Transplantation
Workshop Report

Canadian Institutes of Health Research
Institute of Infection and Immunity

February 1 - 2, 2011
Sheraton Centre Hotel, Montréal, Québec

Canada

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

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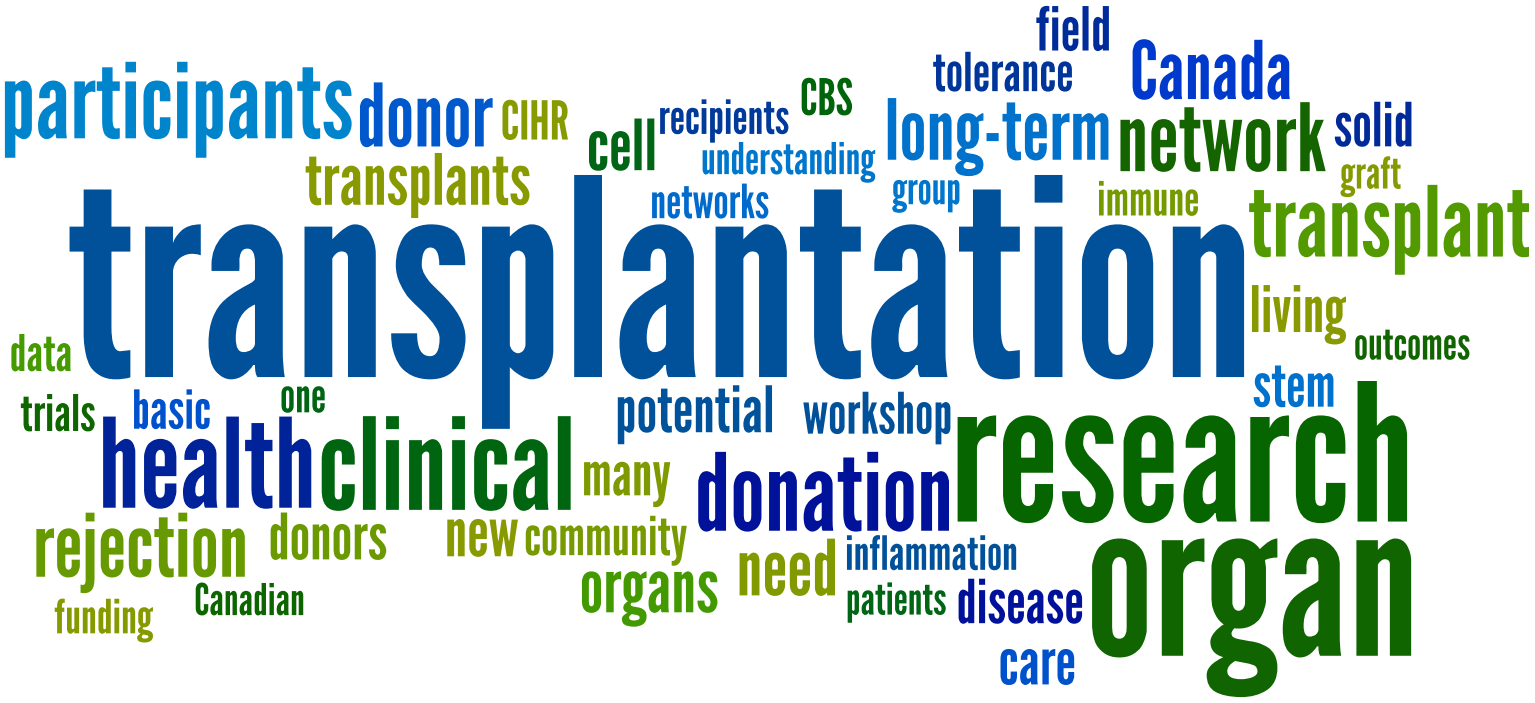
Cat. No.: MR21-159/2011E (paper)
ISBN: 978-1-100-18640-5

Cat. No.: MR21-159/2011E-PDF
ISBN: 978-1-100-18641-2



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EXECUTIVE SUMMARY

Background

The Canadian Institutes of Health Research (CIHR), Canada's premier health research funding agency, is comprised of 13 virtual Institutes - one of which is the Institute of Infection and Immunity (III). In 2010, the III Institute Advisory Board identified solid organ and hematopoietic stem cell transplantation (HSCT) as a field in which strategic investment and targeted programming could improve clinical outcomes. Transplantation is the preferred treatment for end-stage organ failure and HSCT is an established therapy for many conditions, and can be a cure for certain cancers. However, challenges remain in meeting the increasing demand for organs, cells and tissues and in achieving long-term graft survival accompanied by a good quality of life for transplant recipients. An expert working group, comprised of researchers from the different health research theme areas, worked with III staff to organize a consultation workshop. The goal of the workshop was: to stimulate discussion and collaborations among the transplantation community; identify the key research challenges and opportunities in the field; and prepare the transplantation community for funding opportunities emerging from the CIHR suite of Roadmap Signature Initiatives, such as "Inflammation in Chronic Disease". In addition, the workshop provided a forum for III and partners to gather recommendations from the transplantation community on how best to address the current challenges in the field and improve the clinical outcomes in transplantation through innovative research programs.

Consultation Workshop

During the two-day workshop, which took place in Montreal on February 1st and 2nd, 2011, the more than 60 workshop participants identified many challenges and opportunities that could be addressed through research, including:

- Improving both the quantity and quality of living and deceased donor organs;
- Improving our understanding of the immunological mechanisms and pathways mediating transplantation-related infection, inflammation, and immunosuppression in humans;
- Overcoming rejection and establishing long-term tolerance to grafts;
- Developing improved therapeutics to sustain graft survival with fewer adverse side-effects – and expediting their uptake into clinical practice;
- Establishing tailored transplantation policies and programs for children and other vulnerable populations; and
- Developing national standards of clinical care and mechanisms for the long-term follow-up of Canadian transplant recipients.

Outcomes and Recommendations

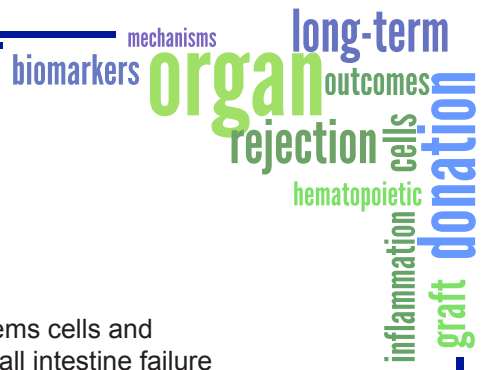
During the workshop discussions it became apparent that members of the transplantation community have much to learn from each other. This was particularly true for the solid organ and HSCT communities who do not have a history of working together, but who share many of the same challenges with respect to long-term graft survival, treatment toxicities and continuity of care. It was also clear that there is a need for increased collaboration amongst the solid organ transplant specialties, as many of the identified challenges apply equally to organ transplantation across a number of different sites. There was considerable support for team funding and/or the creation of a network structure to facilitate collaboration across the transplantation field. As this would be hard to achieve through the CIHR open competitions, it would represent a strategic

advantage to the community. It was recommended that III explore team and network options, in partnership with other interested parties. Potential partners could be other CIHR Institutes, the CIHR Roadmap Signature Initiatives, voluntary sector organizations, and other government agencies such as Canadian Blood Services (CBS). It was felt that a network would foster collaborations across the field; forge the necessary linkages between the solid organ and HSCT communities; support common platforms, infrastructures, databases and operating procedures; and encourage training.

Path Forward

In collaboration with partners, III will explore the available programs and models that would be most appropriate to meet the needs of the transplantation community. There are several potential options, including: the external networking of independent small teams; the support of large teams comprised of individual group projects; several inter-related small multidisciplinary networks; and a large network with a central administrative hub supporting transplantation-related research at many centres and locations across the country. It is possible that the CIHR Inflammation in Chronic Disease Signature Initiative will provide team grant funding and that the CIHR Strategy for Patient Oriented Research (SPOR) program will support network funding at a range of different levels and complexity. The possibility of a “stand-alone” funding opportunity launched by III and partners has also not been discounted. It is hoped that this workshop will have prepared the transplantation research community for these new, emerging opportunities.

Photographs from the Transplantation Workshop



BACKGROUND

The Health Issue

Every year, thousands of Canadians receive transplants of solid organs, stems cells and pancreatic islet cells. End-stage renal, liver, lung, heart, pancreatic and small intestine failure can be treated by organ replacement. For cancer, hematopoietic stem cell transplantation can be a cure. The most rapidly growing group of organ recipients is those over 60 years of age – a segment of the population likely to increase dramatically in the next 20 years. Renal transplants are the most common of the solid organ transplants, representing about 75% of the total. Liver transplantation has undergone tremendous innovation in technique as well as pre- and post-surgical care. As a result, the procedure has vaulted to the forefront as the treatment of choice for end-stage liver disease in Canada[1]. Heart transplantation has grown to encompass both ends of the age spectrum for increasingly complex cardiac diseases, with infant transplants now recognized as having superior long-term outcomes than heart transplants performed at any other time of life. Lung transplants are now used as treatment for end-stage lung diseases such as cystic fibrosis and emphysema. Small intestine transplantation is an emerging and evolving field with the potential to improve the outcomes of children and adults with intestinal failure. Between 1999 and 2008, there were 51 such procedures performed in Canada, with half of the recipients being under 18 years of age.

With more than 4,000 Canadians on wait-lists for organ transplants, our national organ donor rate cannot meet the demand

With more than 4,000 Canadians on wait-lists for organ transplants, our national organ donor rate (deceased) cannot meet the demand. Canada's low deceased organ donation rate cannot be attributed to a lack of public support for organ donation, but while many people agree that they would like to donate their organs, very few actually undertake the actions necessary to do so[2]. Research is needed to increase deceased donor rates and the organs retrieved per donor, and improve the safety and practice of living donation. Research is also needed to improve the quality of transplanted organs and tissues and reduce the risk of rejection. If drug toxicity could be minimized and compliance increased, transplants would last longer, avoiding the need for repeat transplants and ensuring the longest possible healthy life for each transplant recipient.

Research is needed to increase deceased donor rates and the organs retrieved per donor, and improve the safety and practice of living donation

In addition to solid organ transplants, 1200-1400 hematopoietic stem cell transplants (HSCT) are performed each year in Canada, primarily for cancer therapy. Additional forms of cell therapy such as islet cell and stem cell transplantation are becoming more common. Bone marrow transplantation has become an established form of therapy for aplastic anemia, certain autoimmune disorders, bone marrow failure syndromes, immune deficiencies and dysregulation, hemaglobinopathies, and metabolic disorders and is now widely used to treat cancer, including leukemia, lymphoma and solid tumours such as neuroblastoma and brain tumours. Although the two fields share many of the same challenges with respect to graft rejection, recurrent disease, graft-versus-host disease, treatment toxicities and infection, donor quality issues in HSCT are less severe than for solid organ transplantation. The donor source for HSCT can be autologous or allogeneic and has now expanded to include

1200-1400 hematopoietic stem cell transplants (HSCT) are performed each year in Canada

[1] Canadian Institute for Health Information, Treatment of End-Stage Organ Failure in Canada, 1999 to 2008—CORR 2010 Annual Report (Ottawa, Ont.: CIHI, 2010). http://secure.cihi.ca/cihiweb/products/corr_annual_report_2010_e.pdf

[2] Final Report: Views Toward Organ and Tissue Donation and Transplantation Prepared for Canadian Blood Services by Ipsos Reid, July 20, 2010 http://www.bloodservices.ca/CentreApps/Internet/UW_V502_MainEngine.nsf/resources/Releases/$file/IPSOS+Report.pdf

umbilical cord blood. There is also an international network of registries, of which Canada is a member. Canadian Blood Services operates the “One Match Stem Cell and Marrow Network”, which includes the unrelated stem cell donor registry and the nascent national cord blood bank.

Economic factors

In 2009, close to 38,000 Canadians were living with kidney failure - more than triple the number living with the disease in 1990. Over 22,300 people were on dialysis and about 3,000 people were on the wait-list for a kidney transplant. In their most recent report, the Canadian Institute of Health Information (CIHI) estimates the cost for hemodialysis treatment to be $60,000 per patient, per year of treatment, not including the economic impact of work-days lost while undergoing dialysis[3]. Yet, the cost for a kidney transplant is approximately $23,000 for the surgery and about $10,000 per annum for anti-rejection medication. CIHI’s estimate is that, over a five-year period, the cost savings of a kidney transplant is approximately $250,000 per patient. That means that in 2009 alone, the more than 15,000 patients living with kidney transplants saved the health care system an estimated $800 million. The report goes on to note that if the 3,000 people on the wait list for a kidney transplant were all to receive a transplant, it could result in savings of $150 million annually. However, this situation is likely to change as the cost of immunosuppressive medications is increasing, particularly as more marginal donors and more difficult recipients are being considered for transplantation. With the advent of new therapeutics, the cost of future transplant drugs may be prohibitively expensive. Also, transplanted organs can transmit infectious agents and disease to the host adding further complications and costs.

Potential Cost Savings for Kidney Transplants

cost for hemodialysis treatment = $60k per patient

cost for a kidney transplant = $23k for the surgery + $10k for medication

cost savings of a kidney transplant = $250k/patient over 5yrs

In 2009, 15,000 kidney transplantations saved the health care system $800 million

WORKSHOP ORGANIZATION

Transplantation was recently identified by the CIHR-III’s Institute Advisory Board (IAB) as an Institute priority. There are many unanswered research questions in the field - spanning basic mechanisms of transplant injury and repair, clinical challenges, health policy and services issues, and ethics. As there are significant gaps in the current CIHR funding through the open competitions, transplantation was identified as a field where strategic investment could have

Expert Working Group for the Transplantaion Workshop


Dana Devine


Amit Garg

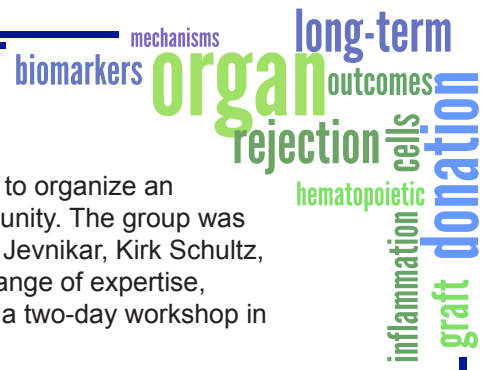

Marie-Josée Hébert


Anthony Jevnikar


Kirk Schultz


Lori West

[3] Annual Report of the Canadian Organ Replacement Register: Treatment of End-Stage Organ Failure in Canada, 2000 to 2009. CIHI downloaded 3 February 2011. http://secure.cihi.ca/cihiweb/products/2011_CORR_Annual_Report_final_e.pdf



a significant impact. As a first step, an expert working group was convened to organize an invitational workshop to solicit input from the broader transplantation community. The group was comprised of: Drs. Dana Devine, Amit Garg, Marie-Josée Hébert, Anthony Jevnikar, Kirk Schultz, and Lori West. Based on their recommendations, participants with a wide range of expertise, including representatives of potential partner organizations, were invited to a two-day workshop in Montreal on February 1st and 2nd, 2011 (see Participant List, Appendix 1).

WORKSHOP GOALS AND OBJECTIVES

The objectives of the workshop were: to generate discussion among the transplantation community; solicit recommendations on the scope and focus of potential strategic research initiatives; identify opportunities for leveraging existing programs and resources; and prepare the Canadian transplantation community to respond to funding opportunities emerging from related CIHR Roadmap signature initiatives, such as 'Inflammation in Chronic Disease'. With a field as broad as transplantation, it was not anticipated that the workshop would yield consensus or that specific research topics would be prioritized. Rather, it was hoped that the discussions at the workshop would enable the expert working group to develop recommendations for the IAB on the best way to ensure clinical impact through strategic investment. The long-term goal for III and partners will be to build capacity in underserved areas, create new collaborations across themes and disciplines, and address research gaps that are currently not adequately funded through the CIHR open competitions.

OVERVIEW OF CIHR ROADMAP INITIATIVES

Dr. Marc Ouellette, Scientific Director of the CIHR Institute of Infection and Immunity gave an overview of CIHR roadmap signature initiatives of potential relevance to the field of transplantation. There is currently a suite of seven such initiatives under development, many of which could be of potential interest to the transplantation community. They are:

- Canadian Epigenetics, Environment and Health Research Network
- Clinical Trials Networks/Support Units
- Community-Based Primary Healthcare
- International Collaborative Research Strategy for Alzheimer's Disease
- Inflammation in Chronic Disease
- Pathways to Health Equity for Aboriginal Peoples
- Personalized Medicine

The Inflammation in Chronic Disease initiative is of particular relevance to the transplantation field, as inflammation plays a key role in organ damage and rejection. A large consensus workshop will take place in May 2011, and participants will include members of our expert working group and the broader transplantation community. It is anticipated that funding opportunities launched through this initiative will be highly relevant to transplantation research.

PRESENTATIONS AND BREAKOUT GROUP DISCUSSIONS

The format of the two-day workshop was a mix of presentations followed by small breakout discussions. The presenters were asked to review their research field, rather than describe their personal contribution to the field, in order to provide a broad overview. Participants were

assigned in advance to seven breakout groups to ensure distribution of expertise, and to facilitate networking. During three breakout sessions, questions were presented to the breakout groups and discussed during open plenary (see Agenda, Appendix 2; Breakout Questions, Appendix 3). The following represents a summation of the two day workshop.

Combining Two Solitudes*: Opportunities for collaboration in the fields of solid organ and hematopoietic stem cell transplantation*

The scene was set by overview presentations by **Dr Lori West** - on solid organ transplantation, and **Dr Kirk Schultz** - on hematopoietic stem cell transplantation. Many of the challenges related to long-term graft survival, treatment toxicities and continuity of care are shared between the two fields, but important differences exist. For example, the relative ease of ensuring stem cell quality vs. the difficulty of ensuring solid organ quality; organ donation is a rate-limiting step for transplantation, while HLA tissue matching is the rate-limiting step for cell transplantation; and the major cause of death for cell recipients is graft-vs-host disease (GVHD) vs. chronic rejection for solid organs (although both are fueled by chronic alloimmune recognition and effector mechanisms – one mediated by the donor and the other by the recipient). Graft rejection due to recipient rejection of infused hematopoietic stem cells can be a significant risk especially for umbilical cord blood or T cell depleted transplants. Importantly, in the case of HSCT, the alloimmune effect in cancer therapy is beneficial for the 'graft-vs-cancer effect, so temporal control of alloimmunity is required. In addition, the hematopoietic stem cell transplantation community is supported by strong national and international networks and has access to large clinical trials and infrastructures that do not currently exist to the same extent in the solid organ transplant field. Both groups highlighted a need for special policies and programs to address the specific needs of children undergoing both solid organ and cell transplants, and emphasized the need for national registries, tissue banks and networks, including clinical trials networks. It was clear that there are missed opportunities for the two communities to work together on the common problems described above, as well as in the development of new strategies for potential organ repair by stem cells.

It it clear that there are missed opportunities for the fields of solid organ and HSCT to work together on the common problems

Breakout Group Discussions

Historically, the Canadian research community has benefited from American investments in registries and in clinical trials networks. However, recent changes in American research funding policy have resulted in the end of a number of fruitful relationships. The downturn of the economy and the end of many drug patents has caused major changes in the pharmaceutical industry with a considerable decrease in research investment. The research and clinical challenges in the field of transplantation and the need for innovative solutions, however, continue to increase.

Workshop participants were quick to recognize the potential gains from bringing the solid organ and HSCT communities together to facilitate sharing of knowledge and resources

Based on the many areas of commonality between the two groups, not only in the biology of rejection, inflammation, tolerance and infection but also in the areas of health policy, economics and ethics an opportunity was identified to combine research strengths, emerging technologies and resources through networking. Both groups use many of the same drugs to prevent rejection, suggesting that there may be common mechanisms in both innate and adaptive immune responses. While GVHD is a disease of the whole body, as opposed to the more localized rejection of solid organs, significant gaps exist in our understanding of the fundamental

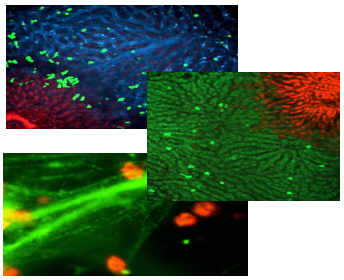
immunology involved in both rejection processes. Research is hampered by the lack of human immunology research and the fact that experimental small animal models do not necessarily mimic human biology, while nonhuman primate studies are expensive and challenging.

Workshop participants were quick to recognize the potential gains from bringing the two communities together to facilitate sharing of knowledge and resources. The solid organ community expressed admiration for the work of the hematopoietic stem cell networks and suggested that the solid organ transplant community needs a mirror image structure. It was acknowledged that Canada has missed opportunities for 'cross-pollination' between the 'two solitudes'. A partnership between these two groups could create a Canadian advantage in the international transplantation field. It was proposed that an additional, smaller and more focused meeting would bring together the leaders in the solid organ transplantation and HSCT fields to explore shared strengths, resources and potential areas for collaboration.

The Biology of Transplantation: *Challenges and opportunities related to organ preservation, rejection, tolerance and current/emerging therapeutics*

This session began with four presentations from: Dr Paul Kubes – on the role of inflammation in transplantation; Dr Ken Newell - on transplant tolerance in the clinic; Dr Bruce McManus – on biomarkers and 'omics; and Dr. John Gill - on the problems with current therapeutics.

Dr. Paul Kubes showcased the exciting new imaging technologies moving into the clinic for the visualization of cellular interactions in both sterile and infectious inflammation. Using these technologies in animal models, it is possible to obtain a 'real time' view of the interactions between immune cells and endothelial cells in the vasculature and to track individual cells over time. These cutting-edge technologies will provide new insights into the human inflammatory response as it relates to transplant rejection.

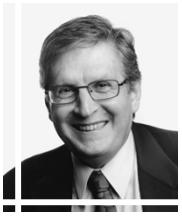


Images from Dr. Paul Kubes

In the field of tolerance, **Dr. Ken Newell** spoke of the changing mechanisms of tolerance by organ and over time; barriers to tolerance; the important role of both regulatory T and B cells in inducing and maintaining immune tolerance to solid organ transplants; and the impact of microbial infections as a barrier to tolerance. There was also a cautionary note on the dangers of using animal models to predict immune responses in humans. The new frontier is the application of emerging technologies in molecular genomics and biomarker identification to reliably predict tolerance in the clinic.

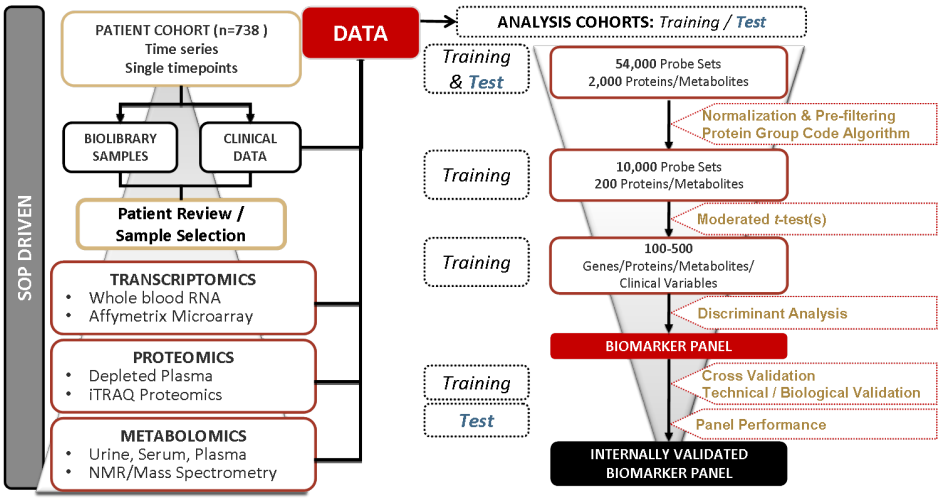
The Hierarchy of Immunogenicity

Zhang et al. Transplantation 1996;62:1267
Jones et al. J Immunol 2001:166:2824



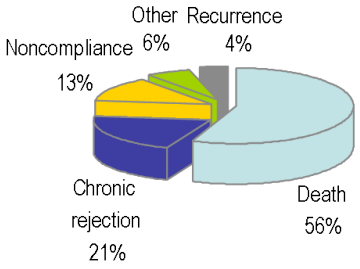
The important role of biomarkers in enabling patient stratification and a personalized medicine approach was also discussed. The successful application of biomarkers in the transplantation field will require a coordinated approach that addresses defined clinical questions and includes individuals with expertise in genomics, computational biology, health economics, regulatory and reimbursement issues, and the people responsible for the delivery of health care such as physicians, governments and private partners. **Dr. Bruce McManus** described his Prevention of Organ Failure (PROOF) centre and his studies on biomarkers of rejection in human renal and heart transplant patients using gene arrays and proteomic approaches. His group has defined a set of markers that may predict, with a specificity of 98%, whether someone will reject their transplant in the first few months. A larger test population is now being sought to validate these results.

Biomarker Discovery Strategy



Dr. John Gill described the need for an improved understanding of the critical balance between immunosuppression and graft survival, particularly with respect to late graft failure. New therapeutic agents and approaches have reduced acute rejection but have not improved long-term graft loss. One factor is patient compliance with lifelong treatment, but there is also a lack of information on the biological causes of long-term organ failure. There is a need for improved biomarkers of risk factors and reliable end-points to allow interventions at an earlier stage to prevent organ graft failure.

Cause of graft loss beyond the first year after transplantation



Peeters J, et al. Kidney Int. 1995;48(Suppl 52):S97S101.

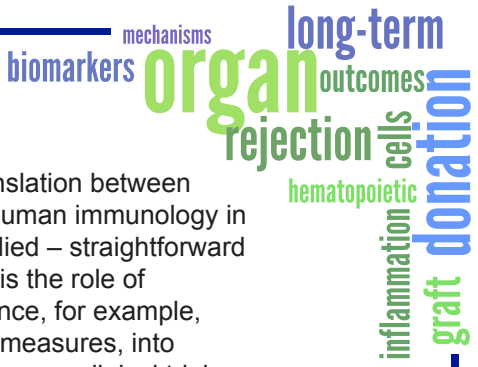
Breakout Group Discussions

Human Immunology

The discussions highlighted our current lack of understanding of the complex interplay of immune pathways that regulate the balance between tolerance and alloimmunity in humans. The use of emerging, more sophisticated tools could enable the development of biological tests to measure human immune function, and to accurately analyze immune responses. In the transplantation field, we need a better understanding of the mechanisms involved in both acute and chronic rejection and immune tolerance and we also need improved methods for organ collection, storage and perfusion. Improving the quality of organs from brain-dead donors by using hormones and small molecules (drugs) is an understudied area of investigation of great potential importance for ameliorating both acute and long-term allograft dysfunction. Considering the long distances that some organs must be transported, improved knowledge and research on how to maximize the quality of the donated organ is not only essential, it is quintessentially Canadian.

There is a growing need to study basic human immunology in humans rather than in mice as basic human immunology is insufficiently studied

Participants emphasized the importance of basic research in advancing transplantation science as a fundamental route for improving the functional understanding of immune responses and immunosuppression in the clinical setting. Noting that Canada has state-of-the art systems biology platforms, there should be an opportunity to capitalize on those investments in order to learn about precise basic mechanisms of inflammation, tissue injury, rejection and tolerance. Partnerships between basic and clinical immunologists could lead to huge leaps in understanding. Despite the inherent value of animal model systems in



elucidating immune responses, challenges are often encountered in the translation between experimental and human systems. There is a growing need to study basic human immunology in humans rather than in mice. Basic human immunology is insufficiently studied – straightforward questions about the longevity of organ function remain unanswered …what is the role of senescence? Is it immune-mediated? Translation of some of the basic science, for example, about ischemia/re-perfusion of organs and anti-inflammatory cytoprotective measures, into clinically relevant information is a major challenge that needs to be met. However, clinical trials are challenging to fund and it is difficult to incorporate basic biological studies. Research-funding agencies fund few transplantation trials, and provincial governments resist providing research funds for clinical networks. One proposed solution was to structure funding so that basic researchers can work in parallel with ongoing clinical trials to do translational research.

Considering the long distances that some organs must be transported, improved knowledge and research on how to maximize the quality of the donated organ is not only essential, it is quintessentially Canadian

Infectious diseases are a part of transplantation in two ways: as a cause of organ failure and as a result of transplantation. For example, hepatitis and the resultant hepatic failure is the driver for liver transplantation. Deaths caused by infection are also a major post-transplant complication, seen in both cell and organ transplantation. Chronic therapeutic immunosuppression with accompanying low-grade inflammation is a larger problem than simply rejection and may fuel chronic maladaptive repair processes leading to fibrosis and loss of function. Without doubt, there is a relationship between infection, inflammation and fibrosis. In order to control immunity without ending up with infection, an improved understanding of the basic biology of tissue injury and repair is needed. The impact of early post-transplant infection in promoting or blocking tolerance has been recognized but has not yet been well-studied and could be a key issue in whether current anti-rejection strategies are effective, particularly in establishment of long-term operational tolerance.

In order to control immunity without ending up with infection, an improved understanding of the basic biology of tissue injury and repair is needed

Therapeutics

Therapeutic opportunities lie in the field of tailoring medication to match biomarker information that predicts levels of rejection risk or other co-morbid conditions such as risk of cancer, infection, and cardiovascular disease. It is entirely relevant to ensure that a therapeutic is used effectively not only at baseline, but for the life of the graft. The goals of this approach would be to reduce overall burden of immune suppressive therapy by drug minimization to improve long-term outcomes for patients. At this point, clinicians' responses are usually reactionary, waiting for something to go wrong before acting. Many of the drugs currently used are not sufficiently effective or cause intolerable adverse reactions. If a clinical trials approach were taken, the best opportunities would be to work with biomarker platforms in order to improve how clinical trials are conducted, and to collect essential information to guide new drug development. Markers should be used to make informed decisions and to stratify risk. For instance, if we can predict who will have acute heart transplant rejection using graft biopsy arrays, will it be possible to identify a trigger for chronic rejection? It was felt that currently, medical scientists don't understand the natural history of transplantation well enough to know if the array of measurements helps to improve long-term survival. Straightforward questions about the longevity of organ function are unanswered but Canada has state-of-the-art systems biology platforms, so there should be an opportunity to capitalize on those investments in order to learn about basic mechanisms of inflammation, tissue repair and rejection.

The translation of basic discovery research to the patient was raised as a current limitation. The current system relies on 'big pharma' in the absence of a well-defined clinical transplant outcomes network in Canada. The researcher with a promising innovation has to contend with institute policies, intellectual property hurdles, ethics, trial funding and access to patients and platforms to successfully perform a trial. There is an opportunity to develop a network in Canada to address this but it will require new resources, enthusiastic champions and commitment from academic centres to share technology platforms.

Canada has state-of-the-art systems biology platforms - there should be an opportunity to capitalize on those investments

Interest in developing biomarkers related to diagnostics, prognostics and therapeutics was expressed, in part because early biomarkers might improve access to clinical trials funding. However, the participants asked, "Where is the research that brings biomarkers and the clinical needs together?" The question of whether biomarkers would provide information to alter outcomes was raised. Missing from the assessment is a grid of basic clinical endpoints, much less crude than those used now. Indeed, researchers are developing tests for antigen-specific responsiveness and unresponsiveness. Surrogate endpoints are essential to reduce the time period of a study and thereby the cost. There were those among the participants who felt that 'big pharma' were starved for ideas and that this was one area in which Canada might have an advantage.

The pre-transplant health of transplantation recipients is a recognized predictor of longevity, but as transplant recipients live longer, the risk of dying as a direct consequence of the transplantation procedure is reduced, allowing other risks to assert, or reassert themselves. Compared to the general population, transplant recipients have a higher risk of cancer, diabetes and cardio-vascular diseases and it is essential that the recipient understands how to avoid other long-term consequences of their primary disease. Research is needed on how to educate transplant patients with respect to the determinants of their long-term health, to ensure that recipients don't lose their organ or experience reduced quality of life due to preventable causes. Over time, adherence to the immune suppression regime may weaken, leading to increased risks of chronic rejection and eventual allograft loss. Research on the determinants and mechanisms supporting long-term adherence to an immunosuppressive drug regime is particularly relevant to children, adolescents and other young patients who tend to experience higher rates of non-adherence with dramatic detrimental consequences on allograft function and survival.

Compared to the general population, transplant recipients have a higher risk of cancer, diabetes and cardio-vascular diseases

Emerging Technologies

Workshop participants identified a myriad of individual technologies of interest, such as deep sequencing of mRNA and cDNA. It is likely that such precise and quantitative technologies could impact biomarker discovery and may even predict tolerance. Imaging studies presented during this workshop were certainly an 'eye-opener' for the participants unfamiliar with the field. Questions arose: *Are markers used in imaging studies? Can imaging be used to study microcirculation? Are there available technologies for clinical follow-up of patients?* Fibroscan®, a technology developed for non-invasively quantifying liver fibrosis, is considered a breakthrough technology potentially applicable to other transplanted organs. It has been approved by Health Canada and can provide images that 'illustrate' the mechanical properties of organs. Other studies are using MRI to predict organ survival by measuring perfusion and edema. Bioluminescence is being used for immune imaging. Nanotechnology of quantum dots in therapy might be useful for immunologic imaging. As exciting as these new technologies are, it will remain important to evaluate how they might be used in a clinical setting. The lack

of translational data between basic research and the clinic was described as both a gap and an opportunity. The range of possibilities included translation of some of the basic science related to ischemia/re-perfusion of organs (including organ 'resuscitation') and anti-inflammatory cytoprotective measures into clinically relevant information. Improvements are needed in the functional understanding of immunosuppression in the clinical setting, including the resolution of disagreements about how to use technology and interpret results.

The lack of translational data between basic research and the clinic was described as both a gap and an opportunity

Regenerative medicine is a growing field in Canada and one of considerable importance to HSC researchers, given that stem cell therapy is, itself, a type of regenerative therapy. The organ transplantation participants felt that important research could arise from understanding, for example, the role of bone-marrow-derived stem cells in the regeneration of myocardial and endothelial cells in the transplanted heart. Will this be the means by which failing hearts are repaired in the future? A secondary question is to ask about the consequences of organ transplantation, because stem cells attached to vascular walls and within the interstitium are certainly being transplanted with an organ graft and could regulate immune recognition and tissue repair thus potentially contributing to allograft function and survival.

The Role of Industry

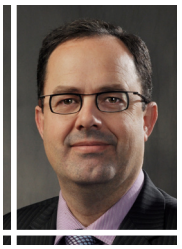
As an investigator dependent upon external funding, the potential for commercial application must always be top-of-mind. The involvement of industry is important because of access to resources and because of the insight industry can provide in determining how to proceed from bench to bedside. Industry investment is decreasing, influenced by the downturn in the economy, the loss of some patents and the extremely high costs of drug development. Industry needs to believe that they will recoup their investment; it can take two decades for a drug to be introduced. In fact it has been over 10 years since the introduction of a new drug class for transplantation. Participants felt that in the current economic environment, industry support would be available only for projects with shorter timelines. Consensus was not achieved: some felt that innovation would be rewarded, while others disagreed. Even after acknowledging the long-standing interest of some manufacturers such as Novartis, participants were concerned about relying on the interests of 'big pharma'. When asked if it was worth thinking about investments in drug development, the participants voiced their sense that as a focus of a strategic initiative, it would not be the best investment. It should be noted, however, that industry may be interested in developing research partnerships related to pharmaceutical policy and regulation, given that Canada is perceived to lag behind other countries in this area.

Organ Donation and Health Services Issues: *Increasing the donor pool and coordinating our efforts*

The Patient Perspective

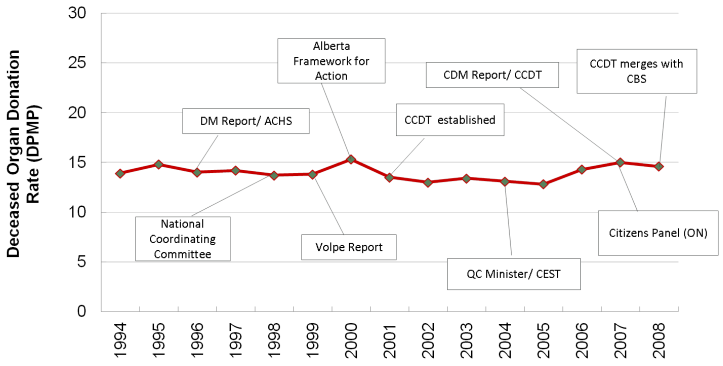
The second day of the workshop began with a presentation from the transplant patient perspective by **Kathryn Richardson** and her son **Tyler Wade**. Both Kathryn and Tyler have a genetic disease called Alport's Syndrome, an inherited disease of the kidney that can also affect the inner ear and eye. The genetic marker is carried on the X chromosome and boys experience the most severe form of the disease, generally leading to kidney failure by the time they reach their teens - as was the case for Tyler. Fortunately, Tyler's father was able to donate one of his kidneys to his son. This was 13 years ago when Tyler was 16; and both father and son are currently thriving. However, both Tyler and his mother spoke of the trials and tribulations of being a transplant recipient: the constant threat of rejection; the need for strong immunosuppressive drugs and their accompanying side-effects; and the long-term psychosocial effects. Both Tyler and his mother urged the research community to collaborate and network in order to reduce the need for transplants in the first place; extend the lifespan of transplanted organs; and find new immunosuppressive drugs with fewer side effects.

The session continued with presentations from: Dr. Peter Nickerson – on the Canadian transplantation landscape; Dr. Sam Shemie – on how to improve deceased organ donation; and Dr. Amit Garg – on how to improve living donor donation.

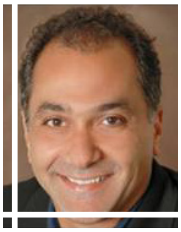


Dr. Peter Nickerson addressed to need to coordinate clinical care in Canada, with reference to the CIHR Strategy on Patient-Oriented Research (SPOR), and the fact that Canada lags behind other countries such as the US and Switzerland in terms of our networks, population cohorts and clinical trials infrastructure. In Canada, donor and transplantation performance have not improved significantly over the last 10 years. There has been no improvement in preventing deaths on waitlists for any organs for the last three years suggesting that, as a country, we are not realizing our potential for organ donation. In 2008, Canadian Blood Services (CBS) acquired the mandate for organ and tissue donation and transplantation and is currently developing a national strategy. The issue of reserving a portion of funds for research in transplantation was discussed and the group supported the concept that CBS should have a mandate to support this in the new structure. However, the issue is complicated by provincial vs. federal funding within CBS for clinical activities and uncertainty of the amount of research funding that will be available.

Deceased Organ Donation Rate in Canada from 1994 to 2008

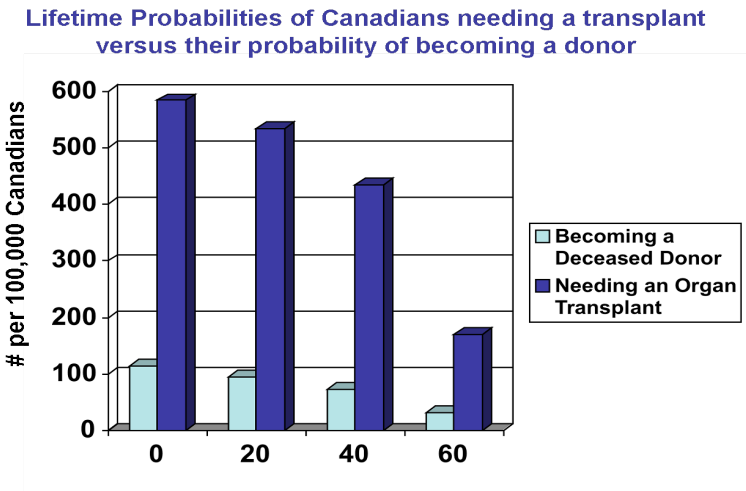


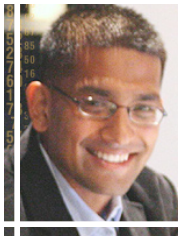
Source: CORR 2007 Annual Report and E-Statistics



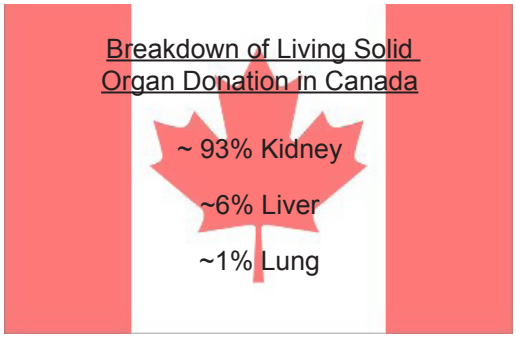
Dr. Sam Shemie spoke of advances in technology that have blurred the lines between life and death for deceased organ donation and of the lack of dedicated interdisciplinary research in this area. There are also challenges in hospital intensive care units (ICUs), in terms of engaging clinician time and interest in addressing donor potential and there is a clear lack of physician specialists trained to deal with organ donation issues. Obtaining donor consent is a further barrier and the process needs to be easier for the public to understand, particularly with respect to their probability

of needing a transplant versus their probability of becoming a donor. At age 20 for example, an individual is approximately five times more likely to need an organ transplant in their lifetime than to become a deceased donor.





For living donors, **Dr. Amit Garg** cautioned that the risks of short-term donor harm need to be outweighed by the psychological benefits of altruism and improved recipient health. For kidney transplantation, as the demand for organs increases, new types of kidney donors are being accepted, including those who are older, obese, hypertensive and those coming from racial backgrounds with predilection for future difficulties. We are also practicing new types of living donation, including individuals who participate in altruistic donation and paired-exchange. We have a responsibility to follow and study patients to ensure there are good long-term donor and recipient outcomes, especially in high-risk groups such as donors and recipients from First Nations communities. Examples of concerns of living donors relate to their subsequent health status, their ability to obtain health insurance and ,for women, the ability to carry a pregnancy without complications. There are many research questions that need to be addressed particularly in the area of ethics as it pertains to living donation, surgical innovation to reduce morbidity, and donor recruitment - where there could be lessons learned from the HSCT community.



Breakout Group Discussions

Existing Resources; Potential for Partnership

The launch of the CBS Organ Donor and Transplantation (ODT) initiatives and registries raised a number of questions. As presented, CBS will not be funded by governments to support fundamental transplant research in biomedical or social science. It is not clear if the proposed ODT database could support the different proposals of this two-day workshop. The participants encouraged connection and cohesion between transplantation and donation initiatives. It was suggested that CIHR evaluate the impact of CBS ODT mandate on the Transplantation Initiative. The CBS ODT programs may create a natural experiment – CIHR may wish to develop an intervention research program to parallel the launch of the ODT. Questions were raised about the potential of CIHR and CBS to partner on the Transplantation platform. The participants were very enthusiastic about the new CBS initiative, regardless of its future role in the Transplantation Initiative. Concern was expressed regarding CBS as data-holders and whether they would be making their data available to researchers; would there be restrictions on sharing and potential costs to the transplantation community?

How to Increase Organ Donation

To get 20 living kidney donors, about 100 potential donors must be screened; 80 donors will not be enrolled because of social considerations, technical issues, ethical restrictions, and underlying disease. Issues exist in deceased donor organ usage as well. About one-third of all hearts available for transplantation are not transplanted. However, because no data are collected, we do not know why discard and non-usage rates are this high. To maximize donation from deceased and living donors, the challenge is two-fold: to improve both the number (including the number of donors and, in the case of deceased donation, the number of organs per donor) and the quality of organs used for transplantation.

About one-third of all hearts available for transplantation in Canada are not transplanted

The participants realized that the general population has misapprehensions about what will happen to their bodies and to their organs after they die, and this is certainly part of the reluctance to donate. Indeed donation rates in Canada are significantly lower than in other industrialized countries. Even among those who agree to donate, 40% don't follow through by properly registering their intention. At the same time, transplantation is dependent upon intensivists for referrals of possible organ donors, and it has been hard to engage intensivists as well as emergency room staff. Should education efforts be targeting the general public or the associated health professionals or both? The recommendation was that attention should be focused on the health professionals as follows:

- Change best practices: organ donor procurement agencies are needed in every province.
- Recruit specially trained donor teams in hospitals, even and perhaps especially, those without transplantation capacity.
- Support research on psychology, social psychology and behavior, attitudes at all levels of the donation process.
- Learn from positive outcomes at other centers, such as accreditation linked to donation performance, which is proving successful in US hospitals.
- Support policy research to inform legislative changes.
- Understand and remove barriers to living and deceased organ donation and hematopoietic stem cell donation (i.e. for example, address financial disincentives for living organ donors)

Children are a priority for deceased donors and there has been a decrease in living donation for children whose parents want to be able to donate if a second transplant becomes necessary. There is a need for specific regulation for vulnerable populations and children and research into the determination of brain death in pediatrics. Neonates for whom life support is withdrawn are generally ineligible for donation and very young infant donors are rare. The societal repugnance for discussions of donations from children is such that it is 'difficult' to explore the options: this clearly contributes to the profound sorrow of parents awaiting a donor organ for their dying child and also deprives parents of a child who dies the opportunity of participating in organ donation. In order to address such sensitive issues, the participants recommended that benchmarking of provinces that do well and others that don't might allow a relatively unencumbered discussion of certain key differences in approach, but much more is required.

There is a need to study the long-term health impact on living donors, particularly new types of donors where knowledge on long-term outcomes is limited. Canada could make meaningful international research contributions in this regard, given the available administrative health care

databases and emerging partnerships with CBS. For kidney donation in particular, living donation may be an economical alternative not always available to other organs. Truly, informed consent requires that living donors have a thorough understanding of the risks, if any to their long-term health. Without understating the risks of the procedure, those who hesitate (particularly recipients who are reluctant to accept the gift) may do so simply for lack of information about long-term safety.

Continuity of Clinical Care

Dr. Nickerson's presentation emphasized the value of coordinating clinical care. The participants felt strongly that an objective clinical evaluation component should be built under the CIHR research umbrella. They pointed out that a clinical care network based on standard operating procedures and able to collect end-point data would help answer questions that a reasonable person in Canada might expect are already being addressed, such as understanding what happens to people who've had transplants, or the validation or refutation of claims of benefit or harm. It might surprise Canadians to know that the universally funded health care system in Canada does not help in follow-up. The clinicians noted that the current system and emerging privacy regulations in every province requires strategic efforts to assemble information from patients and to undertake the record linkages necessary to understand what happens to their patients over the long-term. Several participants felt that the paediatric oncology model was one to follow in this regard. However, creating a functional collaboration is more than simply combining lists. A network needs to ensure that accurate data are collected by all sites in a way that will allow direct comparison amongst centres and that the datasets are complete, otherwise they will not be useful. A national clinical network should be able to develop standards of care. At some point, a standard operating procedure for biobanking might be developed.

In a fully funded health care system, why haven't we realized the opportunity to efficiently follow transplantation recipients from their transplantation throughout their lives?

Of all the needs identified, the difficulty of collecting information for long-term follow-up was, perhaps, the most perplexing for the participants. In a fully funded health care system, why haven't we realized the opportunity to efficiently follow transplantation recipients from their transplantation throughout their lives? Enabling links between existing databases could identify key attributes and threats to survival. With an effort made to ensure that a core data set is identified, even best practices like clinical management might be possible to ascertain. Alerting recipients to emerging problems and benefits would seem to be a natural expectation, particularly given the cohort of child recipients now entering their teen and young adult years.

Knowledge Translation

The participants talked about the need to contextualize their knowledge within the Canadian healthcare system – knowledge translation. The participants identified politicians and decision-makers as targets for improved knowledge translation about the essential issues affecting the health care expenditures in transplantation. Health policy research should inform government decisions and should drive system change. Given the enormous costs, disability and death

caused by end-stage organ failure, it makes sense to study the policies that manage our health care investments. For example, health policy research could inform legislative changes, particularly privacy legislation that impacts data-sharing. Additionally, datasets for more effective health services research in transplantation are both warranted and needed. Provincial and territorial governments who bear the brunt of rising health care costs should be interested in funding research that could maximize health outcomes, ensure best practices and ease health care costs.

Of great importance to the participants was introducing politicians and decision-makers to a greater understanding of the trajectory of research. There are important gaps in medical scientists' ability to communicate with politicians and citizens about the importance of transplantation research. The recent CBS process of development of their ODT platform successfully engaged citizens and politicians; both the CBS ODT platforms and their strategic approach may have important health policy implications for transplantation.

Given the enormous costs, disability and death caused by end-stage organ failure, it makes sense to study the policies that manage our health care investments

Ethics

Many ethical issues were discussed over the course of the two days, including how to overcome the challenge that resources and time are systematically wasted while waiting for approval of each and every research ethics board involved in a multi-centered trial. In the area of organ donation after cardiac death, concerns regarding reports of 'auto-resuscitation' were voiced, resurrecting issues relating to differences between cardiac death and brain death. (*What is cardiac death? Does it make sense from a transplantation perspective? Other questions included: if organs that were found to be unsuitable for transplantation could they be used for research?; for those with cardiac death, is there a way to intervene ex-vivo?; and would it be permissible to intervene with a potential donor in order to ensure that the organ has the best outcome?*) Other discussion focused on social and anthropological issues and the social determinants of health, and how social equity can be threatened in transplantation. The point was raised that maybe it is not sufficient to increase the life span of an individual through transplantation without taking into account the quality of the extended period of life. It was felt that governments, institutions, professionals and society have the duty to optimize available resources, avoid duplication of effort and make resources equitably available to those in need.

Ethics, as a branch of philosophy, is poorly understood by many scientists. The ethno-cultural barriers to deceased and living donation are, in some cases, profound. Developing an understanding of the willingness to donate in various groups is important. The ethno-cultural barrier to both donation and receipt of organs is under-investigated. Some participants felt that trainees do not get sufficient exposure to ethics and the practical tools to apply ethics in research and medicine. In research, ethics should be seen as an enabler, rather than a hurdle, one that levels the playing field for the patient and family when they are working with clinicians and researchers. A common theme emerged: there is insufficient expertise in transplant ethics, which is one of the most complex ethical areas in the medical arena.

In research, ethics should be seen as an enabler, rather than a hurdle, one that levels the playing field for the patient and family when they are working with clinicians and researchers

Vulnerable Populations

Frequently, individuals who are in need of transplants or who received transplants become physically, socially and economically vulnerable. Particularly, children and young people may experience alienation from their peers during crucial developmental stages of life. There was considerable discussion on the need to have pediatric patients recognized as a distinct population. Many aspects of transplantation are so different from those of adults that research and management options must be assessed separately. Paediatric transplants are generally undertaken for conditions for which there are no other therapeutic options. Additionally, the child cannot ameliorate their condition through healthier behavior – they are entirely dependent upon the health care system for their short- and long-term treatment.

SUMMARY OF BREAKOUT GROUP RECOMMENDATIONS

Discussions on the future directions were extra-ordinarily wide. Those who had the experience of working in successful networks communicated their enthusiasm. One of the principle recommendations was for all parties to invest in networking. Canada doesn't have a national transplantation agency, but we have the Canadian health care system and a culture of collegiality. Establishing a national transplant network should be a first priority. Canada's population is simply too small to do otherwise: we need to undertake multicentre research.

Networks

Many voiced their sense that a clinically transformative and unique network would be the best focus of the Transplantation Initiative although participants were concerned about the main focus and purpose of the network, the initial size and structure of the network and the long-term sustainability of a network, noting the great expense involved in formalizing network functions. Emphasis was placed on the need, referred to earlier, to promote collaborations between the solid organ and HSCT communities, something that all agreed could be achieved through a network. The scope of 'network' goals ranged from simple platform inventories, asset management and clearing-house functions to the establishment of registries, clinical networks, bio-banks and clinical trials networks. The approach to achieving a network varied. Some participants called for the initiative to begin by establishing long-term goals (10- and 20-years) such as 'Canadian recipients have best long-term outcomes worldwide (survival, graft survival, HRQOL)', or that 'in 10 years, Canada no longer needs living donor transplants'. It was noted that, in fact, this was a call for a National Transplantation Strategy. Regardless, the majority said networks were essential if Canada was to be competitive on the world stage. Participants referred to the Centre for Drug Research and Development as a model, because many universities across Canada are affiliated. Started by BC-based researchers, it is now part of the MaRS Discovery District including McMaster, McGill, and others. It was noted that a key success factor of the CDRD was a substantial 'no-strings attached' operating fund.

the majority of workshop participants said that networks were essential if Canada was to be competitive on the world stage

A Canadian Transplantation Network would provide the platform to establish standard protocols and operating procedures, create shared databases and core facilities and would facilitate integration with organizations such as CBS. It would also encourage collaborations amongst researchers across the four research themes: biomedical, clinical, health policy and services and population health. Such a network would align well with the CIHR SPOR initiative and would be in a good position to apply to future funding opportunities. It was agreed that standardization of data and protocols would be essential for the network to function. A core platform for data management and analysis could be created through competitive processes and should link with

CBS ODT for better data capture. However, access to the data would not be competitive. A Data Centre is one step beyond simply assembling existing data. The platform could take the form of an 'observatory' that would ensure:

- Integration of requests with the priorities established through the governance structures;
- Clinical networks in which information is collected and measurements are made in a standard way and can be compared across sites;
- Connectivity through information technology;
- Biostatistical, data transfer protocols, enabling links among existing databases that are already collecting data on patients;
- Training for participants; and
- Measurement of adherence to national standard operating procedures (SOPs) e.g. standard transplant protocols, immunosuppression protocols, biobanking

Concerns were voiced that successful networks needed to be self-forming, and that the community must demonstrate its capacity to act in partnership. It was suggested to start with a development grant, to allow participants to get organized. A development grant of as little as $25,000 - $50,000 might be all that is needed by the community to put together an application, as was done by the HIV/AIDS Clinical Trials Network now centered in Vancouver and also by the recently funded CIHR Medical Imaging Clinical Trials Network. Further funding would be dependent upon the achievement of milestones and deliverables as delineated in the proposal.

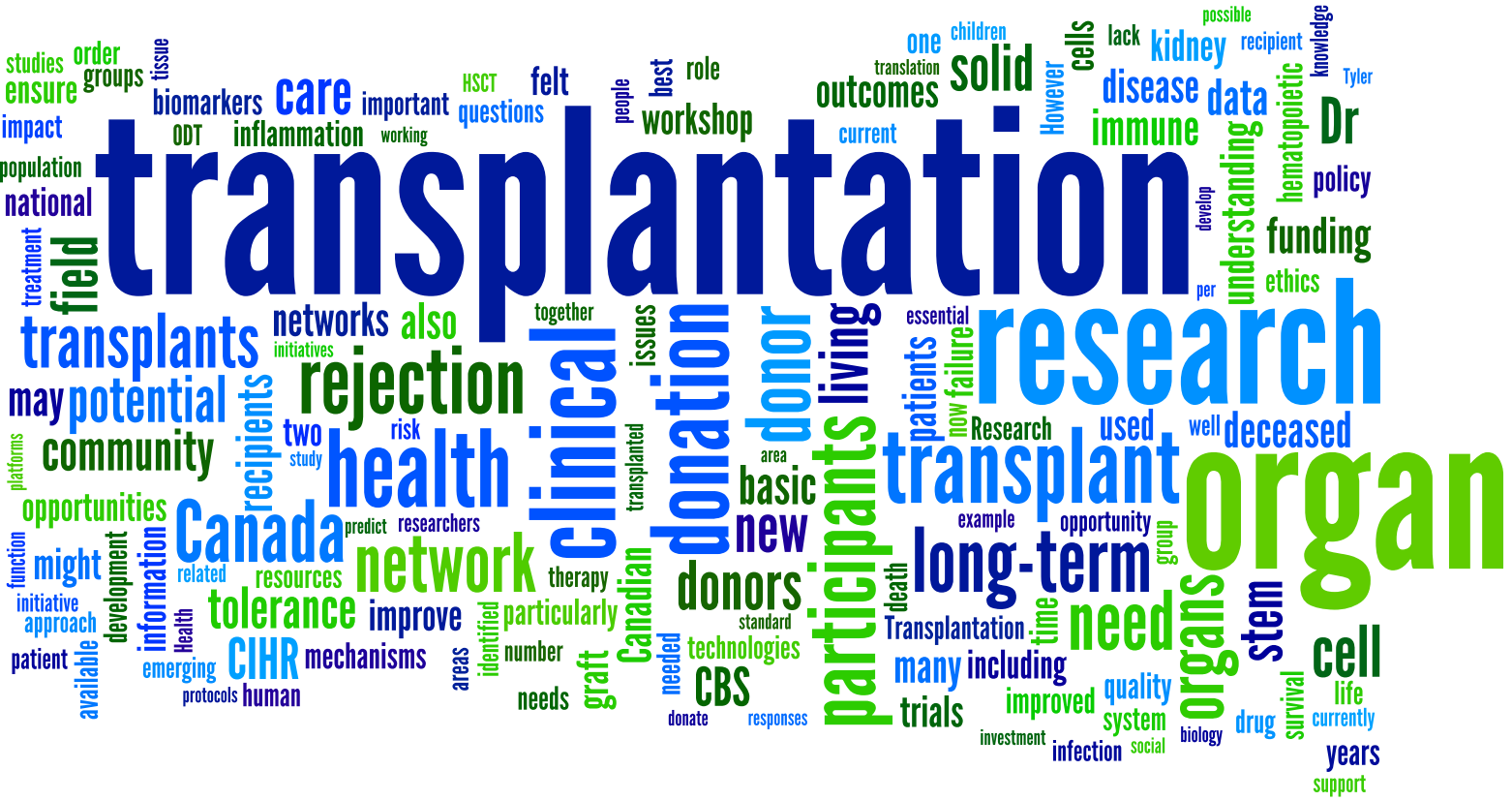
Teams

There were concerns about focusing all efforts on a single network when there are so many pressing concerns. Participants identified core tasks that should be accomplished: ensure adequate donation, improve the quality and safety of grafts, replace short-term outcomes by long-term outcomes, and undertake knowledge translation of existing scientific discoveries. Examples of research areas likely to be of high impact in the short-term would include policy interventions to increase the number of deceased organ donors and new mechanisms of organ preservation and perfusion to improve organ quality and longevity. For the former, this might include strategies to increase deceased organ donor registration. For the latter, noting that the damage from ischemia happens within a few minutes, which is insufficient to cause protein or gene shifts, is there a role for -omics when the damage is clearly post-translational? Will it be possible to stop the first events at the bedside with small molecules? Regardless, the early process of injury progresses over days, which if well understood could yield opportunities for intervention and amelioration. Other potential areas are human immunology studies to explore the immunological mechanisms mediating graft rejection and tolerance, validation of new imaging biomarkers, studies on basic biological processes involved in injury, infection and inflammation. The CIHR Inflammation in Chronic Disease, Signature Initiative will include a focus on transplantation and the transplantation research community may benefit from anticipated funding opportunities related to the role of inflammation in graft rejection.

Therefore, another approach might be a two-step process starting with the support of a number of multi-disciplinary teams to establish initial collaborations – such as between the solid organ and HSCT groups – followed by a networking opportunity to establish a true national transplantation network, potentially though the CIHR SPOR initiative. The expectation would be that these initial teams would expand to form a broader network over time. It was felt that there were advantages to allowing the network to develop somewhat 'organically' over several years. Teams would be brought together on an annual basis to facilitate linkages and collaboration with a view to preparing an eventual application for a national transplantation network. In the meantime, the teams could combine different areas of expertise to focus on many of the concerns described above leading to improved clinical outcomes for transplant patients.

Next Steps

Some participants felt that the workshop had already achieved one of its goals by providing a venue to bring the transplantation community together and that new collaborations had already been forged. In order to build on this momentum, the expert working group will meet and synthesize recommendations for presentation to the III IAB in May, 2011. Institute staff, in consultation with partners, will then develop an implementation plan.



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	**Céline Bergeron** Pneumologue et chercheur	CHUM and CRCHUM 3840 St-Urbain Montreal, QC, H2W 1T8 celine.bergeron.1@ umontreal.ca 514-890-8000 ext 15639	• Research in chronic lung rejection mechanisms • Endothelium/epithelium apoptosis and the remodelling process leading to chronic lung rejection.
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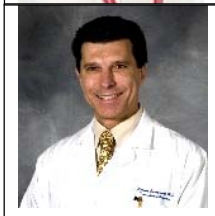
	**Eric Brown** Professor and Chair	McMaster University Dept Biochemistry and Biomedical Sciences, 1200 Main Street West Hamilton, Ontario, L8N 3Z5 ebrown@mcmaster.ca 905-525-9140 x22454	• Cell wall and ribosome biogenesis • Chemical genomics aimed at mapping and understanding the interaction of drug-like small molecules with bacterial cell systems
	**Patricia Campbell** Associate Professor	University of Alberta 11.107 Clinical Sciences Building Edmonton, Alberta, T6G2G3 trish.campbell@ualberta.ca 780-407-7579	• Antibody mediated rejection late and early • Risks for late antibody mediated rejection • Kidney transplantation • HLA antibodies
	**Marcelo Cantarovich** Professor of Medicine, Associate Director	McGill University Health Centre 687 Pine Avenue West Montreal, QC, H3A 1A1 marcelo.cantarovich@ muhc.mcgill.ca 514-934-1936 ext 36223	• Optimizing the use of immunosuppressive medications, optimization of the assessment of renal function • Development of renal protective strategies in solid-organ transplant patients

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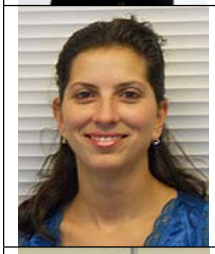
	**Dana Devine** VP, Medical, Scientific & Research Affairs *Working Group Member*	Canadian Blood Services CBR - 2350 Health Sciences Mall Vancouver, BC, V6T 1Z3 dana.devine@blood.ca 604-822-7270	• Transfusion medicine with a particular focus on improvement of the quality of stored blood products • Application of proteomics to understanding the platelet storage lesion at the cellular level and also in terms of donor variability
	**Aida Fernandes** Director, Medical/Scientific Programs	Canadian Cystic Fibrosis Foundation 2221 Yonge Street, Suite 601 Toronto, ON, M4S 2B4 afernandes@cysticfibrosis.ca 416-485-9149 x229	• Infection and inflammation in cystic fibrosis • Enhancements to lung transplantation techniques to improve outcomes for patients with cystic fibrosis
	**Stephen Ronan Foley** MD, FRCPC	Hamilton Health Sciences-Juravinski Site 711 concession Street Hamilton, Ontario, L8V 1C3 elsonlau@hhsc.ca 905-527-4322 x42074	• Stem Cells, Melanoma, Breast Cancer, Dendritic Cells, Hematopoietic Progenitors, Hematology, Adenovirus • Current President of the Canadian BMT Group
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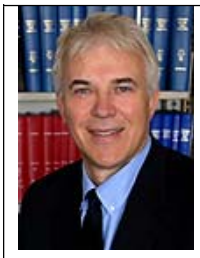
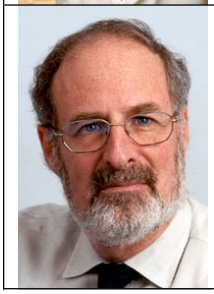
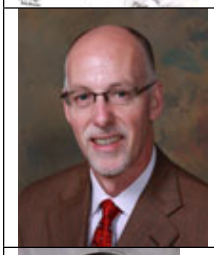
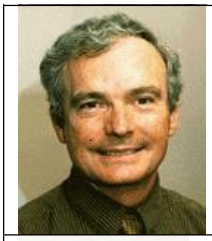
	**Amit Garg** Nephrologist *Working Group Member*	London Health Science Centre 800 Commissioners Road London, ON, N6A 4G5 Amit.Garg@lhsc.on.ca 519-685-8502	• Kidney Donation • Health services research • Health informatics • Clinical trials

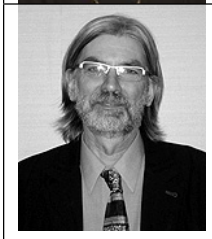
	**Lucie Germain** Professeur, Dépt Chirurgie, Fac. Médecine	Université Laval et Centre LOEX Aile-R, CHA, 1401, 18e rue Québec, P.Q., G1J 1Z4 luciegermain@videotron.ca 418-682-7511#1696 or 1684.	• Stem cells and tissue engineering. • Cultured epidermal sheet for transplantation on burn patients. • Tissue-engineered skin and tissue-engineered cornea for the treatment of severe burns of the skin and corneal stem-cell deficiency • Director of the Cell and Tissue Therapy Network from the FRSQ
	**John Gill** Associate Professor of Medicine	University of British Columbia St. Paul's Hospital-Providence Building Vancouver, BC, V6Z 1Y6 jgill@providencehealth.bc.ca 604.681.7191	• Clinical outcomes in kidney transplantation • Access to transplantation • Organ Donation
	**David Grant** Medical Director Transplant Centre	Hospital For Sick Children 555 University Ave. Suite 6432 Hill Wing Toronto, Ontario, M5X 1X8 david.grant@uhn.on.ca 416-5097532	• Live Liver Donation • Xenotransplantation • Intestine Transplantation • Pediatric Transplantation
	**Marie-Josée Hébert** Professor of Medicine, University of Montreal, and, Director, Organ transplantaion Program, Université de Montréal *Working Group Member*	CHUM HOPITAL NOTRE-DAME 1560 Sherbrooke Street East Montreal, QC, H2L 4M1 marie-josee.hebert.chum@ssss.gouv.qc.ca 514 890-8000 ext. 25017	• Molecular characterization of the paracrine legacy of vascular apoptotic programmed cell death • The impact on vascular remodelling, fibrosis and rejection
	**Atul Humar** Director Transplant ID	University of Alberta 6-030 Katz-Rexall Edmonton, Alberta, T6G 2E1 ahumar@ualberta.ca 780-492-3885	• Transplant virology • Translational study • Cytomegolovirus pathogenesis
	**Thomas Issekutz** Professor and Head, Div of Immunology	Dalhousie University 5850 University Ave. Halifax, NS, B3K 6R8 thomas.issekutz@iwk.nshealth.ca 902-470-8933	• Mechanisms of leukocyte, especially T cell, migration into inflamed tissues and how these cells contribute to tissue injury • Investigating animal models of human inflammatory diseases including rheumatoid arthritis, multiple sclerosis and transplant rejection • Molecular interactions leading to human T cell transendothelial migration

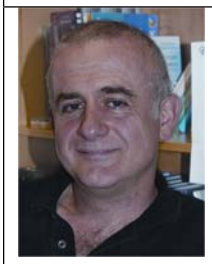
	**Anthony Jevnikar** Co-Director, Multi-Organ Tsp Program, Director Transplantation Nephrology *Working Group Member*	LHSC, University Hospital 339 Windermere Road London, ON, N6A 5A5 jevnikar@uwo.ca 519-663-3688	• Cell death • Apoptosis • Necrosis • Inflammation • Transplant immunobiology
	**Shaf Keshavjee** Director, Lung Transplant	University Health Network 150 Elizabeth St Toronto, ON, M5G 2C4 shaf.keshavjee@uhn.on.ca 416-340-3863	• Lung transplantation • Exvivo organ repair • Regenerative medicine • Gene therapy
	**S. Joseph Kim** Transplant Nephrologist	Toronto General Hospital 585 University Avenue, 11C-1183 Toronto, Ontario, M5G 2N2 joseph.kim@uhn.on.ca 416-340-3228	• Kidney transplantation • Chronic kidney disease • Epidemiologic methods • Outcomes research
	**Greg Knoll** Medical Director-Kidney Transplantation	Ottawa Hospital Research Institute 1967 Riverside Drive Ottawa, On, K1H 7W9 gknoll@toh.on.ca 613.738.8400 est 82536	• Clinical trials, prospective cohort studies and systematic reviews in kidney transplantation. • Focus on measurement of transplant kidney function, proteinuria, • "non-immunologic" issues in transplant patients
	**Paul Kubes** Professor	University of Calgary Faculty of Medicine HRIC 4AA16 3280 Hospital Drive NW Calgary, AB, T2N 4Z6 pkubes@ucalgary.ca 403-220-8558	• Cell biology approaches and mouse transgenic and knockout technology to delineate molecular mechanisms underlying innate immunity • Multi-step cascade of leukocyte recruitment which includes the proteins responsible for catching leukocytes and tethering them to the endothelium
	**Megan Levings** Associate Professor	University of B.C. A4-186 950 West 28th Vancouver, BC, V5Z 4H4 megan.levings@ubc.ca 604-875-2000 ext 4686	• Transplantation tolerance • T regulatory cells • T cell signalling • cellular therapy to induce tolerance • islet transplantation • graft versus host disease
	**Gary Levy** Director, Transplant Institute	University of Toronto 585 University Ave, NCSB-11-1236 Toronto, ON, M5G 2N2 glfgl2@attglobal.net 416-340-5166	• Characterize unique molecules that participate in immune coagulation and examine their role in human disease. • Identified three molecules, tissue factor and fgl2/fibroleukin which are membrane associated serine proteases. These molecules play pivotal roles in the pathogenesis of viral hepatitis (fgl2/fibroleukin), allograft rejection

	**Joaquin Madrenas** Professor and Canada Research Chair	The University of Western Ontario Robart research Institute P.O. Box 5015, 100 Perth Drive London, Ontario, N6A 5K8 madrenas@robarts.ca 519-663-5777 x24242	• Human Immunology • Transplantation • Immunopathogenesis of S. aureus infections • Systems Immunology
	**Locksley McGann** Professor	University of Alberta CBS Building, 8249 114 Street Edmonton, Alberta, T6G 2R8 locksley.mcgann@ualberta.ca 780-431-8764	• Cryopreservation of cells and tissues for transplantation • Focus on processes that involve minimal manipulation after thawing before transplantation
	**Bruce McManus** Director	UBC James Hogg Research Centre, St. Paul's Hospital 1081 Burrard St, Rm 166 Burrard Bldg Vancouver, BC, V6Z 1Y6 bruce.mcmanus@hli.ubc.ca 604-806-8586	• Pathogenesis of vasculopathy • The reliability of the endomyocardial biopsy as monitory tool for rejection surveillance, • The role of molecular biosignatures as tools for managing transplant patients and in assisting drug development
	**Robert McMaster** Executive Director	Vancouver Coastal Health Research Institute #100 2647 Willow Street Vancouver, BC, V5Z 3P1 robm@interchange.ubc.ca 604 875-5641	• Proteomic and genomic biomarkers to detect acute and chronic rejection in heart and kidney transplantation • Mechanisms of immune tolerance
	**Daniel Muruve** Professor	University of Calgary 3330 Hospital Dr. NW Calgary, AB, T2N 4N1 dmuruve@ucalgary.ca 403-220-2418	• Innate immunity and inflammation and how it pertains to chronic disease. • Primary focus on chronic kidney disease.
	**Kenneth A. Newell** Director, Living Donor Kidney Program Professor of Surgery	Emory University 101 Woodruff Circle Suite 5105 WMB Atlanta, Georgia, 30322 kanewel@emory.edu 404-727-2489	• Transplantation tolerance • Alloimmunity • Co-stimulation • Lymphocyte activation • The effects of infection on alloimmunity.
	**Vicky Ng** Medical Director, Liver Transplant Program	The Hospital for Sick Children 555 University Avenue, Black Wing Room 8262 Toronto, Ontario, M5G 1X5 vicky.ng@sickkids.ca 416-813-7733	• Pediatric hepatologist with clinical research interests focusing on the medical outcomes, health status and quality of life of infants and children who have undergone liver transplantation

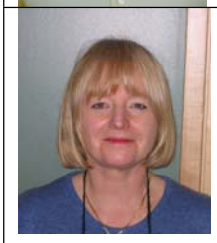
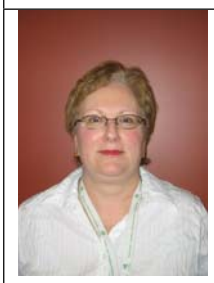
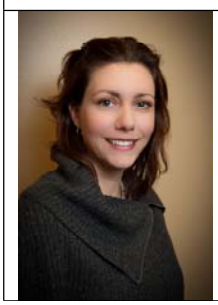
	**Peter Nickerson** Executive Medical Director, Organs & Tissues Division, Canadian Blood Services Associate Dean (Research),	University of Manitoba Canadian Blood Services Bldg., Rm 312 - 777 William Ave Winnipeg, Manitoba, R3E 3R4 pnickerson@hsc.mb.ca (204)789-1125	• Transplant Immunology • Proteomic approaches to identify novel pathways associated with renal allograft rejection
	**Marc Ouellette** Scientific Director	Institute of Infection and Immunity 2705 Laurier Blvd - Room TR Québec, Québec, G1V 4G2 marc.ouellette@crchul.ulaval.ca 418 577.4688	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.
	**Kevork M Peltekian** Medical Director, Liver Team	Atlantic Multi-Organ Transplant Program 1276 South Park Street Halifax, Nova Scotia, B3H 2Y9 kevork.peltekian@dal.ca 902.473.2898	• Regional network formation with focus on knowledge translation and outcomes research in the area of liver disease (including viral hepatitis) and transplantation • Previous member of CIHR III-IAB • President-Elect, Canadian Association for Study of Liver and Past-Chair, Board of Directors, Canadian Liver Foundation
	**Claude Perreault** Professor and Senior Scientist	IRIC - Université de Montréal C.P. 6128, succursale Centre-ville Montréal, QC, H3C 3J7 claude.perreault@umontreal.ca 514-343-6126	• Cell surface major histocompatibility complex (MHC) molecules associated with self peptides collectively referred to as the self immunopeptidome • Systems biology methods to understand how the immunopeptidome is molded • Found that the immunopeptidome i) is cell lineage specific and ii) is influenced by cell stress and by the expression of immunoproteasome subunits.
	**Kathryn Richardson** National President	Kidney Foundation of Canada 300-5165 Sherbrooke Street West Montreal, QC H4A 1T6 Tel.: (514) 369-4806 / 1-800-361-7494 Fax: (514) 369-2472	Kathryn's interest in The Kidney Foundation began when her son, Tyler, was diagnosed with Alport's Syndrome, a form of kidney disease, at three years of age. Thirteen years later, Tyler had a kidney transplant. Kathryn joined the National Volunteer Development Committee in 2003 and helped develop a national orientation program for the Foundation's leadership volunteers. She joined the National Board as Director-at-Large in 2005 and was elected Vice-President in 2006.
	**Michel Roberge** Scientific Director	Centre for Drug Research and Development 2259 Lower Mall Vancouver, BC, V6T1Z4 mroberge@cdrd.ca 604 822 2304	• Chemical biology • Drug discovery • Drug development • mTOR signalling

	**Jean Rouleau** Scientific Director	Institute of Circulatory and Respiratory Health 5000 Belanger Street, S-2096 Montreal, QC, H1T 1C8 jean.rouleau@umontreal.ca 514-593-7431	ICRH supports research into causes, mechanisms, prevention, screening, diagnosis, treatment, support systems, and palliation for a wide range of conditions associated with the heart, lung, brain (stroke), blood, blood vessels, critical care and sleep.
	**Kirk Schultz** Professor Pediatrics *Working Group Member*	BC Children's Hospital/UBC 4480 Oak Street, A119 Vancouver, BC, V6H 3V4 kschultz@interchange.ubc.ca 604-875-3886	• Blood and Marrow Transplantation Clinical Trials • Biomarkers of cGVHD • Immune therapy of Acute Lymphoblastic Leukemia • Biology of Chronic Graft-Versus-Host Disease • Immunology of the Graft Source
	**Sam Shemie** Professor of Pediatrics	Montreal Children's Hospital 2300 Tupper, C-806 Montreal, QC, H3H 1P3 sam.shemie@mcgill.ca 514-412-4400 X 23806	• Biomedical, Humanities and Social Science aspects related to organ donation, including death determination, ICU practices, consent, intent to donate, public awareness. • organ failure support and replacement technologies
	**Lianne Singer** Medical Director, Lung Transplant Program	University Health Network 585 University Ave, NCSB 11C-1194 Toronto, ON, M5G 2N2 lianne.singer@uhn.on.ca 416-340-4996	• Outcomes research and clinical trials in lung transplantation • Health-related quality of life in advanced lung disease and lung transplantation
	**Robyn Tamblyn** Scientific Director	Institute of Health Services and Policy Research 1140 Pine Ave. West Montreal, QC, H3A 1A3 robyn.tamblyn@mcgill.ca 5149341934 x 32997	• Health Services and Policy Research • Chronic Disease • Drug Policy • Health Information • Patient Safety • Primary Healthcare
	**Lee Anne Tibbles** Associate Professor	University of Calgary 3280 Hospital Dr. NW Calgary, Alberta, T2N 4Z6 tibbles@ucalgary.ca 403-220-2064	• Clinician Scientist trained in intracellular signal transduction mechanisms • Role of signalling pathways are activated by ischemia/reperfusion. • Pathogenesis of BK polyoma virus infection post transplantation • Developed a novel therapy which we are testing in vitro and in a multicentre clinical trial
	**Jacques P. Tremblay** Professor	Laval university CRCHUL 2705 boul Laurier room 9300 Quebec, Quebec, G1V4G2 Jacques-P.Tremblay@crchul.ulaval.ca 418-654-2186	• Muscle stem cell transplantation as a possible treatment for muscular dystrophies • Prolonged protection of islet allografts by inhibition of beta cell apoptosis

	**Anne Van Dam** Director, Research & Knowledge Translation	Canadian Lung Association 1750 Courtwood Crescent, Suite 300 Ottawa, ON K2C 2B5 avandam@lung.ca 613-569-6411 ext 222	The Canadian Lung Association is dedicated to its mission of promoting and improving lung health for all Canadians. A non-profit and volunteer-based health charity, The Lung Association depends on donations from the public to support lung health research, education, prevention and advocacy.
	**Bruce Verchere** Professor, UBC Depts of Pathology & Laboratory Medicine and Surgery	Child & Family Research Institute 950 West 28th Ave Vancouver, BC V5Z 4H4 verchere@interchange.ubc.ca 604-875-2490	• Islet transplantation • Immune and non-immune mechanisms of islet graft failure • Islet biology • Beta cell function and death in type 1 and type 2 diabetes • Beta cell regeneration
	**Donald Vinh** Assistant Professor	McGill University Health Centre 1650 Cedar Ave, Rm A5-156 Montreal, Quebec H3G 1A4 donald.vinh@mcgill.ca 514-934-1934 x42419	• Infections in immunocompromised hosts
	**Donna Wall** Director, MBMT Program	CancerCare Manitoba RM ON2009 675 McDermot Ave. Winnipeg, Manitoba, R3E 0V9 donna.wall@ cancercare.mb.ca 204 787-7095	• Clinical blood/marrow transplantation • Supportive care, immune recovery, cord blood as an alternative donor source • Treatment of childhood leukemia with allogeneic transplantation.
	**Lori West** Professor of Pediatrics *Working Group Member*	University of Alberta 6002, Li Ka Shing Research Inst. Edmonton, Alberta, T6G 2E1 ljwest@ualberta.ca 780-492-3200	• Pediatric cardiac transplantation and transplant immunobiology • Translation of basic science research concepts to clinical application in infants and children undergoing heart transplantation
	**Wim Wolfs** National Director of Research	The KIdney Foundation of Canada 5165 Sherbrooke Str Suite 300 Montreal, Quebec, H4A 1T6 wim.wolfs@kidney.ca 514-369 4806 ext. 225	The Kidney Foundation of Canada is the national volunteer organization committed to reducing the burden of kidney disease through: • funding and stimulating innovative research • providing education and support • promoting access to quality healthcare, and • increasing public awareness and commitment to advancing kidney health and organ donation.

	**Linda Wright** Director of Bioethics and Palliative Care	University Health Network, Joint Centre for Bioethics & Dept. of Surgery University of Toronto 585 University Avenue NCSB 11C1270 Toronto, Ontario, M5G 2N2 linda.wright@uhn.on.ca 416-340-4800x8750	• General ethical issues in healthcare such as resource allocation. • Ethical issues in organ donation including the study of international models of organ donation • Ethics in organ transplantation including transplant tourism • Ethical issues in donation from living donors, including Anonymous living organ donors. • Allocation of organs from deceased and living donors
	**Serdar Yilmaz** Medical Director	Foothills Medical CentreRoom 729 North tower, 1403- 29th St. Calgary, Alberta, T2N 2T9 serdar.yilmaz@albertahealthservices.ca 403 944 4266	• Chronic Rejection as well as the development of surrogate markers for Chronic Allograft Dysfunction • Designer of a real time relational database • Design and implementation of a Multi Organ Transplant database for use in routine day-to-day clinical practice and research

CIHR Staff

	**Paul Belanger** Assistant Director	CIHR Institute of Nutrition, Metabolism and Diabetes 160 Elgin St Ottawa, ON, K1A 0W9 paul.belanger@cihr-irsc.gc.ca 613-941-6465	
	**Judith Bray** Assistant Director	Institute of Infection and Immunity and Institute of Cancer Research 160 Elgin St Ottawa, ON, K1A 0W9 judith.bray@cihr-irsc.gc.ca 613-954-7223	
	**Diane Christin** Project Officer	Institute of Infection and Immunity and Institute of Cancer Research 160 Elgin St Ottawa, ON, K1A 0W9 diane.christin@cihr-irsc.gc.ca 613-941-0997	
	**Marilyn Derosiers** Deputy Director, Program Delivery	CIHR - Targeted Initiatives Branch 160 Elgin St Ottawa, ON, K1A 0W9 marilyn.desrosiers@cihr-irsc.gc.ca (613) 954-6242	

	**Serge Desnoyers** Assistant Director	CIHR-Institute of Infection and Immunity 2705, boul. Laurier, room TR-104 Québec, QC, G1V 4G2 serge.desnoyers@crchul.ulaval.ca (418) 656-4141 x46251	
	**Jaime Flamenbaum** Senior Policy Advisor	CIHR Ethics Office 160 Elgin St Ottawa, ON, K1A 0W9 jaime.flamenbaum@cihr-irsc.gc.ca 613-941-0836	
	**David Hartell** Associate, Institute Strategic Initiatives	Institute of Infection and Immunity and Institute of Cancer Research 160 Elgin St Ottawa, ON, K1A 0W9 david.hartell@cihr-irsc.gc.ca 613-941-4329	
	**Erik Landriault** Associate	Institute of Health Services and Policy Research 160 Elgin St Ottawa, ON, K1A 0W9 erik.landriault@cihr-irsc.gc.ca 613-946-3369	
	**Maura Ricketts** Consultant	Maura Ricketts Consulting 2280 Bowman Rd Ottawa, ON, K1H 6V6 maura.n.ricketts@cma.ca 613 986-7852	• health policy • use of evidence to develop health policy • integrating science with risk in the development of public health policy

AGENDA

Meeting: **CIHR Transplantation Workshop**
Date: **February 1-2, 2011**
Location: **Sheraton Hotel, Montreal - 1201 Boulevard Rene-Levesque West**
Room : **Salon A&B – basement level**

Initiative Goal: To support research leading to a paradigm shift in the Canadian transplantation field and improved clinical outcomes for transplant patients.

Workshop Objectives:

- Provide an overview of the Canadian transplantation field, identifying current challenges and opportunities;
- Identify key research areas that are not being adequately addressed through existing funding sources and mechanisms;
- Propose recommendations to III staff and the expert steering committee on the scope and focus of a range of potential **strategic** research initiatives that would improve the clinical outcomes in transplantation;
- Improve dialogue, networking and communication across the different research groups and research communities (pillars) involved in transplantation;
- Identify opportunities to leverage existing programs and resources; and
- Generate a consensus paper describing the observations, conclusions and future directions for Canadian transplantation

Facilitator: Judy Bray

Expert Working Group Members: Dana Devine, Amit Garg, Marie-Josée Hébert, Anthony Jevnikar, Kirk Schultz, Lori West

Participating CIHR Institutes:
Institute of Infection and Immunity (III)
Institute of Circulatory and Respiratory Health (ICRH)
Institute of Health Services and Policy Research (IHSPR)
Institute of Musculoskeletal Health and Arthritis (IMHA)
Institute of Nutrition, Metabolism and Diabetes (INMD)

Tuesday, February 1, 2011 - Meeting Room: Salon A & B

Time	Description	Moderator
8:00	*Breakfast – Salon C*	
9:00	**Welcome and Introduction of Steering Group**	Judy Bray
9:10	**Setting the Scene:** Overview of CIHR's strategic initiatives and potential alignment with the field of transplantation	Marc Ouellette
9:40	**Workshop Overview:** Goals and Objectives	Judy Bray/ Tony Jevnikar
9:50	**Solid Organ Transplantation:** Major challenges and opportunities	Lori West
10:10	**Hematopoietic Stem Cell Transplantation:** Major challenges and opportunities *Speakers: 15 minute presentations, followed by 5 minutes each for questions for clarification.*	Kirk Schultz
10:30	*Health Break – Foyer A,B,C*	
11:00	**Small Group Discussions**	
12:00	**Report Back from Tables**	
12:30	**Lunch –** *Salon C*	
13:30	**Inflammation and Transplantation:** What do we know?	Paul Kubes
13:50	**Transplant Tolerance in the Clinic:** The role of infection, monitoring and future challenges	Ken Newell
14:10	**Biomarkers and Omics:** Separating the hype and the hope	Bruce McManus
14:30	**The Problem with Current Therapeutics:** Evaluation models for the future *Speakers: 15 minute presentations, followed by 5 minutes each for questions for clarification.*	John Gill
14:50	*Health Break – Foyer A,B,C*	
15:20	**Small Group Discussions**	
16:20	**Report Back from Tables**	
16:50	**Summary and Closing Comments**	Marc Ouellette/ Tony Jevnikar
17:00	**Workshop adjourned**	
18:30	***Networking Reception followed by Dinner*** ***Le Restaurant Ariel - 2072 Drummond***	***All***

Wednesday, February 2, 2011 - Meeting Room Salon A,B

Time	Description	Lead
8:15	*Breakfast – Salon C*	
9:00	**Highlights of Day 1**	Maura Ricketts
9:15	**The Patient Perspective**	Kathryn Richardson Tyler Richardson
9:35	**The Canadian Transplantation Landscape:** Organizational Issues	Peter Nickerson
9:55	**How Can Deceased Organ Donation be Improved:** Issues and Challenges	Sam Shemie
10:15	**How Can Living Organ Donation be Improved:** Issues and Challenges *Speakers: 15 minutes presentations, followed by 5 minutes each for questions for clarification.*	Amit Garg
10:35	*Health Break – Foyer A,B,C*	
11:05	**Small Group Discussions**	
12:05	**Report Back from Tables**	
12:30	**Lunch –** *Salon C*	
13:30	**Break Out Sessions – by topic** Strategic planning and recommendations for specific research activities/initiatives	
14:30	**Report Back from Breakout Groups**	
15:00	**Plenary Discussion of Workshop Recommendations**	All
15:30	**Workshop Adjourned**	
15:30 – 16:30	**Steering Committee Meeting – planning the next steps**	

Appendix 3
Breakout Questions

Session 1

- Were there any topics/issues missing from the two talks that should be addressed?
- What are the common themes, challenges and barriers? What are the differences?
- Where are the potentially missed opportunities for collaboration between the fields of solid organ and hematopoietic stem cell transplantation? Are there opportunities to work differently, eg. through networks? Please give examples.
- What are the existing technologies, resources, and expertise that could be shared? What technologies, resources, and expertise are needed?

Session 2

- Was there anything missing from this series of talks that should be discussed?
- What are the most important opportunities, challenges and barriers in the biology of transplantation?
- What are the therapeutic opportunities closest to the clinic? What is the role of industry as partners in transplant-related research?
- What new technologies/ resources are needed for transplantation research and what existing technologies/ resources can be shared?
- What will it take to make Canadian transplantation research outstanding? What Canadian strengths could we harness to strengthen Canada's leadership position?

Session 3

- Was there anything missing from this series of talks that should be discussed?
- What are the key challenges and barriers to organ donation in Canada? How can they best be addressed?
- What are the lessons we can learn from other countries and how can we make them relevant in a Canadian context?
- Is this an area CIHR can address alone or are they key partners who need to be involved and who are they? How can they be engaged?

Session 4

- Based on all you have heard at this workshop, where are the best research opportunities to significantly advance the transplantation field in Canada within five years?
- What resources would be needed and where could they be found? What is feasible?
- What is the role for CIHR, and especially the Institute of Infection and Immunity, in moving the field forward?
- What kind of programs and funding structures are required that do not already exist in the CIHR open competition? What will be value added component of your recommendations?
- What outcomes do you expect in the short, medium and long term and how can they be measured?