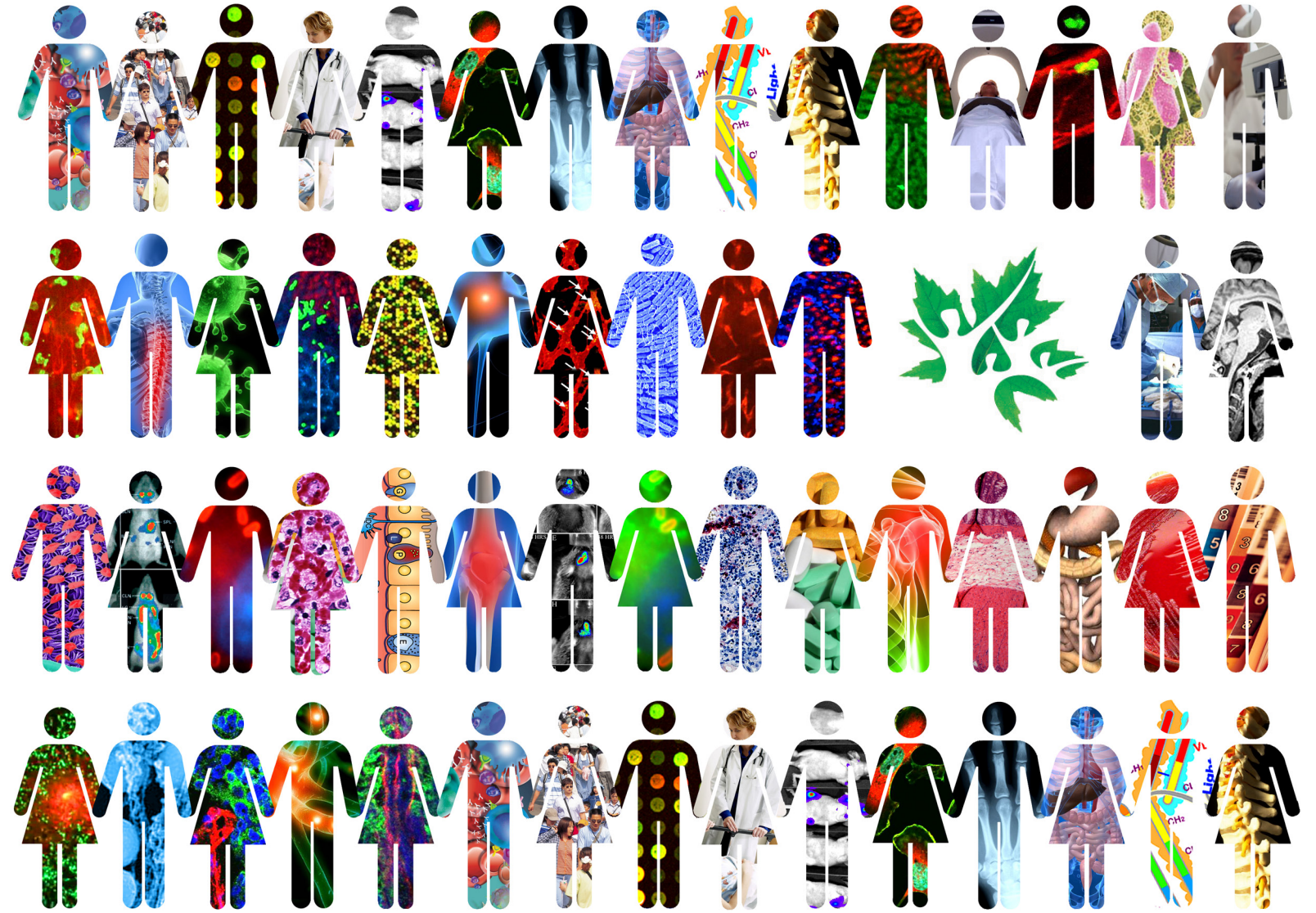

Inflammation in Chronic Disease Signature Initiative

Canadian Institutes of Health Research

Consensus Conference Report

May 17-18, 2011

Sutton Place Hotel
Toronto, ON

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

Canada

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Executive Summary

Inflammation is a physiological process that normally helps us fight infection and aids in tissue repair. Dysfunctional inflammatory responses, however, contribute to the development and progression of several common chronic diseases including asthma, cardiovascular disease, arthritis, diabetes, and cancer. These and other diseases with underlying inflammatory pathology are placing a burden on health care costs and human suffering across the globe.

Recognizing the need for research and innovation in this area, the Canadian Institutes of Health Research (CIHR) recently created the Inflammation in Chronic Diseases Signature Initiative as part of its Strategic Plan. CIHR Institute of Musculoskeletal Health and Arthritis (IMHA) and CIHR Institute of Infection and Immunity (III) are co-leads and have partnered with CIHR Institutes of Cancer Research (ICR), Circulatory and Respiratory Health (ICRH), and Nutrition, Metabolism and Diabetes (INMD) for the Initiative.

In May 2011, CIHR hosted an Inflammation in Chronic Disease Consensus Conference in order to consult over one hundred and fifty researchers, clinicians and other stakeholders about opportunities for research and collaboration in this area. The programme included a keynote address and ten oral presentations that provided an overview of current research and activities in the field. Participants also worked together in breakout groups to identify research questions and opportunities for collaboration.

In his keynote address, Dr. Alan Silman, Medical Director, Arthritis Research UK, summarized some of the major projects that are underway in the UK for the early exploration and development of treatments for chronic inflammation. Dr. Silman noted that targeted treatments are likely to be effective in only a subset of individuals. Therefore, the UK is also developing the tools for personalized medicine, including, biobanks, databases and appropriate ethics protocols.

Four researchers then spoke about the mechanisms underlying tissue inflammation across chronic diseases. Dr. John Wallace focused on the resolution of inflammation. Dr. Dana Philpott then discussed the innate immune system, in particular the Nod-like family of receptors. Dr. Brad Nelson provided an overview of the opposing roles of inflammation in cancer. Finally, Dr. André Cantin discussed lung diseases and novel therapeutic approaches.

During her luncheon address, Dr. Louise Nasmith presented the recommendations of a recent Canadian Academy of Health Sciences (CAHS) assessment on the Canadian health care system and chronic disease. It is anticipated that the assessment will inform discussions on the 2014 federal-provincial-territorial accord on health care.

Afternoon oral presentations focused on imaging technologies and on markers and therapeutic targets of inflammation. Dr. Paul Kubes described his use of spinning disk confocal microscopy to examine the trafficking of immune cells in tissues of live mice during inflammation. Dr. Jasna Kriz discussed her use of biophotonic whole body imaging to examine immune cell movements and gene expression over long periods in living mice with chronic inflammation.

Finally, Dr. Chris Overall discussed the need to have a complete understanding of all of the proteins that regulate inflammatory responses so that drug targets can be appropriately selected.

The final oral presentation session concerned strategies for translation of research results. Dr. Sasha Bernatsky discussed the development of a rheumatology referral and triage form for primary care physicians that shortens patient referral time to specialists. Dr. Manon Choinière described a knowledge translation research program in pain management (ACCORD) that she is undertaking in partnership with researchers, consumers, clinicians and others.

Participants also gathered together in smaller groups for three separate breakout sessions to address assigned questions. The questions and a summary of the discussions follow.

What mechanisms of inflammation and its resolution are currently studied but poorly understood and would benefit from new collaborations across disciplines and chronic diseases?

- Role of environmental and host factors, and their interactions, in triggering, maintaining and resolving inflammation in chronic disease,
- Molecular mechanisms underlying inflammation,
- Commonality and variability in inflammatory responses, and
- Loss of homeostasis in inflammation and chronic disease.

What are the current and potential indicators of inflammation and what tools are needed to identify them? How could we work together? Research and collaborations are needed to identify/validate biomarkers that:

- are common to inflammatory processes in all diseases and organ systems;
- are specific to disease and organ systems;
- can be used for diagnosis, prognosis, and to predict treatment response;
- can be correlated with symptoms of disease such as pain and quality of life; and
- take into consideration sex, age and ethnic differences.

The following tools would assist in inflammation research and collaborations:

- biobanks and cohort studies;
- platforms (e.g. "-omics", imaging, immune, informatics and translational); and
- animal models.

What are the barriers to achieving success in the area of inflammation in chronic disease research? Participants not only described barriers to achieving success, but also suggested ways in which these barriers could be overcome. Suggestions included:

Funding

- partner with provincial health care delivers, non-profit organizations, industry, insurance companies and unions to increase available funds for research;
- create teams with renewable funding opportunities;
- broaden expertise on peer review committees for multidisciplinary grants;
- provide sustained funding for platform infrastructure and highly qualified personnel; and
- better inform the public and policy makers of the importance of the Signature Initiative.

Communication and collaboration

- develop centralized databases and web sites cataloguing research tools and research expertise;
- host/support workshops, meetings and conferences;
- develop and support collaborative teams through new funding mechanisms and novel approaches;
- develop training programs, especially for clinician scientists; and
- engage stakeholders (e.g. decision makers, industry, patient/consumer groups, clinicians) at all stages of the research and knowledge translation process.

Translation

- increase awareness and support for existing translational platforms; and
- develop policies favouring the implementation of new findings and technologies, including engaging pharma and international partners.

What are the topics with the best chance of success and innovation?

- detection of environmental agents that are involved in inflammation;
- fundamental mechanisms of inflammation;
- common mechanisms across chronic diseases;
- multidisciplinary approach to develop methods to improve the symptoms of inflammation and quality of life;
- development, use and accessibility of new technologies ('omics) for the study and treatment of inflammation (i.e. systems biology / systems physiology approaches);
- outcome and cost effectiveness research to determine the usefulness of research and interventions;
- development of mobile technologies for patients to assess their disease and to acquire longitudinal information; and
- research programs that take into consideration what patients and clinicians need.

Translation of research findings into actual health care associated outcomes can be difficult. How would you promote the process of translation of findings in your research field into improved health outcomes for Canadians with inflammation and chronic diseases? (Question posed to the Health Services and Policy Research and Population and Public Health Breakout Group.) We should exploit our strengths in:

- administrative databases (this is an international strength that should be harnessed);
- psychosocial research (e.g. depression/stress, outcomes measures);
- research across diseases (generating etiological questions, linking biomarkers to epidemiology), and
- research on the effect of lifestyle factors (e.g., physical activity) on health.

The conference concluded with a plenary discussion of the key messages from the breakout sessions. Organizers and participants were pleased with the constructive nature of the meeting.

Based on the consensus built at the conference, CIHR in further consultation with the community has developed the following draft strategic priorities for the Inflammation in Chronic Disease Signature Initiative:

1. Molecular mechanisms underlying inflammation.
2. Loss of homeostasis in inflammation and chronic disease.
3. Inflammation prevention, diagnosis and intervention.
4. Commonality and variability in inflammatory responses.
5. Multidisciplinary approach to develop methods to improve the symptoms of inflammation and quality of life (e.g. pain).
6. Development, use and accessibility of new technologies ('omics) for the study and treatment of inflammation (i.e. systems biology / systems physiology approaches).
7. Health services and policy research and population and public health research into inflammation in chronic disease.

Initial funding opportunities will likely be through Meetings-Planning-Dissemination grants. Given the complexity of the Initiative, the Institutes are planning layered funding opportunities.

Conference Overview

On May 17-18, 2011, the Canadian Institutes of Health Research (CIHR) hosted an Inflammation in Chronic Disease Consensus Conference in Toronto. The purpose of the conference was to identify the important issues, challenges and unmet needs in the area of inflammation research within the broader theme of chronic disease. Researchers, representatives from non-governmental organizations and clinicians were invited to attend the conference, and a sub-group were also involved in helping to plan the conference (see Appendix 1 for the members of the Steering Committee). To ensure discussions covered all aspects of health research, biomedical, clinical, health services and population health researchers were included (see Appendix 2 for a List of Participants).

To provide an overview of research and other activities in the field of inflammation and chronic diseases, the conference included a keynote address and several oral presentations. Participants also gathered in smaller groups in three separate breakout sessions to identify research questions and opportunities where inflammation research has a realistic prospect of bettering the health of Canadians (see Appendix 3 for the Conference Agenda). To help to focus breakout session discussions, the following questions were assigned:

1. What mechanisms of inflammation and its resolution are currently studied but poorly understood and would benefit from new collaborations across disciplines and chronic diseases?
2. What are the current and potential indicators of inflammation and what tools are needed to identify them? How could we work together?
3. What are the barriers to achieving success in the area of inflammation in chronic disease research? What are the topics with the best chance of success and innovation?
4. Translation of research findings into actual health care associated outcomes can be difficult. . . . How would you promote the process of translation of findings in your research field into improved health outcomes for Canadians with inflammation and chronic diseases?

The consensus coming out of the conference will aid in the further development of the CIHR Roadmap Signature Initiative in Inflammation and Chronic Disease.

Background

It is well-recognized that there is an increasing burden of chronic disease in aging societies, with escalating health care costs and human suffering across the globe. Many chronic diseases involve a vicious cycle of injury, inflammation, attempted regeneration, re-modeling, and immune activation further exacerbating injury. Inflammation dysfunction contributes to several disorders including autoimmune diseases (e.g., arthritis, psoriasis, inflammatory bowel diseases), asthma, atherosclerosis, obesity, cancer, non-alcoholic fatty liver disease, diabetes (insulin sensitivity), glomerulonephritis, hypersensitivities, myopathies, periodontal disease and tooth loss, transplant rejection, and pain.

Recognizing the need for research and collaboration in this area, the CIHR Institute of Musculoskeletal Health and Arthritis (IMHA) in partnership with the CIHR Institutes of Infection and Immunity (III), Cancer Research (ICR), Circulatory and Respiratory Health (ICRH), and Nutrition, Metabolism and Diabetes (INMD), is leading a new roadmap signature initiative in Inflammation in Chronic Disease. The aim of this Initiative is to gain a broad and unified picture of inflammation across several pathologies and chronic diseases. This will help to identify shared pathways/biomarkers and potentially useful common interventions for inflammation prevention and management.

The Inflammation in Chronic Disease Conference in Toronto represented one of the first steps in developing the Initiative. Along with representatives from the five partner CIHR Institutes, representatives from the CIHR Institute of Aging and of Institute of Health Services and Policy Research (IHSPR) were also invited to attend the meeting and were active participants.

Welcoming Remarks

Alain Beaudet, President, CIHR

Dr. Beaudet welcomed participants to the conference on behalf of CIHR and thanked them for accepting the invitation to engage in deliberations that will help CIHR determine the path forward in efforts to reduce the burden of chronic disease in Canada – one of the priorities outlined in CIHR's strategic plan entitled "Health Research Roadmap: Creating innovative research for better health and health care".

Dr. Beaudet thanked Drs. Aubin and Ouellette for their leadership in guiding the Signature Initiative in Inflammation in Chronic Disease. He believes that the multi-Institute collaboration will help to bridge the silos between research groups working in particular chronic disease areas in order to improve our understanding of common pathways and to develop interventions that will ultimately contribute to a unified Canadian chronic disease strategy. Dr. Beaudet closed by wishing participants a productive meeting.

Jane Aubin, Scientific Director, Institute of Musculoskeletal Health and Arthritis

Dr Aubin noted that during the first ten years since the establishment of the CIHR, individual Institutes generally worked independently to strengthen research within with their own communities. The Signature Initiative in Inflammation in Chronic Disease is a bold new approach that brings together five CIHR Institutes. The conference in Toronto was taking place at a very early stage in the development of the Initiative. Therefore, Dr. Aubin noted that input from everyone at the conference was needed to help to drive the Initiative forward.

Marc Ouellette, Scientific Director, Institute of Infection and Immunity

Dr. Ouellette acknowledged the dedicated contributions of the Steering Committee and CIHR staff (Appendix 4) in helping to organize and set the agenda for the conference. He thanked participants for attending the meeting, and looked forward to receiving their input.

Inflammation - A Patient's Perspective

To set the stage for conference discussions, Dr. Aubin then presented a video in which five Canadians living with chronic diseases involving inflammation spoke about their illness and their hopes for how research might benefit them and others like them in the future. They believe that research will improve our understanding of the causes of their diseases and will aid in the development of new and more effective therapies to reduce inflammation and pain. The video was a compelling reminder of why the conference participants had gathered together for the conference in Toronto.

Keynote Address: Research Strategy in Inflammatory Diseases UK perspective

Alan Silman, Arthritis Research UK

Dr. Silman thanked the organizers for inviting him to the conference. He believes that inflammatory diseases are tractable because we now have a better understanding of the biology of inflammation, are identifying relevant biomarkers and have begun to identify candidate therapeutic molecules. He cautioned that there is a need to choose the right animal model (e.g. chronic vs acute) for both basic research and for early drug development.

Dr. Silman then provided an overview of the major initiatives that are underway in the UK that promise to improve the health of individuals with inflammatory diseases. The Medical Research Council/Association of the British Pharmaceutical Industry (MRC/ABPI) Inflammation and

Immunology Initiative, for example, brings together basic scientists and industry in order to identify potential new drugs and treatments for both inflammatory arthritis and chronic obstructive pulmonary disease. This £5-7 million initiative spans drug discovery from target identification to testing in humans.

Early drug exploration and development is also being fostered via Therapeutic Capability Clusters that bring together several National Health Service (NHS) and academic research centres of excellence. The Capability Cluster of Joint Disease consists of nine centres that will work with industry to understand the mechanism of action of drug targets and will engage in early phase clinical testing. The industrial partners bring candidate therapies to the Cluster for testing. The Clusters are modelled on experimental medicine facilities that were established to facilitate the development of therapies for cancer.

Dr. Silman noted that we are moving to an era of personalized medicine, because targeted biologic treatments are often effective in only a subset of patients. To prepare, resources in databases, informatics and biobanking have and are being developed in the UK. For example, Arthritis Research UK is supporting INBANK -- a national platform of clinical data that is linked to a central archive of stored biological samples. UK Biobank has been ongoing since 2000 and to date has stored blood and urine samples from half a million volunteers aged 40-69 years. The independent biocentre uses the infrastructure and expertise developed by UK Biobank and is open to all external researchers. Dr. Silman closed by wishing participants success in their research endeavours.

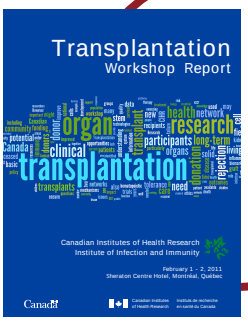
Pre-Conference Reports

In early 2011, two CIHR institutes, III and ICR, hosted workshops to develop research priorities for targeted funding in areas related to inflammation in chronic disease, specifically, transplantation and the immunomodulation of cancer. Given the relevance of these topics to the conference in Toronto, a brief summary of the outcomes of the workshops was provided.

Transplantation Initiative

Marc Ouellette, Scientific Director, III

Dr. Ouellette provided an overview of the Strategic Initiative in Transplantation that is being developed by III. To set research priorities for the Initiative, III hosted a workshop in Montreal in February 2011. The following research areas were identified:



- Explore the role of inflammation and inflammatory processes in organ rejection. This may serve as a general model for chronic inflammation,
- Bring together clinicians working in organ transplantation with biomedical researchers studying inflammation and immune tolerance,
- Support research to identify more specific immunosuppressive drugs with fewer adverse effects, and
- Engage the medical imaging community in the study and validation of markers of inflammation and early signs of rejection.

Workshop participants stressed the need for increased collaboration between solid organ and hematopoietic stem cell researchers, collaborations with Canadian Blood Services to address donor issues and methods to improve clinical translation of existing science.

Immunomodulation of Cancer Workshop

Morag Park, Scientific Director, Institute of Cancer Research

Dr. Park began by stating that ICR is highly supportive of the Inflammation in Chronic Disease Signature Initiative because 20% of all cancer deaths worldwide are linked to unresolved inflammation and infection. To prepare for the conference in Toronto, ICR hosted an Immunomodulation of Cancer Workshop in Vancouver in March 2011. Workshop participants identified the following focus areas for research: the role of inflammation in cancer, the role of the human microbiome in cancer and anti-tumour immunity and immunotherapy. Participants also recommended that research is needed to identify strategies to modulate inflammation to prevent cancers, to improve the outcome of cancer treatments and to develop anti-cancer immunotherapy approaches. Also, collaborative approaches for researchers in different disciplines should be promoted.

Session 1:
Mechanisms underlying tissue Inflammation across chronic diseases

Coordination of the onset and resolution of inflammation

John Wallace

Dr. Wallace provided an overview of the biology of inflammation, emphasizing its dynamic nature. In a normal inflammatory response, pro-inflammatory molecules promote inflammation and then inflammation resolves through the action of anti-inflammatory molecules. Chronic inflammation could result from an imbalance of pro/anti-inflammatory molecules or if one or more anti-inflammatory pathways were absent or lacking. Dr. Wallace noted that traditionally pro-inflammatory pathways have received greater attention and that a better understanding resolution of inflammation will aid in the identification of novel drug targets for the treatment of chronic inflammation.

Dr. Wallace then described his research on the enzyme COX-2, which acts at an early step in the formation of lipid mediators such as prostaglandins that regulate several biological processes including inflammation. He used a mouse model of colitis to show that COX-2 promotes the resolution of inflammation in a prostaglandin D2 (PGD2)-dependent manner. Both COX-2 and PGD2 levels remained higher than normal long after inflammation had resolved. Dr. Wallace then collaborated with Dr. Linda Vong to study whether similar changes might be observed in

humans. In agreement with the animal studies, PGD2 was found at higher levels in individuals with long-term remission of ulcerative colitis. Taken together, the results suggest that PDG2 is important for the induction and maintenance of remission from colitis, and perhaps for the resolution of inflammation in general.

Chronic Inflammation driven by innate immune activation

Dana Philpott

The innate immune system defends our bodies against infection from microbes such as bacteria. A key component of the innate immune system is a family of Nod-like receptors, which sense bacteria and danger inside cells triggering immune responses and cell death, thereby helping to rid the body of the threat. Mutations in the gene coding for one of the Nod-like receptors, Nod2, were the first to be found to increase susceptibility to develop Crohn's disease. Dr. Philpott was part of a research team that discovered that cells with the most common Crohn's-associated mutation of Nod2 failed to respond to peptidoglycan (a component of bacteria). This result suggests that failure to properly sense and resolve infection leads to chronic inflammation.

Dr. Philpott then described results of her more recent research in which cells carrying the same Crohn's-associated mutation failed to induce autophagy of intracellular bacteria. Autophagy is a protective process that is used to remove intracellular bacteria or damaged organelles. In addition, mice with loss-of-function mutations in both Nod2 and a related molecule Nod1 had defective early (Th17) inflammatory responses to bacteria. Based on the results, Dr. Philpott hypothesizes that the chronic inflammation seen in Crohn's disease is caused by defective containment of bacteria that normally reside in the gut resulting in the recruitment of other inflammatory mediators and a vicious cycle of inflammation.

Chronic inflammation in cancer initiation and progression

Brad Nelson

Dr. Nelson began by discussing both positive and negative effects of inflammation and immunity on cancer development and progression. On one hand, twenty percent of all cancer deaths worldwide are linked to inflammation and infection, and products of inflammatory cells are thought to contribute to the genetic changes, proliferation, angiogenesis and metastasis seen in cancer. In fact reducing inflammation with non-steroidal anti-inflammatory drugs helps to reduce the incidence of colorectal cancer in humans. On the other hand, our immune system also protects us against cancer by mounting an anti-tumour response. For example, survival rates from cancer improve when tumours are infiltrated with CD8+ T cells (a type of immune cell that kills abnormal cells).

Dr. Nelson then described the implications of this knowledge in the treatment of cancer. While standard cancer treatments can reduce antigen load and release and generate new antigens, they can also induce inflammation and kill or impair lymphocytes, and more research is needed to understand the overall result of these changes. He also noted that the goal of many targeted cancer treatments (e.g. vaccines, and systemic cytokines) is to enhance anti-tumour immunity, and there is a risk that this would cause autoimmunity. In contrast, treatments to suppress immune responses in autoimmune diseases might promote cancer development. Therefore, Dr. Nelson was pleased that this conference brought together researchers interested in both cancer and autoimmunity so that they could learn from one another.

Oxidants, antioxidants and chronic lung diseases: The good, the bad, and the ugly

André Cantin

Dr. Cantin provided an overview of lung diseases, including asthma, lung cancer, chronic obstructive pulmonary disease, which account for 17% of all causes of death in the United States and Canada. Chronic inflammatory lung diseases often occur when environmental stress, e.g. air pollution, oxygen and cigarette smoke, exceeds the body's protective mechanisms. These protective mechanisms include the unfolded protein response and the production of antioxidants. Dr. Cantin has discovered that individuals with chronic obstructive pulmonary disease have reduced function of Nrf2, a downstream target of the unfolded protein response and a master regulator of antioxidant production. As well, numerous antioxidant enzymes and glutathione-dependent detoxification systems are increased in healthy smokers.

Dr. Cantin then described promising therapies for chronic lung diseases that target these and other pathways. A possible nutritional intervention for chronic obstructive pulmonary disease is broccoli and cabbage, which supplies the body with sulforaphane, an Nrf2 agonist. Bardoxolone methyl, a drug that is in clinical trials for the treatment of chronic kidney disease is a potent activator of the Nfr2 pathway, so it might also have clinical use in chronic lung diseases. Interestingly, the CFTR chloride channel which is defective in cystic fibrosis has reduced activity in smokers. A new drug called Vertex VX-770 increases the activity of CFTR channels and modestly improves lung function in cystic fibrosis patients. This drug might also be useful in improving the symptoms of smokers and those with other types of chronic lung disease. Dr. Cantin concluded by stating that drug development along with smoking prevention, dietary interventions and stem cell research are promising approaches to prevent and control chronic inflammatory respiratory diseases.

Speaker Panel Question & Answer Session

Q: Periodontal infections increase the risk of cancer of the kidney and other visceral cancers. I've always wondered how this might be mediated. Please comment.

A: It is possible that inflammatory mediators are released into the bloodstream. Certainly, the tissue of the gastrointestinal tract is directly exposed to these mediators.

Q: Concerning the correlation between inflammation of the gastrointestinal tract and the development of cancer, why does it take so long for cancer to develop following the onset of inflammation?

A: It is known that cancer develops in cells that have acquired at least six genetic mutations. It is likely that it takes a considerable amount of time for this to occur. Also, it is possible that aging might have additional adverse effects.

Q: There is a body of literature regarding the effect of certain foods in modulating immune cells and on epigenetics. Can you please comment on studies of nutrition and inflammation in animal models?

A: Diet is extremely important. For example, foods can alter the level of the antioxidant glutathione and also cause histone modifications, which influence gene expression. This area of research in inflammation is understudied, but is cross-disciplinary in nature. In addition, diet, including probiotics, alters the microbiome in the gut, which can in turn influence both local and systemic immune responses. Diets rich in omega-3 fatty acids are known to reduce inflammation and cancer risk.

Q: The stroma was not discussed in any of the presentations, but it seems to me to be an area of study that warrants attention. Also, I think that we need to use a broad, systems-based approach to truly understand the basic biology of inflammation.

A: I agree that the stroma is very important for cancer progression and has an influence on immune responses.

Comment: Neutrophil extracellular traps are also emerging as an important component of inflammation. For example, they appear to play a role in the inflammation associated with cystic fibrosis.

Luncheon Presentation

Transforming care for Canadians with chronic health conditions: a panel assessment by the CAHS

Louise Nasmith

The Canadian Academy of Health Sciences (CAHS) provides timely, informed, and unbiased assessments of urgent issues affecting the health of Canadians. Dr. Nasmith recently co-chaired the CAHS assessment on the Canadian health care system and chronic disease and provided a summary for meeting participants. The goal of the assessment was to create a strategy to improve health outcomes for people with chronic disease through the reorientation of Canadian health services and better use of system resources within the next five years. Currently 16 million Canadians live with one or more chronic diseases, and this is placing an enormous burden on health care systems and the economy.

After providing an overview of the assessment process, Dr. Nasmith summarized the key recommendations of the assessment. The overall recommendation is to enable all people with chronic health conditions to have access to a system of care with a specific clinician or team of clinicians who are responsible for providing their primary care and for coordinating care with acute, specialty, and community services throughout their life span. This should be accomplished by:

- aligning system funding and provider remuneration with desired health outcomes;
- ensuring that quality drives system performance;
- creating a culture of lifelong education and learning for health care providers;
- supporting self-management as part of everyone's care;
- using health information effectively and efficiently; and
- conducting research that supports optimal care and improved outcomes.

The federal, provincial, and territorial ministers of health should review these recommendations with a view to making them part of the 2014 renewal of the federal-provincial-territorial accord on health care. Dr. Nasmith noted that if changes are not made and current trends prevail, provincial health care expenditures will make up 80% of total government program spending by 2030, up from 46% today. To access a copy of the full report see: http://www.cahs-acss.ca.

Speaker Question & Answer Session

Q: Did you have recommendations about patient responsibilities?

A: The recommendation around self-management involved good discussions, but we must not blame patients.

Q: What do you think will be cost of implementing this plan?

A: Hopefully the recommendations will be used by health ministers and policy makers to reorient existing resources.

Q: I did not see anything about prevention. Was that incorporated into your recommendations?

A: An excellent point. This was beyond the scope of the report. Although we recognized the importance of prevention, we purposely looked at health care delivery.

Q: The nature of chronic inflammatory diseases often involves co-morbidities, which usually necessitates specialists, so I am not sure whether the primary care provider has enough expertise in these complex cases.

A: We think that the primary care provider should play a key role, and there is evidence to support the importance of primary care providers despite complexity.

Q: The government is contemplating regulating junk food; do you think this is a positive endeavour?

A: This is prevention, and we did not really look into this, although I think we need to look into it in another assessment.

Session 2: Identification and validation of markers, therapeutics targets and imaging strategies

Imaging innate immunity following sterile and infectious stimuli

Paul Kubes

Dr. Kubes began by offering his suggestions for the resources that he thinks are needed in order to make progress in the area of inflammation research and translation. He believes that we should invest in platform technologies including genomic and functional screens, mouse models of human diseases, and mouse phenomics (e.g. imaging). Translation of research results requires facilities such as the Centre for Drug Discovery and Development (CDRD) that has been established in British Columbia, along with novel drug delivery systems.

Dr. Kubes then described research of the AHFMR Alberta Sepsis Network. One project involved using metabolomics to identify patients with sepsis. Metabolites can be rapidly measured in small samples of biological samples. The research team, led by Dr. Hans Vogel, has successfully identified a panel of metabolites that are altered in sepsis forming a basis for the rapid diagnosis of this life-threatening condition.

Dr. Kubes then described and showed videos of images taken with spinning disk confocal intravital microscopy, which he and collaborators have used to examine the trafficking of immune cells through capillaries in live mice. Using this technology in concert with genetically modified mice, the research team has developed a model of neutrophil recruitment to a site of sterile tissue injury [see McDonald, B. et al. (2010) Science 330:362]. Dr. Kubes is also examining mechanisms involved in the migration of monocytes and natural killer cells, along with platelet/neutrophil interactions. Together these experiments will enhance our understanding of the mechanisms underlying inflammation.

Development of model systems for biphotonic/ bioluminescence imaging of inflammation

Jasna Kriz

Several imaging technologies are being developed for use in small animals. These include neuroanatomical imaging such as magnetic resonance imaging (microMRI), computed

tomography (microCT) and positron emission tomography (microPET); and optical imaging such as multiphoton microscopy and biophotonic whole-body imaging. Dr. Kriz focused on her use of biophotonic whole body imaging of bioluminescence in the study of inflammation. In this technique, cells or whole animals are engineered to produce light (via luciferase) or fluorescence (e.g. green fluorescent protein (GFP)) under specific conditions. This approach has been used to follow immune cell trafficking, to visualize inflammation, and to examine the activation of gene expression over long time periods in living mice.

Dr. Kriz provided several examples of the use of this technology in the study of inflammation including visualizing the trafficking of CD4+ T cells in a mouse model of multiple sclerosis and analysis of myeloperoxidase activity and NFkB activation in a model of arthritis. She has also produced mice that express both luciferase and GFP in order to detect activated cells at the microscopic level while still allowing for live imaging. In these mice, the expression of both markers is controlled by activation of the Toll-like 2 receptor (TLR2) allowing for the study over months or years of TLR2 activation in conditions such as stroke, Alzheimer's disease and amyotrophic lateral sclerosis. To bridge the gap between basic and translational research, Dr. Kriz is also performing longitudinal therapeutic studies on the effects of diet and antibiotics in reducing inflammation in various neuroinflammatory conditions.

Dampening of inflammation by MMP processing of chemokines, complement and coagulation factors in arthritis revealed by proteomics

Chris Overall

Dr. Overall emphasized that we need to have a comprehensive understanding of biomarkers associated with inflammation before we will be able to successfully create new therapeutics. He believes that this requires a systems-based approach that includes categorization of all of the proteins involved in the process, and how proteins are modified once they have been synthesized. A key modification, for example, is cleavage of the protein into smaller pieces, which can completely change the protein's biological activity (e.g. an activator becomes an inhibitor). Dr. Overall studies a family of enzymes called metalloproteinases (MMPs) that were first identified for their role in the degradation of the extracellular matrix, but are now known to have diverse biological effects including regulating inflammation. Proteins that are cleaved by MMPs include chemokines and cytokine binding proteins both involved in inflammation.

Dr. Overall then described results from experiments in which genes for specific MMPs were knocked out in mice. Mice lacking MMP-8 had earlier and more severe joint inflammation than normal mice. The change was due to reduced cell death of neutrophils, which resulted in an accumulation of neutrophils at sites of inflammation. MMP-12 knock-out mice have exacerbated collagen-induced arthritis. These results suggest that both MMP-8 and MMP-12 help to resolve or reduce inflammation. Dr. Overall closed by informing participants that Genome Canada is proposing to the Human Proteome Organization that Canada should map the proteome of chromosome 6 – a key chromosome in immunology.

Speaker Panel Question & Answer Session

Q: MMPs are known to have adverse effects in chronic kidney disease. How do you propose to tease out the beneficial effects from the adverse effects of MMPs?

A: Before we rush to translation, we need to have a thorough understanding of the basic biology of MMPs. Target validation is very important.

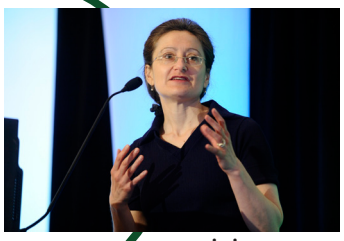
Q: Do you think that there are tissue-resident neutrophils?

A: That is a possibility, but I do not know.

Session 3:
Strategies for Translation

Chronic disease, inflammation, and knowledge translation

Sasha Bernatsky



Dr. Bernatsky described two approaches that have been used to involve health care consumers in both research and knowledge translation. This is particularly important in chronic diseases with an inflammatory component in which disease onset and outcomes are negatively influenced by factors such as physical inactivity, unhealthy eating, obesity, tobacco use, and stress. The first approach involved individuals with rheumatoid arthritis (RA), a devastating disease requiring prompt rheumatology care. Studies from Quebec, however, showed that in 2000 only 25% of those with RA were referred for specialty care and referral was often delayed for greater than six months. Focus groups with RA patients identified the need for better communication between specialists and other health professionals. In response, Dr. Bernatsky created a rheumatology referral and triage form for primary care physicians. It was assessed at two clinics, and results showed that use of the form reduced reliance on lab tests and shortened referral time.

Discussions with consumers at a Café Scientifique led to a novel strategy to advertise sources of arthritis information to a targeted group of consumers. Dr. Bernatsky and colleagues are currently working with a pharmacy chain to include a label with the link to the Arthritis Society's educational web site and phone number on non-steroidal anti-inflammatory drug prescriptions. The effectiveness of this intervention is being assessed.

Improving chronic pain management using KT strategies: what are the challenges?

Manon Choinière

Dr. Choinière described a knowledge translation research program in pain management that she and colleagues have developed entitled "Application Concertée des Connaissances et Ressources

en Douleur" (ACCORD). About 20% of Canadians suffer from chronic pain, and it is frequently undertreated. The overall objective of the program is to create active partnerships between research teams and community organizations that will foster high quality research and knowledge translation. ACCORD partners include researchers with diverse and complementary expertise, health care users, clinicians, decision makers at the Quebec Ministry of Health, specialists in continuing medical education and industry partners.

Projects involve: mapping the geographic distribution of pain and treatment resources in Quebec; and developing, assessing and implementing multidisciplinary education and intervention programs to improve chronic pain management in primary care, in nursing homes and for those suffering from fibromyalgia and back pain. The challenges in developing the projects included: bringing together individuals from diverse cultures and getting them to communicate and work together, but there were also several factors that have helped facilitate the program. These included the Quebec Health Government's reorganization of health care resources allocated to chronic pain, strong support from provincial pain networks, the contributions of dynamic consumers and dedicated clinicians, creation of sub-teams with project leaders, a grassroots approach and respect of the institutional cultures.

Speaker Panel Question & Answer Session

Q: One of the roadblocks in doing this kind of research is that the patients/consumers are not paid to do the research, while the traditional researchers are on a salary. A second issue is that we need to train consumers, and not simply involve them blindly. Can you please comment?

A: In many cases it has been my experience that the patients/consumers do not want to get paid. As well, there are other methods of compensation such as invitations to conferences.

Q: In terms of the epidemiology of inflammation, it seems like it would be very difficult to define higher than normal rates of disease and cancer in relation to the effect of therapies (i.e. what is the control group?).

A: The best way to examine the effects of an intervention in rare diseases is to create large cohorts and follow them for 40 years. Within the cohort, only some will have been treated with a specific therapy.

Facilitated Breakout Sessions

To further develop the Signature Initiative in Inflammation and Chronic Disease, conference attendees participated in three separate breakout sessions. For these sessions, participants were specifically assigned to one of nine breakout groups in order to ensure that each group had members with diverse expertise. In introducing the breakout sessions, Dr. Aubin asked participants to engage in discussions as representatives of their communities rather than individual laboratories in order to ensure that all points of view were included. Each group discussed the same question within a specific breakout session with one exception in breakout session #3 (as noted below).

Immediately following each breakout session, participants gathered in plenary sessions to hear summaries of each of the nine breakout session discussions. For the purposes of this report, overlapping topics both within and between sessions have been grouped together and are summarized below.

Breakout Session #1

What mechanisms of inflammation and its resolution are currently studied but poorly understood and would benefit from new collaborations across disciplines and chronic diseases?

Role of environmental and host factors in triggering, maintaining and resolving inflammation in chronic disease

Participants identified several environmental and host factors that should be investigated to determine their role in causing and maintaining inflammation. Environmental factors that were discussed included viruses, bacteria, xenobiotics, pollution and polymicrobial infections. In this area, deep sequencing of tissue samples could be used to look for microbes involved in inflammation. Host factors that were discussed included stress, diet, nutrients (e.g. vitamin D), antioxidants, metabolism, obesity, physical inactivity, hormones, smoking, early life events, age, sex, co-morbidities, injury, hypoxia, genetic susceptibility/resistance, and epigenetics.

Several breakout groups suggested that study of the role of the brain in inflammation could benefit from new research collaborations. This not only includes the role of stress in promoting and exacerbating inflammation in chronic disease, but also the impact of psychological responses to disease on the inflammatory response (e.g. pain and stress) and the impact of inflammation on the ability to cope.

In the area of aging, we need a greater understanding of the relationship between the biological mechanisms of aging and inflammation. This includes understanding the regulatory inflammatory networks and how they change with age, the impact of immune suppression on the emergence of disease states, and fibrosis and wound healing.

Molecular mechanisms underlying inflammation

There is still a lack of basic understanding of the molecular mechanisms underlying inflammation and its resolution. This includes the interplay between the vasculature, stroma and other cells of the inflammatory response, the biology of repair, the long-term impact of inflammation on the emergence of secondary diseases such as cancer and fibrosis, and the molecular mechanisms underlying the effect of lifestyle changes on the inflammatory response.

Commonality and variability in inflammatory responses

Research gaps discussed include the reasons for tissue specificity in inflammation, chronic vs acute inflammation, and the influence of inflammation/infection at one site (e.g. dental infections) on other tissues. Other areas for research include an examination of the similarities

and differences between microbial and non-microbial induced inflammation and innate immunity in different chronic diseases. Research in this area should include diseases/conditions such as heart disease, neuroinflammation, metabolic syndrome, type II diabetes, and HIV and HCV infections in which the contribution of inflammation generally has not been well studied.

Loss of homeostasis in inflammation and chronic disease:

Inflammation is a beneficial physiological process, but it is thought to cause disease when it is dysfunctional. Hypofunctional responses, for example, are associated with diseases such as inflammatory bowel disease, chronic obstructive pulmonary disease, autoimmune diseases and cancer, but this area requires further study. A greater understanding of the role of stem cells in both pathogenesis and therapy is needed (e.g. bone marrow transplantation can cause disease remission in individuals with severe Crohn's disease, but the underlying mechanism is not understood). We also need to examine the mechanisms underlying the episodic nature of inflammation and its resolution in chronic disease.

Breakout Session #2

What are the current and potential indicators of inflammation and what tools are needed to identify them? How could we work together?

Indicators of inflammation

Rather than identify specific indicators (biomarkers) of inflammation, participants stated that research and collaborations are needed to identify and validate biomarkers that:

- are common to inflammatory processes in all diseases and organ systems;
- are specific to disease and organ systems;
- can be used for diagnosis, prognosis, and to predict treatment response;
- can be correlated with symptoms of disease such as pain and quality of life; and
- take into consideration sex, age and ethnic differences.

To make these biomarkers relevant for both research and the clinic, participants stated that it is important to:

- identify patterns of biomarkers rather than single markers and use them in conjunction with clinical information;
- determine which markers are most needed/valued by collaborating with clinicians since currently there seems to be a relative lack of clinical application of biomarkers;
- determine the relative importance of biomarkers during disease progression/development of chronicity/prediction of flare-ups;
- consider the dynamic aspects of chronic inflammation by attempting to capture variability and time sequence changes; and
- perform ongoing cross validation: bench to bedside to determine, for example, how the biomarkers relate to specific symptoms and with lifestyle changes.

Biobanks and cohort studies

Access to biobanks and cohort studies (e.g. birth cohorts, specific disease) would facilitate research in the area of inflammation including the identification of biomarkers. Banked samples should include serum, urine, peripheral blood mononuclear cells, stool, microbiome, saliva, and tissues. The samples must be fully annotated with information such as donor age, sex, body mass, ethnicity, drugs, psychological variables, disease, clinical history, treatment and outcome, etc. This requires appropriate bioinformatic tools and uniform standard operating procedures for both sample and data collection and storage. Ideally, the biobanks and cohort studies should be open to all researchers for broad use across diseases and disciplines. Frameworks for ethics, access and funding need to be developed, but there are opportunities to learn from existing national biobanks in other countries. Participants noted that it would be useful to have an inventory of existing biobanks and cohort studies.

Platforms

Participants identified several platform technologies that would aid them in their research including: imaging (e.g. live cell imaging/tracking), systems physiology, immunology, -omics (e.g. second generation sequencing, proteomics, metabolomics), mass spectroscopy, NMR, informatics, statistics, health service utilization and translational platforms (e.g. medicinal chemistry). The platforms must be accessible and sustainable. This requires dedicated funding support for both equipment maintenance and for the employment of highly qualified personnel to operate and manage the platform facilities. Funding could also support the training of researchers who could come from other sites to learn the technology. Participants said that CIHR should take a leadership role in the development and support of platform technologies, which would involve partnering with universities, institutes, industry and international organizations.

Appropriate and integrative animal models

New animal models are needed in inflammation research that more closely approximate human diseases. Current animal models may be limited because, for example, they are generally specific pathogen free (SPF) and are housed in clean facilities. Also, acute inflammation models may not be adequate to look at inflammation over long time scales. In addition, better and relevant preclinical models of disease are needed, along with ready access to aged animals.

Breakout Session #3

What are the barriers to achieving success in the area of inflammation in chronic disease research?

During this report back session, participants not only described barriers to achieving success, but also suggested ways in which these barriers could be overcome.

Sustained funding and novel funding mechanisms

As one presenter noted in the report back session, "If you want to study a chronic disease, you need chronic funding". This requires novel approaches and a change in culture. Rather than launching an request for applications that targets specific research areas with limited funding and duration, CIHR should focus on fostering research collaboration within broad theme areas and play a leadership role in partnering with other organizations to increase the level and duration of funding.

Participants noted that often CIHR "stands alone", and there is a disconnect between basic research and health care delivery. Funding partners could include provincial health care agencies, industry, non-profit organizations, and nontraditional funders such as unions and insurance companies. Partnering would also allow for development of long-term research plans and coordination between funding partners to prevent redundancy.

A CIHR initiative in inflammation and chronic disease should facilitate interactions and the creation of teams. This would allow researchers to identify their own research priorities within a broad theme. The grants should be renewable to ensure sustained interaction between all team members. Researchers should be required to incorporate project management to ensure accountability.

CIHR peer review committees have too narrow a focus, so it can be difficult for researchers to get approval for multi-disciplinary projects that cross diseases and pillars. There is a need to develop ways to evaluate grant applications for teams and collaborative research that bridges multiple disciplines.

Platforms should be funded so that they can be run as a mixture of national and regional centres of technical expertise that not only generate, but help to analyze datasets. Platform development and maintenance requires equipment purchases and funding for support personnel. Currently CFI is the primary source of funds for equipment purchases in this area. It was suggested that CIHR and CFI funding should be realigned. Universities and research institutes should also commit resources and have strategic involvement in platform development. Time protection for mid-career/senior scientists is needed for those who help to establish and oversee these faculties.

Communication and collaboration

Much of the multi-disciplinary, multi-disease collaborative research proposed by participants will not reach its full potential unless efforts are made to enhance communication and collaboration within the research community and between researchers, clinicians, policy makers, industry, funders and patients. Participants noted that it takes time to develop linkages with disparate groups, but provided several possible solutions to foster communication and collaboration. These included:

Develop centralized databases and web sites

These could include descriptions of existing research tools such as biobanks and research platforms including animal models. Specific Facebook or LinkedIn groups could be created to help researchers identify and communicate with potential collaborators with specific expertise or interest in inflammation and chronic disease. The use of existing health-related research networks would also help foster collaboration.

Host/support workshops, meetings and conferences

These could include consensus building workshops, workshops to build interdisciplinary research teams, imaging and inflammation workshops, workshops with international partners to discuss international links, workshops that bring together all stakeholders, and global conferences addressing overarching issues in the field of inflammation. In this regard, CIHR should enhance awareness of the funding programs that are currently available to bring researchers together (e.g. Meetings, Planning and Dissemination grants). These could be extended in order to fund larger groups.

Develop and support collaborative teams

New mechanisms are needed to develop and support multi-disciplinary research teams. There should be guidance to ensure that the research is truly collaborative. The team should have long-term goals with the possibility of renewable funding. Participation in the team should be valued, and teams should include both senior and junior investigators. In order to foster true collaboration, team membership should not be strictly proscribed, but each member should bring value to the research enterprise.

Develop training programs

Clinicians and other health professionals (at all levels, including primary care) and basic scientists should receive training so that they can better collaborate and communicate with one another. This could include training more clinician scientists or having basic science students shadow clinicians. It could also include providing more protected time and flexibility for clinicians who show an interest in working with basic scientists.

Also, to foster true interdisciplinary research and translation, it will be necessary to provide training programs for basic scientists, so they can learn new techniques and about one another's discipline.

Stakeholder engagement

Decision makers (administrative staff, vice-presidents for research and perhaps representatives from industry) and patient/consumers and patient/consumer groups should be involved early in order to support development of training programs, cohorts, biobanks, and technology platforms so that these resources can be realistically developed and to ensure that they are needed. A model

to follow is the Canadian Arthritis Network, but it can take a long time to develop meaningful and effective connections.

In addition, for this Signature Initiative to be successful, it is essential to better inform the public and policy makers of the importance of inflammation in chronic disease and the need for ongoing research.

Translation

Participants noted that Canada generally has limited expertise, facilities and resources for drug development, and where such facilities exist (e.g. National Research Council, CDRD), many researchers do not know about them. Also, the current grants that are available provide insufficient funds for periods of time that are not long enough for drug development. There is a lack of assistance in developing drugs at the proof-of-principle stage or "off patent" drugs for clinical use. Therefore, there is a need to increase awareness and support for existing translational platforms and to develop policies favouring the implementation of new findings and technologies, including engaging the pharmaceutical industry and international partners.

A potential model to follow for early drug development is the Science Moving towArds Research Translation and Therapy (SMARTT) program that has been established by the National Heart, Lung, and Blood Institute (NHLBI) at the National Institutes of Health (see http://www.nhlbi.nih.gov/new/SMARTT.htm). It encompasses production facilities for therapeutics, a pharmacology and toxicology centre, and a coordinating center. Participants also suggested that we need a pre-proof-of-principle mechanism that is accessible in all provinces.

What are the topics with the best chance of success and innovation?

- detection of environmental agents: bacteria, viruses, xenobiotics, etc, that are involved in causing and maintaining inflammation;
- fundamental mechanisms of inflammation;
- common mechanisms across chronic diseases such as the initiation and resolution of inflammation and long-term effects of inflammation (e.g. fibrosis);
- multidisciplinary approach to develop methods to improve the symptoms of inflammation and quality of life (e.g. pain);
- development, use and accessibility of new technologies ('omics) for the study and treatment of inflammation (i.e. systems biology / systems physiology approaches)
- outcome and cost effectiveness research to determine the usefulness of research and interventions;
- development of mobile technologies for patients to assess their disease and to acquire longitudinal information; and
- research programs that take into consideration what patients and clinicians need.

Breakout Session #3: Health Services and Policy Research and Population and Public Health Group

An alternate question was posed to one breakout group composed of experts in the areas of health services and policy research and in population and public health research:

Translation of research findings into actual health care associated outcomes can be difficult, and can be dependent on the area of research (e.g. biomedical versus health systems research). How would you promote the process of translation of findings in your research field into improved health outcomes for Canadians with inflammation and chronic diseases?

Participants in this group were concerned that the conference discussion had focused too much on biomarkers and research platforms. They noted that the vision of "if we build it they will come" is shortsighted. Biobanking can be helpful in understanding mechanisms of disease; however, biobanks will bring value to society only if the biomarkers are applied to populations. This poses a challenge in the appropriate phenotyping of populations and patients, such as describing the course of disease, outcomes, and characteristics of the person in relation to the biomarker. Participants in this session felt strongly that if biobanks are established they should be developed with pre-meditated research questions that have clinical and/or public health relevance and with an established series of methods for analysis (e.g., advanced statistical methods, economic analysis, decision-making research, health services research, etc). As well, they agreed that there is a need for better communication between all types of researchers so that each group can understand the research methods of each other and harness opportunities.

Participants in this session also identified the strengths that we have in Canada in the areas of health services and policy research and population and public health research that could be exploited and built upon to further research and also knowledge translation in the area of chronic disease and inflammation. We have strengths in:

- administrative databases (this is an international strength that should be harnessed);
- psychosocial research (e.g. depression/stress, outcomes measures);
- partnering across diseases (generating etiological questions, linking biomarkers to epidemiology), and
- examining the effect of lifestyle factors (e.g., physical activity) on health.

Participants in this group emphasized the need to go beyond paying lip service to knowledge translation. Health services and policy researchers and population and public health researchers are a voice to policy makers, industry and the public. We need to recognize the importance of bringing knowledge translation research methods to the area of chronic disease and inflammation.

Discussion of the Conference Recommendations

Jane E. Aubin, Scientific Director, IMHA

Marc Ouellette, Scientific Director, III

Over lunch on the second day of the meeting the Scientific Directors and Assistant Directors of the five CIHR Institutes involved in the CIHR Inflammation in Chronic Disease Signature Initiative met to discuss the recommendations from breakout sessions. Rather than attempting to rapidly reach a consensus on areas for specific research, the group discussed the key messages to CIHR made by conference participants. These were presented by Drs. Aubin and Ouellette in a plenary session that immediately followed the luncheon meeting and are summarized below.

Key messages

- be committed for the long-term;
- bring together people and themes using a variety of mechanisms and incentives;
- apply a prevention paradigm as well as a diagnosis/intervention paradigm;
- create an inventory of existing platforms and cohorts;
- enhance multi-sectoral partnerships (e.g. provincial health care delivery, institutions, industry, consumers, NGOs);
- breakdown disease and discipline silos;
- work together! CIHR is a leader, convener and broker, but CIHR can't do it alone.

Dr. Aubin and Dr. Ouellette, who were joined by Scientific Directors Dr. Nancy Edwards (IPPH), Dr. Morag Park (ICR) and Dr. Philip Sherman (INMD), and Dr. Lori West representing ICRH, then opened the session for questions and comments. In the ensuing discussion, there was a general consensus amongst meeting participants that the conference had succeeded in getting people from many disciplines together to talk to one another and that more of these types of meetings would be beneficial in helping researchers develop research projects in the area of inflammation and chronic disease. A summary of individual questions and comments follows.

Q: I'm pleased that you are including prevention and was wondering if you had an idea about the relative weighting of funding for prevention versus intervention.

A: Will not comment on the weighting, but believe we need to instill from the start the importance of prevention. We also need funding mechanisms that speak to the wider community including both health services and policy research and population and public health research.

Q: It is nice to see the conference coming to a consensus. What appeared to be lacking is how to go from discovery to the development of treatments. There are several steps after discovery that need to be facilitated and many millions of dollars worth of work. I think scientists should not attempt to do this, nor are we are good at it. Also, in terms of creating inventories of resources, you need to provide easy access to that information.

A: We need to get partners involved early so we can deal with the cost and complexity of drug development.

Q: When developing requests for applications, please give researchers enough lead time so that they can meet with one another to develop their research proposal.

A: Yes that is what we intend to do.

Q: There has been a lot of talk about biobanks and tissue banks; a word of caution about the need for quality control. If quality control is not present at a given facility, the data obtained will corrupt the overall research results and conclusions. Perhaps CIHR could access international resources. Also, I think that prevention should fall under the provincial health care jurisdictions, and view CIHR as a discovery enterprise.

A: On the issue of biobanks, we fully agree that we cannot fund biobanks across the country. We know about examples (e.g. British Columbia) where people are sharing operating procedures across disciplines; we could help do more of that. Also we may be able to leverage additional international opportunities. ICR has supported biobank-related programs. An important area are large cohorts studies, however, different communities have not yet identified the required needs (e.g., what needs to be collected, how samples should be stored, etc), and these groups need to reach a consensus.

Regarding the question of the research focus of CIHR, this is always a question, especially with limited resources. We do work with the provinces; it is not an-us-against them strategy. Public health interventions have had major impacts on human health. Population health evaluations are useful in assessing both the impact and potential of various interventions. We need to take an integrative approach to research rather than the old model of the Medical Research Council of Canada.

Q: If CIHR gives overhead money to universities, it should demand accountability. Perhaps CIHR could survey researchers to learn how the overhead is being spent. I think that most researchers here will agree that the overhead is not being spent wisely. Also, I don't want to see new biobanks, as there is no point if we can't have access to them. A model to follow might be Germany, where when tissue samples are taken for tests, the patients are informed that 10% of the sample will be used for future testing. In addition, I think that we need to tone down our expectations about translation. Companies have many resources, yet few new drugs actually reach the market, thus to think that CIHR-funded labs can do this better is not realistic.

A: The key is to develop partnerships differently. We can't do drug development, but we can bring things forward with partnerships with industry and/or with the provinces, who are involved in health care delivery.

Comment: We have to lower our expectations about what we can do with the current initiative. Impacting diseases and bringing things to market is beyond the capacity of the initiative. I think that Canada needs to change from a resource-based economy to one with a science and technology focus.

Q: Is there a way to bring us up to speed in the area of inflammation in chronic disease, such as, for example, a repository of meaningful work.

A: That is a good point. Obviously there needs to be a leader to do that type of thing, but it is doable with a relatively small amount of money.

Next Steps

Jane E. Aubin, Scientific Director, IMHA

Marc Ouellette, Scientific Director, III

Before closing the conference, Drs. Aubin and Ouellette outlined the next steps for the Initiative. This conference report was submitted to the working group and steering committee in early June 2011 and formed the basis for the draft strategic priorities for the Inflammation and Chronic Disease Signature Initiative (below). A final version of the report was circulated to meeting participants at the end of the summer. Given the complexity of the Initiative, the Institutes are planning layered funding opportunities.

Drs. Aubin and Ouellette closed the conference by thanking all participants for their valuable contributions. They wished participants a safe journey home and said that the dialogue begun at the meeting would continue.

Draft Strategic Priorities in the Inflammation in Chronic Disease Signature Initiative

Based on the recommendations made at the conference in Toronto, IMHA, III, ICR, ICRH and INMD developed the following draft strategic priorities that are relevant across various communities and chronic diseases for the Signature Initiative in Inflammation and Chronic Disease.

- Molecular mechanisms underlying inflammation.
- Loss of homeostasis in inflammation and chronic disease.
- Inflammation prevention, diagnosis and intervention.
- Commonality and variability in inflammatory responses.
- Multidisciplinary approach to develop methods to improve the symptoms of inflammation and quality of life (e.g. pain).
- Development, use and accessibility of new technologies ('omics) for the study and treatment of inflammation (i.e. systems biology / systems physiology approaches).
- Health services and policy research and population and public health research into inflammation in chronic disease.

Appendix 1:
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Debbie Feldman

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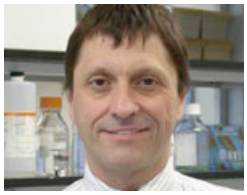

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INFLAMMATION IN CHRONIC DISEASE CONSENSUS CONFERENCE

May 17th and 18th, 2011; Toronto, Canada

PROGRAM

DAY ONE, Tuesday, May 17th, 2011

Time	Session	Speakers
7:30 am	*Continental Breakfast*	
8:30 am	Welcome	Alain Beaudet *President, CIHR*
8:40 am	Conference Overview	Jane E. Aubin/Marc Ouellette *Scientific Directors IMHA and III, respectively*
8:55 am	Inflammation - A Patient's Perspective	Video Presentation
9:05 am	Keynote Address: Research Priorities for Inflammatory Disease: the example of rheumatoid arthritis	Alan Silman *Arthritis Research UK*
9:20 am	Transplantation Initiative Immunomodulation of Cancer Workshop	Marc Ouellette Morag Park
SESSION 1: Mechanisms underlying tissue inflammation across chronic diseases. **Chair: Wallace MacNaughton / Professor, University of Calgary; Inflammation Research Network**		
9:30 am	Coordination of the onset and resolution of inflammation	John Wallace
9:45 am	Chronic inflammation driven by innate immune activation	Dana Philpott
10:00 am	Chronic inflammation in cancer initiation	Brad Nelson

Time	Session	Speakers
	and progression	
10:15 am	Oxidants, antioxidants and chronic lung diseases: The good, the bad, and the ugly	André Cantin
10:30 am	Speaker Panel / Q&A	
10:45 am	Setting the Inflammation Research Agenda : Introduction to Breakout Session	Jane E. Aubin
10:50 am	*Health Break*	
11:05 am	Facilitated Breakout	
12:15 pm	*Lunch* Transforming care for Canadians with chronic health conditions: put people first, expect the best, manage for results	 Louise Nasmith
1:15 pm	Weighing In: Breakout Reports (5 m/grp x 9 grps)	Breakout Leaders
SESSION 2: Identification and validation of markers, therapeutics targets and imaging strategies. **Chair: Amira Klip/Senior Scientist, Cell Biology Program, The Hospital for Sick Children; Professor, Departments of Paediatrics, Biochemistry, and Physiology, University of Toronto**		
2:00 pm	Imaging Innate Immunity following sterile and infectious stimuli	Paul Kubes
2:15 pm	Development of model systems for biophotonic/bioluminescence imaging of inflammation	Jasna Kriz
2:30 pm	Dampening of inflammation by MMP processing of chemokines, complement and coagulation factors in arthritis	Chris Overall

Time	Session	Speakers
	ervealed by proteomics	
2:45 pm	Speaker Panel / Q & A	
3:00 pm	*Health Break*	
3:15 pm	Facilitated Breakout	
4:25 pm	Weighing-In: Breakout Reports	Breakout Leaders
5:10 pm	Wrap-Up and Adjournment	Jane E. Aubin
5:10–7:00 pm	Reception	

DAY TWO, Wednesday, May 18th, 2011

Time	Session	Speakers
7:15 am	*Continental Breakfast*	
8:15 am	Overview Day Two	Marc Ouellette
SESSION 3: To develop strategies for translation **Chair: Lori West/Professor of Pediatrics, Surgery and Immunology; Director of Heart Transplant Research, University of Alberta; CRC in Cardiac Transplantation**		
8:20 am	Chronic disease, inflammation, and knowledge translation (tentative title)	Sasha Bernatsky
8:35 am	Improving chronic pain management using KT strategies: what are the challenges?	Manon Choinière
8:50am	Speaker Panel / Q & A	
9:05am	*Health Break*	
9:25am	Facilitated Breakout	
10:40 am	Weighing-In: Breakout Reports	Breakout Leaders

11:25 am	*Check out and Lunch*	
SESSION 4: Recommendations		
1:00 pm	Synthesis and Recommendations to Conference Participants	Jane E. Aubin/Marc Ouellette
1:20 pm	Participant Feedback	
1:30 pm	Concluding Remarks and Conference Closure	Jane E. Aubin/Marc Ouellette
2:00 pm	Adjournment	

Appendix 4: CIHR Staff Involved in Organizing the Conference

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- Tanya Gallant
- Marc Milot
- Elizabeth Robson
- Esther Rosenthal

III: Serge Desnoyers, Assistant Director (Staff Co-Lead)

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