p>The NRC Institute for Biological Sciences (NRC-IBS) is a team of excellent life science researchers in Ottawa, dedicated to unearthing the next breakthrough discoveries and technologies in neurobiology, immunobiology and glycobiology. NRC-IBS is focused on research and development associated with neurodegenerative diseases, infectious diseases, cancer vaccines, immunotherapeutics and of bioproducts - and moving these discoveries out to the marketplace.</p>
<p><b>John D. Rioux</b></p> 	<p><u>Montreal Heart Institute</u>  5000 rue Belanger  Suite Room S-6200  Montreal, QC H1T 1C8  514-376-3330 ext. 3741  <a href="mailto:john.david.rioux@umontreal.ca">john.david.rioux@umontreal.ca</a></p>	<p>Genetics and genomic medicine in inflammation; how genetic variation influences disease risk, phenotypic expression and response to therapy.</p>
<p><b>Noel Rose</b></p> 	<p><u>The Johns Hopkins Hospital</u>  Johns Hopkins Center for  Autoimmune Disease Research  MMI-E5014 615 N. Wolfe Street  Baltimore, MD 212057, USA  410-955-0330  <a href="mailto:nrose@jhsp.edu">nrose@jhsp.edu</a></p>	<p>Immunological tolerance mechanisms; autoimmune disease; autoimmune pathogenic responses; the interplay of genetic, infectious and environmental factors.</p>

NAME	CONTACT INFORMATION	AREA OF RESEARCH
<p><b>Stephanie Robertson</b></p> 	<p>Assistant Director, CIHR- Institute of Genetics (IG)</p> <p><u>CIHR</u> 160 Elgin Street, 9th Floor Address Locator 4809A Ottawa, ON K1A 0W9 <a href="mailto:srobertson@cihr-irsc.gc.ca">srobertson@cihr-irsc.gc.ca</a> 613-954-0533</p>	<p>IG supports research on the human genome and in all aspects of genetics, basic biochemistry and cell biology related to human health and disease, including interaction of genes with physical and social environments.</p>
<p><b>John Schrader</b></p> 	<p><u>University of British Columbia</u> BRC 2222 Health Sciences Mall 2329 West Mall Vancouver, BC V6T 1Z4 604-822-7822 <a href="mailto:john@brc.ubc.ca">john@brc.ubc.ca</a></p>	<p>The secreted proteins - the cytokines and antibodies - through which the cells of the immune system coordinate defence against pathogens and repair damaged tissues; discovery-based approaches to the intra-cellular signals that regulate the production and function of blood cells; evolutionary foundations of signalling paths and antibody responses.</p>
<p><b>Ernest Seidman</b></p> 	<p><u>McGill University</u> Digestivelab, Research Institute of McGill University Health Center MGH Campus, C10.145 1650 Cedar Avenue Montreal, QC H3G 1A4 514-934-8304 <a href="mailto:digestivelab@hotmail.com">digestivelab@hotmail.com</a></p>	<p>Genes and environmental influences on chronic bowel disorders; immune mediated disorders, e.g. Crohn's disease, ulcerative colitis, and celiac disease; mucosal immune systems; cell and molecular biology and animal models of colitis; genetic and epidemiological approaches, using patients and their families.</p>
<p><b>Rafick-Pierre Sékaly</b></p> 	<p><u>University of Montreal</u> Centre de recherche du Centre hospitalier de l'Université de Montréal Hôpital St-Luc Pavillon Édouard-Asselin 264, Rene-Levesque Blvd. East Room 1307 Montreal, QC H2X 1P1 514-890-8000 ext. 35289 <a href="mailto:rafick-pierre.sekaly@umontreal.ca">rafick-pierre.sekaly@umontreal.ca</a></p>	<p>Cellular biology, imagery infrastructure, HIV; class II MHC molecules interaction with T-cells and HIV; new therapies; human immunology; CD4; tyrosine kinase; activation of T cells; vaccines and immunomodulators for cancer and chronic viral diseases.</p>
<p><b>Katherine Siminovitch</b></p> 	<p><u>Mount Sinai</u> Samuel Lunenfeld Research Institute Room 656A 600 University Avenue Toronto, ON M5G 1X5 416-586-8723 <a href="mailto:ksiminovitch@mtsinai.on.ca">ksiminovitch@mtsinai.on.ca</a></p>	<p>Genetic and cellular mechanisms Modulating expression of the immune response and development of immunologic diseases; human X-linked immunodeficiency disease, Wiskott-Aldrich syndrome, and a murine model of systemic autoimmune and chronic disease known as the motheaten syndrome. Gene products, autoimminty; inflammation; chronic inflammatory diseases, and in particular asthma and the inflammatory bowel diseases (IBD), Crohn's and ulcerative colitis.</p>

NAME	CONTACT INFORMATION	AREA OF RESEARCH
<p><b>Bhagi Singh</b></p> 	<p>Scientific Director – CIHR Institute of Infection and Immunity (III)</p> <p><u>University of Western Ontario</u> The Siebens-Drake Research Institute 1400 Western Road, Room #224 London, ON N6G 2V4 519-661-3228 <a href="mailto:bsingh@uwo.ca">bsingh@uwo.ca</a></p>	<p>The CIHR Institute of Infection and Immunity (III) supports research and helps to build research capacity in the areas of infectious disease and the body's immune system. Through the Institute's programs, researchers address a wide range of health concerns related to infection and immunity including disease mechanisms, disease prevention and treatment, and health promotion through public policy.</p>
<p><b>Robert Sladek</b></p> 	<p><u>McGill University</u> <u>and Genome Quebec Innovation Centre</u> 740, Dr. Penfield, Suite 6214 Montreal, QC H3A 1A4 514-398-5458 <a href="mailto:rob.sladek@mail.mcgill.ca">rob.sladek@mail.mcgill.ca</a></p>	<p>The role of disease-related genetic variation in altering gene regulatory networks.</p>
<p><b>Jana Stankova</b></p> 	<p><u>Université de Sherbrooke</u> Service d'immunologie Dept. de Pédiatrie Faculté de Médecine 3001 N. 12th Avenue Sherbrooke, QC J1H 5N4 <a href="mailto:jana.stankova@usherbrooke.ca">jana.stankova@usherbrooke.ca</a></p>	<p>Inflammation; structure-function studies and signaling pathways of G-protein-coupled receptors for lipid chemo-attractants.</p>
<p><b>Alain Stintzi</b></p> 	<p><u>University of Ottawa</u> Center for Research on Environmental Microbiology and Ottawa Institute of Systems Biology Department of Biochemistry, Microbiology and Immunology Faculty of Medicine 451 Smyth Road Ottawa, ON K1H 8M5 613-562-5800 ext. 8216 <a href="mailto:astintzi@uottawa.ca">astintzi@uottawa.ca</a></p>	<p>Microbial genomic, gene expression and regulation, microarray and functional genomic; foodborne pathogens, host-pathogen interactions, colonization and virulence factors, animal models of human infection, and gut-microbe interactions; campylobacter jejuni, iron acquisition and metabolism, and stress responses.</p>
<p><b>Jon M. Temme</b></p> 	<p><u>Multiple Sclerosis Society of Canada</u> National Vice-President, Client Services &amp; Research Multiple Sclerosis Society of Canada 175 Bloor St E, Suite 700, North Tower Toronto, ON M4W 3R8 416-967-3011 <a href="mailto:Jon.Temme@mssociety.ca">Jon.Temme@mssociety.ca</a></p>	<p>The mission of the Multiple Sclerosis Society of Canada is: <b><i>To be a leader in finding a cure for multiple sclerosis and enabling people affected by MS to enhance their quality of life.</i></b> The two major programs provide hope for the future through the support of MS research into the cause, treatment and cure of the disease and hope for today through our many services that assist people with MS and their families.</p>

NAME	CONTACT INFORMATION	AREA OF RESEARCH
<p><b>Rusung Tan</b></p> 	<p><u>University of British Columbia</u>  Children's &amp; Women's Health  Centre of British Columbia  Room 2G5  4480 OAK ST  Vancouver, BC V6H 3V4  604-875-3605  <a href="mailto:roo@interchange.ubc.ca">roo@interchange.ubc.ca</a></p>	<p>Role of cytotoxic lymphocytes in human disease including cytotoxic T lymphocytes (CTL), natural killer and natural killer T cells. Specifically, their role in promoting and regulating infectious (Epstein-Barr virus) and autoimmune diseases (type 1 diabetes/lupus) and primary immunodeficiencies (X-linked lymphoproliferative disease)</p>
<p><b>George Tolomiczenko</b></p> 	<p><u>Crohn's and Colitis Foundation of Canada</u>,  600-60 St. Clair Avenue East  Toronto, ON M4T 1N5  416-920-5035 ext. 214  c/o: <a href="mailto:jwilson@CCFC.ca">jwilson@CCFC.ca</a></p>	<p>The Crohn's and Colitis Foundation of Canada (CCFC) is a national not-for-profit voluntary medical research Foundation. Its mission is to find the cure for inflammatory bowel disease. To achieve its mission, the Foundation is committed to raising increasing funds for medical research.</p>
<p><b>Gabriel Wainer</b></p> 	<p><u>Carleton University</u>  1125 Colonel By Drive  3216 V-Sim Building,  Ottawa, ON K1S 5B6  613-520-2600 ext 1957  <a href="mailto:gwainer@sce.carleton.ca">gwainer@sce.carleton.ca</a></p>	<p>DEVS formalism; Real-Time modeling; cellular models; modeling and simulation methodologies and tools; parallel/distributed/Web-based simulation; Real-Time operating systems.</p>
<p><b>Gillian Wu</b></p> 	<p><u>York University</u>  Lumbers Building  4700 Keele St.  Toronto, ON M3J 1P3  416-7362100 (23070)  <a href="mailto:gillwu@yorku.ca">gillwu@yorku.ca</a></p> <p><u>UK Contact:</u>  Visiting Fellow,  Clare Hall, University of  Cambridge  Herschel Road, Cambridge  CB3 9AL, UK  011 44 1223 332374</p>	<p>Generation of lymphoid diversity; polymorphisms in the immune system, especially in autoimmune diseases such as arthritis.</p>

# AGENDA

**Workshop:** Systems Biology Approaches to Immune Modulation and Inflammation

**Hosted by:** CIHR Institute of Infection and Immunity

**Date:** January 22-23, 2008

**Location:** St. Laurent Room, Delta Hotel Centre-Ville, Montreal

**Attendees:** Invited participants, IAB working group members and III staff

**Material:** Background documents on immunotherapy and systems biology, participant list, travel claim forms

## Tuesday, January 22

Time	Agenda Item	Presenter
8:15	Breakfast	All
9:00	Introductions	Dr. Judy Bray
9:05	Welcoming remarks	Dr. Bhagi Singh
9:10	Goals and Objectives of the Workshop	Dr. J. Madrenas
9:20	<b>“Bioinformatics &amp; Systems Biology: partners for life”</b>	Dr. Francis Ouellette, Canada
10:10	Health Break	
10:30	<b>“Restoring Tolerance in Autoimmunity”</b>	Dr. Michael Ehrenstein, UK
11:20	<b>“How to Develop a Systems Biology Program Useful to Biologists (including immunologists!)”</b>	Dr. Ron Germain, US
12:15	Lunch	
13:00	<b>“The Ottawa Institute of Systems Biology: Bridging systems biology and diseases”</b>	Dr. Daniel Figey
13:30	<b>Breakout Session 1 – theme specific</b>	All
15:00	Health Break	
15:30	Report back from Breakout groups 1-3 and discussion	
17:00	Concluding remarks for Day 1	J. Bray
17:15	Networking reception	All
18:30	<b>Dinner – Tour de Ville – roof-top restaurant, 30th Floor, Delta Centre-Ville</b>	<b>All who have reserved</b>

## Wednesday, January 23

Time	Agenda Item	Presenter
8:15	Breakfast	
9:00	Re-cap of day 1 and process for Day 2	J. Madrenas
9:15	Some examples of CIHR funding programs	J. Bray
9:30	<b>Break-out Session 2 - multidisciplinary</b>	All
11:00	Health Break	
11:30	Each breakout group will present their project and answer questions from the other groups. Everyone will then vote, by a show of hands, on the project deemed “most likely to succeed.”	All
12:45	Wrap-up and Next Steps	J. Madrenas and J. Bray
<b>Workshop adjourned – boxed lunch available</b>		

### Breakout Sessions

#### Day 1, Session 1 – by theme

Group 1 – Systems Biology

Group 2 – Clinical aspects of immunotherapy

Group 3 – Immunology (general)

The first breakout session will provide an opportunity for participants to discuss, from the perspective of their own field of research, the value of a systems biology approach to immunological research, building on examples provided by the four speakers. Group members will be asked to consider key topics such as: potential barriers to collaboration between systems biology and immunology researchers and ways to overcome them; infrastructure requirements; mechanisms to support the integration of systems biology into immunotherapy/immunology research under different funding scenarios; and suggestions for research areas/topics ready for pilot studies.

#### Day 2, Session 2 – multidisciplinary

For the second breakout session participants will be divided into three multidisciplinary groups to build on the recommendations from the theme-specific discussions on the previous day. By developing a mock research project, group members will be encouraged to: identify a research topic that would clearly benefit from a systems biology approach; confront and solve potential barriers to collaboration; address requirements for knowledge translation and evaluation; identify appropriate funding tools and time frames for a successful research application; and explore the role of partnerships in building a collaborative research agenda. Each group will present their project, as if to a review panel, and address questions and/or concerns raised by other workshop participants. At the end of the session, the whole group will vote, by show of hands, for the “project most likely to succeed.”

Following the workshop, a report will be written and circulated to all participants and the Institute of Infection and Immunity, in consultation with its Institute Advisory Board and partners, will determine the next steps.

***Thank you all, in advance, for your participation in the workshop and your help in determining the best approach to developing a research agenda which will bring systems biologists and immunologists together to advance the field of immunological research.***

APPENDIX THREE

**Breakout Session Groups**

**Tuesday, January 22, 2008 – Break-out session 1**

**Day 1 - Group 1**  
**Systems Biology**  
Facilitator: Gillian Wu  
Recorders: Noel Rose and Judy Bray

Gary Bader  
David Bickel  
Alexandre Blais  
Daniel Figeys  
Jennifer Gardy  
Jack Greenblatt  
Phil Kieter  
Mads Kaern  
Jacek Majewski  
Francis Ouellette  
Theodore Perkins  
Stephanie Robertson  
Robert Sladek  
Gabriel Wainer

**Day 1 - Group 2**  
**Clinical Aspects of Immunotherapy**  
Facilitator: Quim Madrenas  
Recorders: Chris Power and Bethany Heinrichs

Jane Aubin  
Amit Bar-Or  
Paul Bélanger  
Charles Bernstein  
Dale Dempsey  
Michael Ehrenstein  
Eleanor Fish  
David Parrish  
Ernest Seidman  
Rafick-Pierre Sékaly  
Katherine Siminovitch  
Rusung Tan  
Jon Temme  
George Tolomiczenko

**Day 1 - Group 3**  
**Immunology – general**  
Facilitator: Jana Stankova  
Recorders: Diane Christin and Carol Richardson

Phil Branton  
Earl Brown  
John Ficele  
Jack Gauldie  
Ron Germain  
Paul Kubes  
Jean Marshall  
Pamela Ohashi  
Claude Perreault  
Andrew Potter  
Jim Richards  
John Rioux  
John Schrader  
Alain Stintzi

**Wednesday, January 23, 2008 – Break-out session 2**

**Day 2 - Group 1**

**Facilitator: Gillian Wu  
Recorders: Noel Rose and Judy Bray**

Jane Aubin  
Gary Bader  
David Bickel  
Earl Brown  
Dale Demsey  
Jack Gaudie  
Jennifer Gardy  
Mads Kaern  
Jean Marshall  
Pamela Ohashi  
Dave Parrish  
Jim Richards  
Robert Sladek  
Katherine Siminovitch

**Day 2 - Group 2**

**Facilitator: Quim Madrenas  
Recorders: Carol Richardson and Diane Christin**

Paul Bélanger  
Charles Bernstein  
Alexandre Blais  
John Ficele  
Eleanor Fish  
Ron Germain  
Francis Ouellette  
Claude Perreault  
Ernest Seidman  
John Schrader  
Alain Stinzi  
George Tolomiczenko  
Gabriel Wainer

**Day 2 - Group 3**

**Facilitator: Chris Power  
Recorders: Jana Stankova and Bethany  
Heinrichs**

Amit Bar-Or  
Phil Branton  
Michael Ehrenstein  
Daniel Figeys  
Jack Greenblatt  
Phil Hieter  
Paul Kubes  
Jacek Majewski  
Theodore Perkins  
Andrew Potter  
Stephanie Robertson  
Rafik-Pierre Sékaly  
Rusung Tan  
Jon Temme

## APPENDIX FOUR

### **Breakout Sessions – Group 1** **DAY 1 - JANUARY 22<sup>nd</sup>**

#### **Group 1 – Systems Biology - 14**

**Location: St Laurent Room**

**Facilitator/Recorder – Gillian Wu (Facilitator); Noel Rose and Judy Bray (Recorders)**

#### **Questions:**

- What is your definition of “systems biology” and what would a systems biology approach to immune systems research look like? Please give examples to illustrate the benefits of using a systems approach.
- What do you consider to be the biggest challenges in bringing together the systems biology and immunology communities and how would you overcome the challenges identified?
- What infrastructure is needed to bring the systems biology and immunology communities together? What infrastructure already exists and how could we make better use of it?
- Given that systems biology is highly technologically driven, what type of technologies and ensuing analyses should be emphasized in the future (e.g. proteomics, degradomics, transcriptomics, lipidomics, metabolomics etc)?
- What kind of programs could we develop that would facilitate the process of integrating systems biology approaches into immunotherapy/immunology research if we had :
  - a) no new funds
  - b) modest amount of new funds –up to \$1 million per year
  - c) substantial new funding - \$1-5 million per year
- The Institute of Infection and Immunity is taking the lead by exploring opportunities for systems biology approaches in the field of immunotherapy/inflammatory research. In order to move the process forward and maximize the impact what is the single most important piece of advice you would give the Institute?

### **Breakout Sessions – Group 2** **DAY 1 - JANUARY 22<sup>nd</sup>**

#### **Day 1 - Group 2 – Clinical Aspects of Immunotherapy – 14**

**Location: Room 518**

**Facilitator/Recorder – Quim Madrenas (Facilitator), Chris Power and Bethany Heinrichs (Recorders)**

#### **Questions:**

- What is your definition of “systems biology” and what would a systems biology approach to immunological research look like? Please give examples to illustrate the benefits of using a systems approach
- Which areas of clinical research related to immunotherapy and inflammation might benefit the most from a systems biology approach? Please give specific examples
- Are you aware of any existing examples of systems biology projects in these areas? – if so, please describe

- How could the clinical research groups supported by the III Clinical Autoimmunity initiative work together to develop an overarching systems biology strategy and what new infrastructure (if any) would be required?
- What kind of programs could we develop that would facilitate the process of integrating systems biology approaches into clinical immunotherapy/immunology research if we had:
  - a) no new funds
  - b) modest amount of new funds –up to \$1 million per year
  - c) substantial new funding - \$1-5 million per year
- The Institute of Infection and Immunity is taking the lead by exploring opportunities for systems biology approaches in the field of immunotherapy/inflammatory research. In order to move the process forward and maximize the impact what is the single most important piece of advice you would give the Institute?

### **Breakout Sessions – Group 3** **DAY 1 - JANUARY 22<sup>nd</sup>**

#### **Day 1 - Group 3 – Immunology – general**

**Location: Room 528**

**Facilitator/ Recorder – Jana Stankova (Facilitator); Diane Christin and Carol Richardson (Recorders)**

#### **Questions:**

- What is your definition of “systems biology” and what would a systems biology approach to immunological research look like? Please give examples to illustrate the benefits of using a systems approach
- Name three areas in which you think this kind of integrative approach might be most beneficial and/or timely. Explain why you chose these particular research topics.
- What do you consider to be the biggest challenges in bringing together the systems biology and immunology communities and how would you overcome the challenges identified?
- What infrastructure is needed to bring the systems biology and immunology communities together? What infrastructure already exists and how could we make better use of it?
- What kind of programs could we develop that would facilitate the process of integrating systems biology approaches into immunotherapy/immunology research if we had :
  - a) no new funds
  - b) modest amount of new funds –up to \$1 million per year
  - c) substantial new funding - \$1-5 million per year
- The Institute of Infection and Immunity is taking the lead by exploring opportunities for systems biology approaches in the field of immunotherapy/inflammatory research. In order to move the process forward and maximize the impact of any initiatives that might be developed what is the single most important piece of advice you would give the Institute?

## **Breakout Sessions – Group 1,2 & 3**

### **DAY 2 - JANUARY 23<sup>rd</sup>**

#### **Break-out Session 2 – multidisciplinary**

##### **Day 2 - Group 1**

**Location – St Laurent Room**

**Facilitator/ Recorder – Gillian Wu (Facilitator) Noel Rose and Judy Bray (Recorders)**

#### **Questions:**

Based on yesterday's discussions, list at least three topic areas that would be ideal for a systems biology approach. Select one of these topics and develop a project for further development. Use this project as a "model test case" to address the questions below and prepare a PowerPoint presentation to "sell" your project to the whole group

- What is the title of your research project?
- How would this project advance the integration of systems biology approaches into immune system research? What would the innovative aspects be?
- How would you facilitate collaboration between systems biology and immunology researchers and what infrastructure would be required?
- What potential partners might be interested in your project, how would you engage them and what role would they play?
- What kind of deliverables and outcomes might be expected in the short (1-2 year) and long (5-10 year) time frames
- How would you evaluate whether your project had been successful at the end of the term? What criteria would you use to measure success? Please give specific examples
- How would you address the requirement for an integral KT strategy? What might such a strategy look like in an integrated systems biology approach?
- What kind of research programs would be most appropriate for your proposed project e.g. short-term pilot projects, team science, multi or single institute programs, cross-disciplinary training programs, inter-disciplinary fellowships etc?
- Why should your project be voted the best?