Canadian National TRANSPLANT Research Program | Programme national de recherche en TRANSPLANTATION du Canada

Extended Progress Report

Canadian National Transplant Research Program

Year 2

Prepared by the CNTRP Executive Council
and the CNTRP Management Team

July 24, 2015

Table of Contents

The Canadian National Transplant Research Program Central Report

Director: Dr. Lori West, University of Alberta
Co-Director: Dr. Marie-Josée Hébert, Université de Montréal

The CNTRP: uniting the community

In January 2012, the Canadian Institutes for Health Research presented the transplant research community with a challenge: to bring the solid organ transplant (SOT), cellular transplant and donation/critical care research communities together into a national research program that would transform the field of transplantation and improve the health of Canadians. The research community responded to this challenge by building a national program that is not only innovative and unique in Canada, but that has also not been achieved elsewhere in the world.

The Canadian National Transplant Research Program (CNTRP) is a nationally funded research network that unites over 200 researchers, collaborators and trainees from 29 universities and institutions across Canada, representing the major health researchers from basic biomedical, clinical, health services/policy and population health arenas. The CNTRP weaves the solid organ transplant, cellular transplant and donation/critical care communities into a highly integrated national research coalition. The Program is led by Dr. Lori West, CNTRP Director at the University of Alberta, and Dr. Marie-Josée Hébert, CNTRP Co-Director at the University of Montreal.

The CNTRP develops new knowledge and health care practices to:

- Increase the availability of donors and access to transplants
- Extend the longevity of grafts
- Improve long-term survival and quality of life of transplant patients
- Develop and enhance the pool of talent in the transplant field
- Integrate and coordinate donation and transplantation research nationwide

The CNTRP is a uniquely Canadian initiative, drawing on our strength in scientific collaboration, our history of transplantation research, our publicly funded health care system, and the federal and provincial support and leadership provided to this initiative. The CNTRP framework is innovative and trans-disciplinary, nurturing synergistic and transformative collaborations that would not be possible without this interactive program structure.

Over the last two years, the major accomplishment of the CNTRP has been to create and nurture interactions and synergies across all levels of the program including:

- Uniting teams of basic and clinical scientists in organ and tissue donation, cellular transplantation, and liver, heart, lung, pancreas, and kidney transplantation, as well as health economics, legal and ethics researchers, policy experts and knowledge users into a dynamic research coalition focused on six thematic projects and supported by three comprehensive cores.
- Bringing both junior and senior investigators into the program to collaborate on important studies, including clinical trials.

- Creating linkages with industry, health charities and provincial and federal governments to leverage additional research funding and to disseminate new knowledge.
- Linking the pediatric, adolescent and adult transplant programs across the country to participate on several multicenter studies and share samples and data.
- Engaging patients and citizens to share their expertise and experience in donation and transplantation and by beginning to integrating them into the structure of the program.
- Developing provincial, federal and international partnerships to overcome research barriers and begin sharing research data.
- Working and interacting in both French and English to unite colleagues across the country and disseminate new knowledge in both languages.

Since 2013, the CNTRP is working to combine the efforts of the researchers across the country to solve the prevailing problems in organ donation and transplantation, and to provide the best health care for people with life-threatening diseases. The CNTRP is positioning Canada as a world leader in transplantation research and is on track to build an enduring legacy that will transform the transplant field.

Expanding the CNTRP:

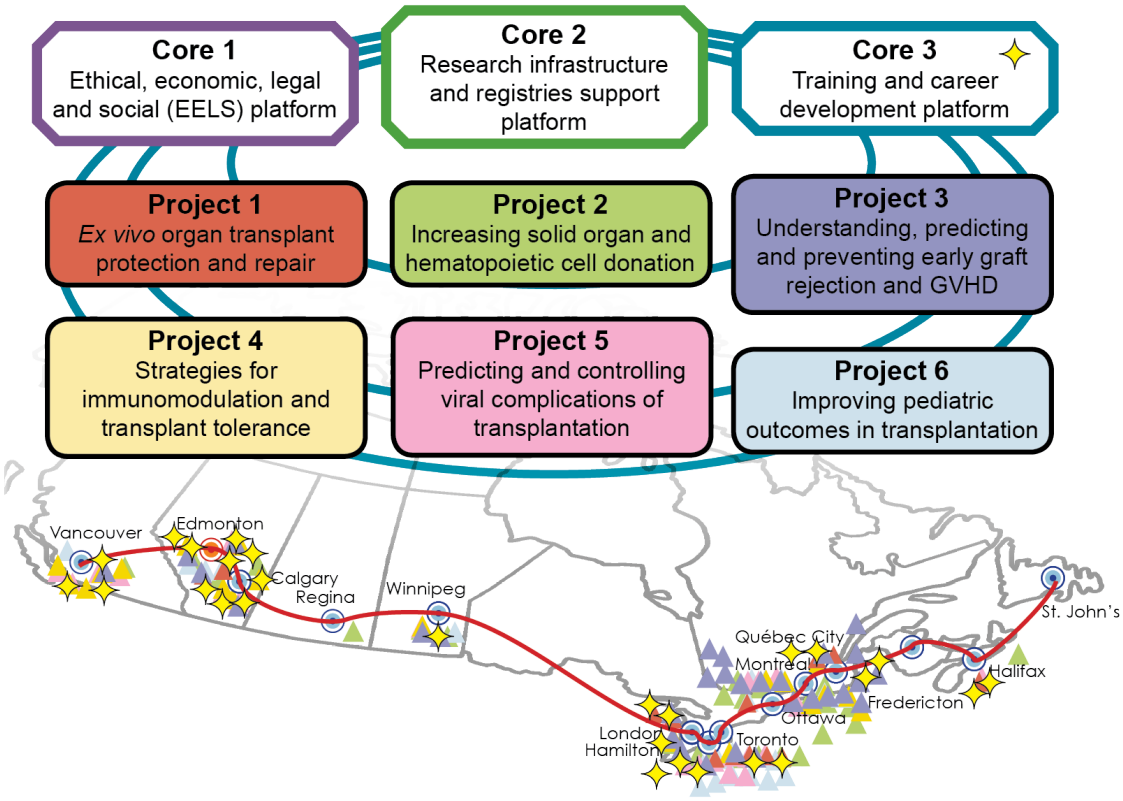
Since December 2012, the number of participants in the CNTRP has increased from 210 to 358 individuals. CNTRP by the numbers, compared against our numbers from December 2012:

- 139 Researchers, including 12 Canada Research Chairs[1] (+34)
- 112 Collaborators (+35)
- 64 stakeholders (patients, partners, industry, health charities) (+36)
- 28 Trainees (+28)
- 8 Program/Project Managers (+7)

The CNTRP is currently comprised of 6 projects and 3 core platforms made up of over 35 interconnected sub-projects or sub-aims.

Project 1: *Ex vivo* organ transplant protection and repair
Project 2: Increasing solid organ and hematopoietic cell donation
Project 3: Understanding, predicting, preventing early graft rejection and GVHD
Project 4: Strategies for immunomodulation and transplant tolerance
Project 5: Predicting and controlling viral complications of transplantation
Project 6: Improving pediatric outcomes in transplantation
Core 1: Ethical, economic, legal and social (EELS) platform
Core 2: Research infrastructure and registries support platform
Core 3: Training and career development platform

[1] **List of Canada Research Chairs (CRCs) in the CNTRP**: Tim Caulfield, Patrick MacDonald, Dan Muruve, James Shapiro, Lori West, Jeremy Grimshaw, Lucie Germain, Quim Madrenas, Tommy Nilson, Claude Perreault, Jean-Claude Tardif, Pierre Thibault



One of the early changes to the structure of the CNTRP was the decision to move the training program out of **Core 2** and officially become a new **Core 3** to focus entirely on academic and professional training and career development. In March 2013, Dr. Lee Anne Tibbles was appointed as the Lead for **Core 3**; Drs. Silvy Lachance and Sonny Dhanani were recruited as co-Leads for **Core 3** to share their expertise and leadership from the hematopoietic cell transplant and critical care/donation perspective. The three Leads of **Core 3** represent the three distinct communities of the CNTRP – solid organ transplant, hematopoietic cell transplant and donation and together they worked to create a platform to serve the entire CNTRP and Canadian academic and research community.

In order to operationalize and enable collaboration across institutions and across provinces, the first major task of the CNTRP was to develop a series of operational policies, a governance structure, financial reporting system and working committees. The CNTRP worked closely with the Research Services Office at the University of Alberta to draft a comprehensive legal coalition agreement that would set the terms for how all CNTRP investigators would collaborate, share results and publish together. The coalition agreement took over a year to create and another year to fully execute but now has been signed by 29 participating institutions in 9 provinces. The following CNTRP policies were drafted and ratified over the past two years and have now been put into practice:

- Publication
- Data sharing
- Conflict resolution
- Project evaluation and progress reporting
- Financial reporting
- Intellectual property
- Adding new projects and people into the CNTRP

Five committees were established to facilitate the operations of the CNTRP, including:

- New Initiatives Committee – Chaired by Dr. Tom Blydt-Hansen
- Evaluations and Project Support Committee – Chaired by Dr. Bethany Foster
- Academic Training Support Committee – Chaired by Dr. Lee Anne Tibbles
- CNTRP Management Support Committee – Chaired by David Hartell
- Patient Engagement Committee – Chaired by Dr. Marie-Chantal Fortin

The New Initiatives Committee makes recommendations to the CNTRP Executive about new research and funding opportunities, expanding the scope of existing projects or cores, and developing new collaborations and partnerships that will benefit and expand the scope of the CNTRP. It supports the process for new investigators to join existing CNTRP programs and cores, and to establish new collaborations, including letters of support for new project applications seeking external funding. The major accomplishments of this committee include:

- Hosting the first "*New Initiatives Research Session*" during the 1st CNTRP Annual Scientific Conference, allowing members of the research community to propose new research ideas for collaboration with the CNTRP that resulted in three new sustained partnerships.
- Developing and launching three research grant competitions in partnership with Astellas Pharma Canada, Inc., the Canadian Society of Transplantation, the Alberta Transplant Institute, and the University Health Network in Toronto that together provide $250,000 in new peer-reviewed funding to bring new projects into the CNTRP. To date, we have funded five new pilot grants that are now part of the CNTRP and expect to fund five new projects this fall.
- Drafting and implementing the terms of reference for bringing new projects and investigators into existing CNTRP projects, bringing established research projects into the structure of the CNTRP, and working with investigators to develop new ideas and seek new funding opportunities to bring new projects into the CNTRP.
- Discussions about creating a new CNTRP **Project 7** focusing on improving outcomes for transplant patients. This new project would bring in several new projects and investigators into the CNTRP including Dr. Maureen Meade and Dr. Frederick Daragon from the ICU community to lead a project on donor intervention studies as well as a project on rehabilitation exercise therapy for pre- and post-transplant patients.
- Through the support of the NIC, the following projects have been added to the CNTRP:

Exercise Rehabilitation Therapy: The Canadian Network for Rehabilitation and Exercise for Solid Organ Transplant Optimal Recovery • Drs. Sunita Mathur and Tanya Janaudis-Ferreira – University Health Network Toronto • Part of a new Project 7 examining long-term outcomes of transplantation • CIHR funded	***Randomized Controlled Multicentre Trial of Ex Vivo Oxygenated, Normothermic Liver Perfusion (OrganOx Metra) Compared to Standard Cold Storage in Clinical Liver Transplantation*** • Dr. James Shapiro (University of Alberta) and Dr. Markus Selzner (University Health Network Toronto) • New clinical trial in Project 1 • New funding from the Alberta Transplant Institute, the University Health Network Toronto, Astellas and the CNTRP
Improving Neurological Death Diagnosis • Dr. Michaël Chassé – Ottawa Hospital Research Institute • New Aim 5 for Project 2 • CIHR funded	***Optimizing autologous anti-EBV T-cell lines from seronegative patients for adoptive immunotherapy; a pre-clinical study*** • Dr. Jean-Sébastien Delisle – Hôpital Maisonneuve-Rosemont • New Aim 4 of Project 5 • Recipient of 2014 CNTRP/Astellas grant

Non-invasive diagnosis of nonalcoholic steatohepatitis in liver transplant recipients: a prospective, longitudinal study employing serum citokeratin 18 and transient elastography • Dr. Giada Sebastiani - McGill University • New sub-aim of Project 3 • Recipient of 2014 CST/Astellas grant	***ABO Immunobiology and Glycobiology in Organ and Cell Transplantation*** • Dr. Lori West and Dr. Todd Lowary – Univ. of Alberta • New sub-aim of Project 4 • Funded by CIHR, Heart and Stroke Foundation and Alberta Glycomics Centre/GlycoNet
Detection of Cardiac Allograft Vasculopathy Using Myocardial Contrast Perfusion Imaging: A Multicenter Study in Adult and Pediatric Transplant Recipients • Dr. Nowell Fine – University of Calgary • New sub-aim of Project 4 • Recipient of 2014 CST/Astellas grant	***The BK: KIDNI Trial (BK: Kinase Inhibition to Decrease Nephropathy Intervention Trial)*** • Dr. Lee Anne Tibbles – University of Calgary • Ongoing clinical trial now part of Project 5 • CIHR funded
Tracking a Pneumoncystis jirovecii pneumonia outbreak in solid organ transplants in Canada: Case-control study • Dr. Seyed Hosseini – University of Western Ontario • new piece of Project 5 • will receive funding from Project 5	***Pharmacogenomic-guided immunosuppression in pediatric transplant recipients*** • Dr. Seema Mital – Hospital for Sick Children • Additional sub-aim of Project 6 • Astellas funding
Urinary markers of intra-renal renin angiotensin system activity in renal allograft recipients • Drs. Joe Kim and Ana Konvalinka – University Health Network Toronto • New sub-aim of Project 3 • Recipients of 2014 CNTRP/Astellas grant	***Extreme Phenotypes of PTLD*** • Dr. Upton Allen – Hospital for Sick Children, Toronto • New piece of Project 5 & 6 • Funding from Enduring Hearts Inc. (USA)
Thymic Regulatory T Cells as a Therapeutic Tool for Islet Xenotransplantation • Dr. Lori West and Dr. Esmé Dijke – University of Alberta • Project 4 • Funding from the Alberta Diabetes Institute	

Building excellence through partnerships

One of CNTRP's key objectives is to integrate and coordinate transplantation research nationwide; much of this work is accomplished by developing strong partnerships. Since the launch of the CNTRP, the program has worked closely with our provincial/regional, federal and international partners, including industry, governments, funding agencies and health charities, to strengthen and enhance our national research efforts. New partnership activities are under constant development as we seek to expand the CNTRP effectively.

To support the research performed by the CNTRP, we have developed integral partnerships with several international companies who provided funding and equipment, reagents, training, and/or personnel. For example:

- Beckman Coulter Life Sciences partnered with the CNTRP on our immune monitoring initiative, part of **Core 2**, to help standardize how we organize, analyze, and share data across Canada on immune parameters in transplant patients. Beckman Coulter provided three CNTRP research labs with new NAVIOS 10-colour Flow Cytometers, funded access to two clinical NAVIOS machines, provided on-site set up and training, a substantial discount on the flow panels developed by the ONE Study consortium and the ability to develop our own custom CNTRP panels. Only through this partnership was the CNTRP able to develop a comprehensive standardized immune monitoring strategy that is now being implemented in our studies and trials across the country.
- Kiadis Pharma is partnering with the CNTRP on our CARE Trial, part of **Project 4**, by providing the TH9402 photosensitizer and shipping and installing two Theralux devices in each of our three cell processing centres. Additionally, Kiadis is assisting with obtaining Health Canada approvals and will analyse intracellular TH9402 concentration in PDT-treated cells during the trial.
- Professor Peter Friend's group at Oxford University, together with their spin-off company OrganOx, have developed a portable normothermic liver perfusion device called the Metra and are partnering with CNTRP **Project 1** to launch the *Ex Vivo* Normothermic Liver Perfusion Randomized Clinical trial in three sites across the country. OrganOx is providing the CNTRP with considerable in-kind contribution by way of subsidized perfusion circuits and Metra devices to allow these studies to move forward in Edmonton, London and Toronto.

As previously mentioned, the CNTRP has launched several research innovation grant competitions to bring new funding to the research landscape in Canada. The partners for the research grant competition include Astellas Pharma Canada, Inc., the Canadian Society of Transplantation, the Alberta Transplant Institute and the University Health Network. Together these partnerships have generated $250,000 in new funding for the research community.

Several partners have supported our meetings and symposia, including Alexion Pharma and several of the Institutes from the Canadian Institutes of Health Research.

Beyond new funding partnerships, the CNTRP is striving to unite the research community and forge important relationships with patient groups, national stakeholders, professional societies, and research programs to increase the impact of the CNTRP.

- To strengthen links between the SOT, cellular transplant and donation communities, the CNTRP co-hosted our Annual Scientific Meetings with each of the major professional societies representing these communities including the Canadian Society of Transplantation (SOT) March 2013 in Banff, the Canadian Blood and Marrow Transplant Group (cellular transplant) June 2014 in Halifax, and the Canadian Critical Care Trials Group (donation) June 2015 in Montebello. By co-hosting our meetings with these professional societies, the CNTRP initiated new conversations and brought together groups of researchers who typically would not attend the same meetings.
- Beyond these three main communities, the CNTRP is also developing new partnerships with CellCAN, the national network representing the five GMP cell processing facilities in Canada, and with GlycoNet, the new national glycomics research network, by co-developing training webinars, creating new research proposals and exploring joint funding opportunities to unite our research communities.
- The CNTRP entered into formal partnership in April 2014 with the Montreal Health Innovation and Coordination Centre (MHICC) to act as the Academic Research Organization (ARO) for the CNTRP. The MHICC will work with Core 2 to provide design, analysis and infrastructure support for upcoming CNTRP trials and will help implement the CNTRP Patient Registration Database.
- One of the most important partnerships for the CNTRP is the relationship with the Canadian Transplant Association (CTA), the patient advocacy group comprised of transplant recipients, athletes and volunteers dedicated to promoting organ donation through public advocacy and events. The CNTRP is working closely with the CTA to develop our patient engagement strategy. The CTA has greatly supported our work by promoting the patient research priorities survey, sharing our research results and helping organize our two patient engagement workshops. We will continue to work closely with the CTA to support the upcoming Canadian Transplant Games in 2016 and continue bringing patients' priorities of the forefront of CNTRP research endeavours.

Translating our research

The CNTRP has sought to embed knowledge translation and communication into the basic structure of the program; we work to refine custom knowledge exchange strategies for each of our major initiatives. A priority for the CNTRP Central Management Team is to ensure that all levels of the program, our researchers, our trainees, the patients, our collaborators, our funders and partners and the general public are informed about recent and upcoming research developments in the field of donation and transplantation. In managing such a large complex research network, it was important to develop multiple lines of communication across the program:

- Our primary source of dissemination is through academic peer-reviewed publications and presentations at local, national and international conferences (see attached list of publications).
- To inform our research community internally and share the most recent published research and clinical knowledge, the CNTRP partnered with Sosido (www.sosido.com), an online network for healthcare professionals that connects members within a specialty community

and broadcasts important work across silos of centre, discipline and disease. Through Sosido, the CNTRP broadcasts a weekly newsletter that includes important program updates and a list of all recently published academic articles from CNTRP researchers.

- The CNTRP created and actively updates our public website www.cntrp.ca. This site provides a space to share information about our program, new research results, information about research grant competitions, upcoming events and important CNTRP publications.
- The CNTRP has developed a private website for CNTRP members to share data, protocols, presentations, draft publications, webinars, contact information and policies.
- To engage with researchers, journalists, patients, advocacy groups, health charities, government officials, and members of the general public, the CNTRP has been active on twitter by sharing new CNTRP-generated knowledge, new publications, our 'Fast Policy Facts', social commentary, and news stories. Since joining twitter, the CNTRP generated 267 active followers, posted 410 tweets, was retweeted 120 times, mentioned 197 times, and actively engaged 1,633 individuals. Several of our CNTRP members, including Tim Caulfield (@caulfieldtim) and Jennifer Chandler (@jnfrchandler) are highly active on Twitter and use the medium for enthusiastic promotion of CNTRP work. The CNTRP Facebook page has reached over 1600 individuals and engaged with 182 members of the public.
- The CNTRP has actively engaged journalists and publishers to promote the important work originating from the CNTRP and our research has been featured in over 30 print, newspaper, online, radio and TV news stories, including the Globe and Mail, Le Devoir, the National Post, le Canal Savoir, Canadian Health and Lifestyle Magazine, CBC Radio, CBC Television and CBC Online, Reuters US, Global TV, CTV News, the Edmonton Sun, Edmonton Journal, MacLean's Magazine, Telequebec, Radio Canada and Metro News. (www.cntrp.ca/media)
- The CNTRP is working closely with two award-winning independent documentary filmmakers, Rosie Dransfeld and Dr. Niobe Thompson, on two new transplant film projects that are currently in production, as well as on a national social media campaign to increase organ donation. The first film is a point of view (POV)-style full-length feature documentary on donation, set for theatrical release. This film is being co-produced with the National Film Board of Canada with filming to begin in Sept. 2015 at the University of Alberta. The second film will focus on the science of transplantation for CBC's science series *The Nature of Things* that will feature groundbreaking and innovative work undertaken by CNTRP researchers.

Next Steps:

As CNTRP prepares for its 3rd year of funding, the focus for the program will be on integrating patients, families and caregivers into the structure of the CNTRP, exploring additional international partnerships and collaborations, and building the framework with our research community to secure long-term and renewable funding for the CNTRP.

Publications and Presentations

See attached list of publications and presentations.

Project 1 - *Ex vivo* organ transplant protection and repair

Lead: Dr. A.M. James Shapiro, University of Alberta
Co-Leads: Dr. Markus Selzner, University Health Network and Dr. Darren Freed, University of Alberta

Original aims/sub-aims and changes

Project 1 represents the national pre-clinical and pilot study of *ex vivo* oxygenated perfusion modalities for organ preservation and repair, with a focus on the elimination of cold ischemic organ preservation, across the following five (5) major transplant organs:

- Heart (Dr. Freed, Edmonton; Dr. Badiwala, Toronto)
- Lung (Dr. Nagendran, Edmonton)
- Liver (Dr. Selzner, Toronto; Dr. Alwayn, Halifax; Dr. Shapiro, Edmonton)
- Kidney (Dr. Luke, London; Dr. Selzner, Toronto)
- Pancreas (Dr. Shapiro, Edmonton; Dr. Paraskevas, Montreal)

Through collaboration, investigators have worked to optimize this new technology by leveraging organ commonalities while respecting physiologic differences that require organ-specific approaches. The team is driven by the desire to increase transplant organ availability and utility by reducing organ injury caused by current transplantation processes and through the possible perfusion of reparative compounds to organs *ex vivo* that will reduce recipient exposure and risk.

Global Aims:

- The use or development of *ex vivo* oxygenated perfusion systems to diagnose, protect and repair organs across all five transplant organ areas.
- Restoration of physiologic organ support promptly after donor removal until recipient receipt.
- Increase utilization and improve outcomes of injured organs for transplantation.
- Elimination of cold ischemic organ preservation.
- Increase the quality of transplantable organs to Canadians with end-organ failure.
- Increase use of “marginal’ and “donation after cardiac death” (DCD) organs for transplant.
- Pre-clinical testing of drugs to protect/repair organs during *ex vivo* perfusion (BMX, F573, AAGP) using animal organs and unused (“discard”) human organs.

Sub-Aims (Organ-specific):

Heart

- Establishing preclinical *ex vivo* protocols for cardiac perfusion in a pig transplant model.

Lung

- Completion of clinical trial enrolment (INSPIRE trial; OCS lung TransMedics machine).
- Investigating marginal lungs protected on OCS for clinical transplantation.

Liver

- Establishing preclinical *ex vivo* optimization of liver perfusates in pig transplant model.

- Establishing a working, survivable transplant model to test injured and repaired *ex vivo* livers.
- Investigating novel delivery of hemoxygenase-1 (HO-1) for transfection in mouse models.
- Multi-centred clinical study of a portable *ex vivo* normothermic oxygenated perfusion system (OrganOx).

Kidney

- Development of an *ex vivo* normothermic oxygenated perfusion system.

Pancreas/Islets

- Investigating novel approach(s) to preserve pancreas organs in transit for islet isolation.

Changes:

- The OrganOx pilot and randomized trials are new initiatives not originally part of the CNTRP budget infrastructure.
- New project focused on normothermic *ex vivo* kidney perfusion for marginal kidney grafts.
- Investigation into the delivery of the recombinant protein sHO-CPP in mouse model islet cells.

Major accomplishments

Clinical

- Four (4) clinical trials (INSPIRE; OrganOx; BMX and Giner) are currently active.
- INSPIRE RCT has completed enrolment – 17 subjects from the Alberta site.
- 4 subjects have received islet transplants under the Giner Persufflator protocol.
- 5 subjects have received islet transplants using the BMX protocol.
- 4 patients have now undergone successful liver *ex vivo* perfusion in Edmonton using the OrganOx device, and all continue to do well with normal liver function; two of the four livers were derived from DCD donors.
- Development and Health Canada approval of a multi-center randomized trial for liver *ex vivo* perfusion during transplant in Edmonton, Toronto and London.

Pre-Clinical

- The development of an *ex vivo* mutli-organ repair centre at the Abacus facility in Edmonton.
- Set-up of an *ex vivo* gene perfusion facility in the Heritage Medical Research Centre.
- Development of a model of normothermic *ex vivo* kidney perfusion establishing that prolonged perfusion can be performed without detectable kidney injury and with stable kidney function.
- Demonstration that recombinant protein sHO-1-CPP penetrates zones 1-3 of the liver during these *ex vivo* conditions and is functional.
- Completion of studies on the optimal resuscitation of hearts from DCD donors, in pig model.
- Anti-inflammatory agent CORM401 minimizes kidney injuries and improves kidney function upon normothermic whole blood reperfusion.

Interactions within the project

As previously noted, investigators have committed to collaborate in order to optimize this new technology by leveraging organ commonalities. Project 1 galvanizes cooperation and synergy

between institutes at the University of Alberta, University Health Network (UHN) – Toronto, McGill University, Dalhousie University and London Health Sciences Centre, which would likely not occur otherwise. Building our platform as a bridge between these Institutes draws additional expertise to our team, and has the added advantage of engaging a large cadre of students, fellows and other trainees across all aspects of our CNTRP project; such interactions include:

- The group has been successful in securing a CFI grant to help establish a multi-organ perfusion centre in the Abacus facility at Level 0 of the Mazankowski Heart Institute in Edmonton.
- The group has been successful on a University Hospital Foundation grant to examine gene therapy in the setting of *ex vivo* perfusion and is being set up in the Heritage Medical Research Centre with operational approval already obtained and renovations being done.
- Collaboration in the set-up of pig kidney *ex vivo* models in Edmonton, London and Toronto.
- The adaptation of the system developed by Dr. Freed for *ex vivo* lung, liver, heart and kidney perfusion.
- Initiation of experiments to assess the ability of recombinant protein sHO-1-CPP to penetrate murine pancreatic islets obtained from Dr. Shapiro's lab.
- Assessment of mtDAMPs during *ex vivo* (sub)normothermic pig liver perfusion obtained from Dr. Selzner's lab.
- Knowledge transfer and training between Edmonton's Clinical Islet Lab (CIL) and the McGill University Health Centre Human Islet Transplant Laboratory (MHITL)

Interactions across the CNTRP

The interdisciplinary approach to research has helped achieve the team's objectives through synergies between **Project 1** and **Project 3** as follows:

Islet:

Collaboration in investigation of death and tissue inflammation pathways, and an ability to control these effectively, is essential to further advancements in clinical islet and potentially surrogate beta cell transplantation:

- The Shapiro lab has been collaborating with Prof. Andreas Linkermann in Germany to investigate the role of novel cell death pathways including necroptosis and ferroptosis. Extensive testing of ferrostatin-1 and induction of ferroptosis with erastin is revealing important data.
- The Shapiro group has been testing a clinical caspase inhibitor (IDN-6556) in patients receiving islet transplants, and 12 subjects have been enrolled to date. Samples of islets, supernatants and serum blood samples have been collected from these and other islet patients in Edmonton to be batch-shipped to Dr. Marie-José Hebert in Montreal for investigation of DAMPs, autoantigen reactivity, and other potential biomarker studies.

Liver:

- Perfusate and bile output samples have been collected systematically by the Selzner and Shapiro groups for potential collaboration with **Project 3** members studying patterns of molecular injury.
- Dr. Alwayn's group in Halifax NS has been investigating ischemia-reperfusion injury and mitochondrial damage patterns in mouse models. Importantly their mechanistic studies, with ongoing collaborations between **Project 1** and **Project 3** members, have demonstrated that release of mitochondrial DAMPs is able to induce downstream damage and inflammation at distant organ sites.

- A planned collaboration between Dr. Alwayn and Dr. Eric Boillard from **Project 3** at Laval University will further address extracellular vesicle reactivity in mouse models.
- Dr. Hébert is in the process of devising standard operating procedures in **Project 3** for specimen collection at specified time points. The goal is to collect systematically a library of materials from Project 1 perfused organs in different settings, to further understand patterns of cellular injury and opportunities for future protection of transplanted organs.

New research & collaborations

As studies have yielded results or outcomes, directions for further research and collaborations have presented themselves, theses include:

- The OrganOx pilot and randomized trials are new initiatives not originally part of the CNTRP budget infrastructure.
- New project focused on normothermic *ex vivo* kidney perfusion in Toronto for marginal kidney grafts.
- Investigation into the delivery of the recombinant protein sHO-CPP in mouse model islet cells.
- A planned collaboration between Dr. Alwayn and Dr. Boillard at Laval University will further address extracellular vesicle reactivity of perfused organs in different settings, to further understand patterns of cellular injury and opportunities for future protection of transplanted organs.
- There are currently negotiations with Alberta Health Services and Alberta Health & Wellness to find ministry funding for on-going support of the *ex vivo* OrganOx liver perfusion program.
- Investigation in Toronto into liver graft modification using subnormothermic *ex vivo* liver perfusion of micro RNA targeted against Hepatitis C virus replication as a novel strategy against hepatitis C infection during transplantation.
- Study in Edmonton of the metabolic state of the heart during *ex vivo* heart perfusion, with an emphasis on provision of metabolic substrates and mediators that will likely have an important role in supporting safe extended *ex vivo* heart perfusion.

Next Steps (Year 3 plan)

Heart

❖ **Dr. Freed - Edmonton:**

- Completion of the ongoing metabolic studies with the ex vivo perfused heart.
- Initiation of a DCD heart and lung donation large animal model (ethics nearly approved).
- Employing our previous findings on resuscitation of the DCD heart (completed in Winnipeg) with a view to transplantation of the resuscitated, ex vivo perfused, DCD heart.
- Initiation of ex vivo perfusion of the neonatal heart (ethics approved).
- Initiation of a neonatal DCD heart donation protocol (ethics nearly approved).

❖ **Dr. Badiwala - Toronto:**

- Treatment of dysfunctional hearts, from a porcine model of brain death, with targeted therapeutics during EVHP.
- Evaluation of pharmacologic therapies such as L-Arginine, Adenosine, Bosentan, and Nrf2 induction with Sulforaphane on their abilities to repair dysfunctional hearts.
- Evaluate of the effect of these interventions on coronary vascular/endothelial function in

addition to overall cardiac function.
- Parallel experiments using non-utilized dysfunctional human hearts.
- Recovering of hearts from DCD donors, with EVHP, and evaluating their potential for repair and use for transplantation in a porcine model of heart transplantation.

Lung

❖ **Dr. Nagendran - Edmonton:**
- Clinical use of the TransMedics Lung OCS device at the University of Alberta.
- Expand experience with DCD procurement using ex-vivo lung perfusion.
- Use of the Lung OCS for extended criteria marginal donor lungs for clinical transplantation.
- Training of lung transplant surgeons at the University of Manitoba on application of the Lung OCS.
- Non-viable donor lungs will be perfused with the attempt to improve function and repair damage in a pre-clinical setting.

Liver

❖ **Dr. Selzner - Toronto:**
- Optimizing hepatic artery flow during subnormothermic ex vivo liver perfusion by comparing prostacyclin, BQ123, and Verapamil as vasodilators
- Graft modification by inducing resistance against Hepatitis C infection using micro RNA during subnormothermic ex vivo kidney perfusion
- Graft Assessment by determining Rocuronium and Midazolam metabolism during subnormothermic ex vivo liver perfusion
- Pilot clinical trial of normothermic ex vivo liver perfusion for liver transplantation
- Assessment of normothermic ex vivo kidney perfusion for the storage and repair of kidney grafts in heart beating and DCD pig kidney transplant models

❖ **Dr. Alwayn - Halifax:**
- Process samples from pig DCD liver perfusions and transplants for mtDAMPs (Alwayn/Selzner)
- Process same from pig kidney perfusions (Alwayn/Selzner)
- Further elucidate role and mechanisms for mtDAMPs in IRI (Alwayn/Boilard – project 3)
- Provide sHO-1-CPP for islet transplantation (Alwayn/Shapiro)
- Validate sHO-1-CPP in vivo IRI (Alwayn)

❖ **Dr. Shapiro - Edmonton:**
- Complete OrganOx Metra pilot clinical trial and begin RCT (including marginal graft arm) at 3 sites: Edmonton, Toronto, London.
- Pig livers and human “discard’ livers by ex vivo perfusion device optimization. Optimize perfusate in the pig ex-vivo model.
- Pre-clinical testing of protective modalities: Anti-oxidants (BMX), caspase inhibitors (F572, IDN-6556), glycol-peptide (AAGP).

Kidney

❖ **Dr. Luke - London:**
- Compare DCD-type donor condition vs. non-DCD (NDD) kidneys
- To identify optimal thermal and oxygenation conditions for both hypo- and normothermic storage
- To see the effect of washed/filtered blood based normothermic (36^0C) vs. KPS solution based hypothermic (4^0C) perfusion

- To determine if an anti-inflammatory agent CORM401 added to the cold KPS perfusion solution can minimize kidney injury upon washed blood reperfusion

Pancreas/Islet

❖ **Dr. Paraskevas - Montreal:**

- Increased Number of pancreases retrieved in Québec using the P3S Persufflator.
- Both Marco Gasparrini and Craig Hasilo will assist in back table trimming and connection of the pancreas vasculature to the P3S, as well as operating the P3S unit and troubleshooting any problems that may arise.
- Optimizing of already implemented by Transplant Québec an algorithm for pancreas allocation to both our site at the MHITL in Montréal, and in Edmonton.
- For pancreases that may be transported to the CITL in Edmonton, AB, a courier will be required to accompany the P3S unit in transit.
- Marco and Craig will be on call and alternate being on stand-by for retrievals at any site in Québec and fly to Edmonton.

❖ **Dr. Shapiro - Edmonton:**

- Complete Giner Persufflator clinical trial - pilot study (DBD & DCD); perform analysis; obtain ethics/Health Canada approval for RCT and initiate RCT.
- Complete BMX-010 clinical trial - pilot study; perform analysis to determine whether to proceed with RCT using BMX-010, or if to switch to BMX-001.
- In vitro and islet transplant models to test “protective’ effects of glycol-peptide AAGP, caspase inhibitor F573, and anti-oxidant BMX in islet transplantation; continue Silicone Membrane Flask validation.

Publications and Presentations

See attached list of publications and presentations.

Project 2 - Increasing solid organ and hematopoietic cell donation

Lead: Dr Greg Knoll, Ottawa Hospital Research Institute
Co-Leads: Dr Sam Shemie, McGill University & Linda Wright, University Health Network

Original aims/sub-aims and changes

The CNTRP provides a unique opportunity to study important issues in donation with immediate clinical impact on increasing, in a low-risk and ethical manner, the number of organs available for transplant. **Project 2** focuses on aspects of organ donation for which Canadian data are lacking, with the expectation that this research will have an immediate impact on patients waiting for transplantation. The research aims of this project address multiple aspects critical to successful organ and cell donation including: public attitudes and opinion, appropriate legal and ethical frameworks, and novel epidemiological and clinical research investigations. Although not specified in each aim, Project 2 encompasses issues relevant to both pediatric and adult donation.

5 Aims of Project 2:

- **Aim 1:** Define national strategies for recruitment of organ and HSC donors
- **Aim 2:** Minimize the risk and understand outcomes for new types of living kidney donors
- **Aim 3a&b:** Monitor the physiology of death following withdrawal of life-sustaining therapies and predict the time of death following withdrawal of life-sustaining therapies (WLST)
- **Aim 3c:** Knowledge translation (KT) intervention to increase donation after cardiac death (DCD) in Canada
- **Aim 4:** Enhance and optimize use of 'increased risk' deceased donors
- **Aim 5:** Improving neurological death diagnosis

Aim1 is focusing, to this point, on the issue of family override and on helping to develop the CNTRP patient engagement strategy, in partnership with **Core 1**. **Aim1** will also investigate systems of incentives for organ donation and study ethical issues and disparities in public solicitations for organs and tissue. For the family override study, **Aim1** investigates the legal and ethical issues in this override, specifically the moral weight attached to the wishes of the deceased and of the family; the responsibility of healthcare professionals to respect a registered wish to be an organ donor and the reasons for the override.

The goal of **Aim2** is to minimize the risk and understand outcomes for new types of living kidney donors. Specifically, to 1) determine if it is safe for individuals with risk factors (expanded-criteria donors, e.g. older age, obesity, abnormal glucose) to become living kidney donors, and 2) compare psychological outcomes between standard-criteria donors, paired-exchange donors, and anonymous donors. This will be done through continued follow up of living kidney donor participants, conducting medical chart audits for recipients, and maintaining the database for the Living Kidney Donor study.

The goal of **Aim3a&b** is to successfully predict which patients, who are eligible for DCD and undergoing WLST, will die within a time period to enable them to be donors and determine the

time intervals, after cardiac arrest, associated with the disappearance of key cardiocirculatory and neurological measures and to describe the frequency with which there is an unassisted, spontaneous return of these measures. This will be achieved by conducting observational studies in 13 Canadian ICUs to determine the natural history of cessation of physiological function, after WLST, in adult and pediatric patients who are eligible for DCD.

Aim3c is working to understand the discrepancy in the utilization of DCD across Canada. Since 2006, DCD has grown in many Canadian provinces while remaining stagnant or not used at all in some regions and the reasons for the wide discrepancy in DCD usage remain unknown. **Aim3c** is identifying stakeholder (clinicians and donor coordinators) beliefs and attitudes to DCD, developing a knowledge translation intervention based upon these beliefs and will then implement the intervention nationally with the ultimate goal to sharply increase numbers of available donors.

The overall objective of **Aim4** is to determine why certain deceased donor organs are not used for transplantation, evaluate the outcomes of organs deemed "increased risk" from either a graft failure or transmissible disease point of view, and to expand the use of these organs in an ethical way. As a group, we will:

- Assess the determinants of use or non-use of organs from deceased donors offered to Canadian transplant centres;
- Evaluate the outcomes of organ transplants from deceased donors perceived to be at increased risk for graft failure or transmissible diseases and;
- Define the optimal ethical framework for the use of organs from "marginal" or "increased risk" deceased donors.

We recently added the new **Aim5** to Project 2 to improve the neurological death determination (NDD) process by establishing accurate ancillary test(s) as a reference standard(s) for NDD. This CIHR funded study is led by Dr. Michaël Chassé at the Ottawa Hospital Research Institute and is being brought into Project 2 to:

1. investigate the accuracy of currently used ancillary tests;
2. explore the views of Canadian practitioners involved in NDD the use of ancillary test for NDD, NDD diagnostic practices and their opinion regarding NDD;
3. understand clinician, families and caregivers' satisfaction/dissatisfaction regarding the NDD process.

Major accomplishments

Aim1 completed the literature review on family overrides and is now analyzing this data. The team has also completed a media review on the topic and is presenting the data at upcoming conferences. In collaboration with Trillium Gift of Life Network, Aim 1 is examining the prevelance of family veto and reviewing decision-making processes of families. Educational initiatives and changes to practice are being examined.

Aim2 successfully recruited 820 standard-criteria donors, 150 expanded-criteria donors, 104 paired-exchange donors, and 68 anonymous donors and conducted medical-chart audits for 756 recipients from centres across Canada. The study will now begin to collect data measuring the 3-year percent decline in kidney function between standard-criteria and expanded-criteria living kidney donors, the 3-year risk for graft loss among recipients of kidneys from standard-criteria vs. expanded-criteria living kidney donors and the Health-related quality of life (SF-36), the Beck Depression and Anxiety Inventories, and the Rosenberg Self-esteem Scale for these

patients. This data will help determine whether it is safe and ethical to expand living kidney donation in novel areas with minimal risk (e.g. donors with pre-existing medical conditions, anonymous donors etc).

Aim3a&b recruited a strong central coordinating study team that worked to finalize the contracts between the University of Alberta and participating sites. The group created a web-based electronic system capable of transferring de-identified physiologic waveform data from participating study sites to a central server and developed a preliminary "Waveform Viewer" application that can read in the different file formats from the different waveform capture software options so that all files will be viewed with the same units and a visible scale. The DePPaRT study is now up and actively screening at 5 study sites with another 9 sites that are now ready participate and one international study site opened in Prague, Czech Republic that is enrolling patients. To date, the study has enrolled 13 patients of the anticipated 500.

Over the past year, **Aim3c** complete study recruitment, interviewed 55 donor professionals (24 Intensivists, 16 ICU Nurses, 15 Organ Donor Coordinators) and completed first draft of belief statements for all coded interview data. The team will meet to prioritize intervention components based on the data.

Aim4's accomplishments have laid the groundwork to achieve all of the goals of this project within the next two years. A research team, including project coordinator, from the Institute for Clinical Evaluative Sciences (ICES) Kidney, Dialysis, and Transplantation (KDT) Program was assembled to assist in moving this project forward. The team worked with Trillium Gift of Life Network (TGLN) in Ontario to solidify the donor variable list and determine the data quality available in the provincial system and are now finalizing a data sharing agreement between TGLN and ICES and the ethics applications to prospectively collect donor samples. Our goal is to include BC Transplant in the study in the coming months.

Interactions within the project

Aim1 will endeavour to increase the potential pool of donors available for transplantation (which will invariably increase the range of donor quality) and thus defining factors that predict transplant outcomes in donor organs at increased risk for graft failure will increase in importance. **Aims3a-c** may increase the availability of DCD organs for transplantation so the influence of prolonged warm ischemia on already vulnerable donor organs (due to advanced age and comorbidity for example) will need to be further clarified via the studies in **Aim4**.

The new **Aim5** was added onto Project 2 specifically to take advantage of the expertise developed within the CNTRP and this donation-centered project. **Aim5** will collaborate with **Aim1** to include diagnostic process into the database and evaluate the public perception of brain death. **Aim5** will also link intrinsically with both arms of **Aim3** to compare and contrast results.

Interactions across the CNTRP

- Project 2 worked closely with **Project 5** and the Canadian Society of Transplantation (CST) on the development of national guidelines to safely increase the use of increased risk organ donors (**Aim4**).

- Project 2 **Aim1** lead and supported the creation of new Fast Policy Facts with **Core 1** on the topics of Ethics, Incentives, Consent, and Death Determination (available at www.cntrp.ca/policy_facts)
- Project 2 Aim 1 has worked collaboratively with Core 1 on the creation and implementation of a Patient Engagement Strategy within CNTRP. This initiative has included hosting a pilot workshop held in Montreal in August 2014, conducting a national survey in the Spring of 2015 and leading a national workshop to be held in Toronto in November 2015.

New research & collaborations

- The addition of the new **Aim5 - Improving Neurological Death Diagnosis** study is of great value to the CNTRP as it broadens our perspective on donation research, creates a stronger link with the ICU research community and offers new opportunities for collaboration. The funding for this new aim comes from independently funded CIHR grants and therefore helps to increase the overall value of the CNTRP.
- Project 2 has helped the CNTRP strengthen collaborations and integration with Canadian Blood Service (CBS) as well as Canada's largest OPOs, such as Trillium Gift of Life, BC Transplant and Quebec Transplant to engage them in research and promote knowledge exchange.
- Canadian Child Health Clinician Scientist Program – SJ Anthony (postdoc) granted a Career Enhancement Program award.

Next Steps (Year 3 plan)

Over the next period, **Project 2** seeks to accomplish the following milestones**:**

- Complete the patient engagement process and publish findings (**Aim1**)
- Complete the Family Veto study (**Aim1**)
- Begin work on public solicitation and incentives for organ donation (**Aim1**)
- Continued follow up of living kidney donor participants to determine whether it is safe and ethical to expand living kidney donation in novel areas with minimal risk (**Aim2**)
- Finalize contracts, complete study training, and launch the *DePPaRT* study at all participating sites (Aim3a&b)
- Ramp up *DePPaRT* study patient enrollment and complete mid-point analysis to assess purposive sampling goals(**Aim3a&b**)
- Complete development of the intervention we will use to enhance DCD across Canada based on our interviews with practitioners (**Aim3c**)
- Begin implementation of the intervention noted above at sites across Canada (**Aim3c**)
- Begin data collection in Ontario on all organ donors to answer the research questions posed regarding the optimal use of increased risk donors (**Aim4**)
- Complete the systematic review and national survey on ancillary testing for neurological determination of death (**Aim5**)

Publications and Presentations

See attached list of publications and presentations.

Project 3 - Understanding, predicting and preventing early graft rejection and GVHD

Lead: Dr Marie-Josée Hébert, Université de Montréal
Co-Leads: Dr Claude Perreault, Université de Montréal & Dr Dan Muruve, University of Calgary

Original aims/sub-aims and changes

The death and release of inflammatory cytokines by parenchymal cells within solid organ transplants play major roles in modulating the immune response to the graft. In bone marrow transplantation, the programmed death of vascular cells due to immune and metabolic stressors is also central to the development of Graft-vs-Host Disease (GVHD). Although deemed important, the specific molecular mechanisms that regulate «response to injury» (i.e. the inflammatory response to cell death and cell damage) in an alloimmune context remain poorly defined. The goal of Project 3 is to characterize the importance of programmed cell death pathways and inflammasome activation as predictors and regulators of rejection and GVHD. To this end, scientists within Project 3 focus on developing cell and animal models of regulated cell death pathways and inflammasome activation, exploring these models with unbiased proteomics and transcriptomics strategies and validating promising biomarkers of rejection or GVHD in transplant patient samples. Our group also strives to characterize novel targets of pharmacological interventions, within these molecular pathways, for better prevention and/or treatment of rejection/GVHD. This multifaceted approach, developed by closely integrated teams nationwide, is aimed at gaining novel mechanistic insights and concomitantly characterizing novel tools for prediction and diagnosis of rejection and GVHD. Project 3 is led by Dr. Marie-Josée Hébert, senior nephrology clinician-scientist and director of the multi-organ transplant program at Université de Montréal, and co-led by Drs. Claude Perreault, Canada Research Chair in Immunobiology at Université de Montréal, and Dan Muruve, Canada Research Chair in Inflammation and Kidney Disease at the University of Calgary.

Aim 1: Define the role and signatures of programmed cell death (PCD) and inflammasome activation in enhancement of solid organ transplant (SOT) rejection and graft-versus-host disease (GVHD) transplant injury
Aim 2: Identify components of the PCD and inflammasome pathways that represent novel, clinically relevant pharmacological modifiers to prevent graft injury, rejection and GVHD

The overall goal of Project 3 for the reporting period was to identify key components of regulated death pathways in endothelial cells, pancreatic islets and renal epithelial cells that:

- Regulate rejection/GVHD
- Predict rejection/GVHD
- Can serve as pharmacological targets of intervention in treating or preventing rejection/GVHD.

The specific objectives were:

- To characterize the molecular signatures that follow necroptosome and inflammasome activation in renal epithelial cells

- To determine if activation of necroptosis has an impact on renal allograft function and survival.
- To develop inflammasome inhibitors (NLRP3 modulating drugs) using chemoproteomics.
- To initiate development of protocols for using an epoxide-based cysteine protease probe in normal urines, which will then be translated to clinical transplant samples as a new methodology to assess renal caspase activation in transplant patients.
- To perform the proteomic analysis of human islet-derived membrane vesicles (MV) that are produced during ex vivo islet preparation
- To characterize the protein markers of the different types of MV produced by apoptotic endothelial cells
- To characterize the immune-modulating functions of the various types of endothelial MV in models of vascular rejection, solid organ rejection and allogeneic hematopoietic cell transplantation (AHCT)
- To characterize protein components of endothelial MV as biomarkers of rejection or allograft dysfunction in renal transplant patients

There have been only minor changes in the project's design that are discussed in the report below. Overall, the global direction has not changed and major goals have been reached within the expected timeline.

Major accomplishments

Regarding progress on the role of programmed cell death and inflammasome pathways in rejection/GVHD, Project 3 has made the following achievements:

1. We have developed and implemented standardized operating procedures (SOPs) for isolation of kidney epithelial cells and TNFα-induced apoptosis in London, ON and Calgary AB.
2. We have found that death receptors (TNF alpha receptor -1 or Fas) trigger tubular epithelial cell (TEC) apoptosis and necroptosis. Blocking necroptosis-regulating molecule RIPK1 or RIPK3 prevents TEC necroptosis, kidney ischemic reperfusion injury and chronic rejection in allogeneic kidney transplantation. These results identify RIPK1 and RIPK3 as novel regulators of renal allograft rejection.
3. We have developed SOPs for storage and purification of endothelial membrane vesicles
4. We have identified and characterized a novel type of membrane vesicle (apoptotic nanovesicles) released by apoptotic endothelial cells as accelerators of vascular rejection and accelerators of GVHD in animal models.
5. We have identified a cryptic fragment of perlecan (LG3) and the 20S proteasome core subunit, as important components of endothelial apoptotic nanovesicles regulating the immunogenic activity of these nanovesicles during rejection/GVHD. We found that the caspase-like proteasome activity, present within apoptotic nanovesicles, increases allograft vascular inflammation and leukocyte infiltration.
6. We have demonstrated that apoptotic nanovesicles accelerate, at least in part, rejection through the production of autoantibodies that in turn aggravate vascular inflammation and we have identified anti-LG3 antibodies as a prototypical autoantibody implicated in this maladaptive auto-immune response.
7. We have determined that large amounts of anti-LG3 antibodies are produced in recipients early after allogeneic hematopoietic cell transplantation through T-cell dependent pathways.
8. We have identified endothelial apoptotic bodies (another type of membrane vesicle) as components that can block the immunogenic activity of apoptotic nanovesicles in animal models of rejection.

Regarding progress on identification of programmed cell death/inflammasome components as predictors/biomarkers of rejection/GVHD, Project 3 has made the following achievements:

9. We have identified HMGB1 and osteopontin as important components of the necroptosis pathway that activate NK cells which in turn attack tubular epithelial cells and mediate long term kidney allograft injury.
10. We have demonstrated that renal tubular epithelial cells release MVs when they undergo apoptotic and necroptotic cell death. RIPK3 deficiency inhibits release of MVs, suggesting that MVs represent potential biomarkers of RIPK3 activation in renal tubular epithelial cells.
11. We identified and characterized NLR/inflammasome-dependent microparticle formation and secretion in vitro. These microparticles show evidence of inflammasome proteins (NLRP3, ASC and caspase-8), and are secreted during inflammasome activation and pyroptosis. These results support the concept that components of microparticles represent novel biomarkers of inflammasome activation.
12. We have optimized the reaction conditions for an epoxide-based cysteine protease probe that will be developed for monitoring cysteine protease activity in the urine of renal transplant patients, as a non-invasive test to monitor renal allograft cell death.
13. We have demonstrated that caspase activation during purification of pancreatic islets leads to the release of MVs and have initiated proteomic characterization of pancreatic MVs. We have identified the diabetes autoantigen, GAD65 as a component of pancreatic MVs.
14. We have completed the comparative proteomic characterization of different types of endothelial membrane vesicles produced by human and murine apoptotic endothelial cells and identified LG3 and 20S proteasome as biomarkers of immunogenic endothelial apoptotic nanovesicles. We showed in models of vascular and renal ischemia-reperfusion and in renal transplant patient plasma samples that nanovesicle LG3 and 20S proteasome are good candidate biomarkers of vascular injury.

Regarding progress on the characterization of programmed cell death/inflammasome components as targets of intervention in treating or preventing rejection/GVHD, Project 3 has made the following achievements:

15. Using a chemoproteomic screen for NLRP3-binding small molecules, we have identified 8 candidate “hits” revealing one lead compound that effectively inhibited ATP-mediated activation of the inflammasome.
16. We showed that inhibiting activity of the 20S proteasome within endothelial apoptotic nanovesicles with bortezomib significantly decreases their capacity to accelerate rejection, identifying proteasome inhibition as a novel «druggable» pathway for prevention of rejection.

In summary, all specific objectives listed for Year 2 have been reached.

Interactions within the project

One of the most significant successes of Project 3 to date has been the high degree of collaboration within the group and with other CNTRP projects. Within Project 3, we have access to human renal transplant and bone marrow transplant patients biobanks. We also plan to enhance our interactions with other Projects to enhance our capacity to test these biomarkers in the following context:

- ischemia-reperfusion injury associated with donor maintenance and ex vivo organ preservation
- during the treatment of GVHD patients
- virus-induced allograft tissue injury (ex. Polyomavirus nephropathy).

Tissue damage has been known for decades as an important regulator of rejection, but the specific molecular basis of this observation remained elusive. In recent years, major progress in the characterization of the molecular pathways that control tissue injury, cell death and inflammation have opened new research avenues for transplantation. The nationwide, complementary and integrated expertise in programmed cell death and inflammasome activation within CNTRP Project 3 uniquely positions this group to make rapid progress in this booming field of investigation and assume an international leadership position. The hopes and promises for transplantation raised by recent achievements by Project 3 members include:

- The possibility of standardizing new tests for monitoring organ injury and predicting allograft function and risk of rejection/GVHD
- The possibility of creating algorithms for allocation of organs and donors that take into consideration these new findings for increasing early and late allograft function and survival
- The possibility of defining new treatments for ameliorating the quality of organs at the time of transplantation and for preventing and treating rejection/GVHD

Interactions across the CNTRP

Project 3 is the only project within CNTRP focusing on a largely basic and translational research program. Although the major goal of Project 3 is to explore the importance of cell death/inflammation molecular pathways on alloimmunity, the potential for translation of these mechanistic finding by far outreaches the sole examples of rejection and GVHD. Therefore Project 3 strives to interact with other CNTRP projects and cores to maximize translation of findings to various transplantation relevant area, including organ perfusion and repair (**Project 1**), donor maintenance (**Project 2**), treatment of GVHD (**Project 4**), viral complications of transplantation in renal transplant patients (**Project 5**), biomarkers of rejection in pediatric patients (**Project 6**).

Project 3 also benefited from fruitful interactions with **Core 1** for developing a patient-engagement strategy, **Core 2** for development of SOPs and biorepositories and **Core 3** for helping the many Project 3 trainees and support personnel to develop skills essential for enhancing productivity in a multidisciplinary research environment.

As Project 3 research program hinges mostly on basic, translational and clinical research strategies, Project 3 scientists are fully aware that they need to take extra steps to ensure translation of these results towards the Canadian transplant population. To this end, Dr Hébert, Project 3 lead and CNTRP Co-Director has been fully involved, in collaboration with **Core 1**, in the development of the CNTRP Patient Engagement Strategy. Members of Project 3 (Hébert, Paraskevas) worked with the CIHR/III to organize a Café Scientifique on Transplantation, aimed at engaging a fruitful dialogue with the Canadian public. Also, work developed within Project 3 has been the feature of media coverage including science broadcasts on national television (Découverte, Code Chastenay).

New research & collaborations

The following external collaborations have contributed to the progress of Project or will support experiments to come:

- Collaboration with Prof. Roslyn Bill (Aston University, Birmingham UK), an expert in protein engineering and biotechnology with links to the Oxford Protein Production Facility at the Diamond Light Source in the UK.

- Collaboration with Emmanuel Zorn (Columbia Center for Translational Immunology, New York) for concomitant assessment of anti-LG3 and ant-apoptotic cell antibodies in kidney transplant patients
- Partnership with Fisher Technologies/One Lambda for development of clinical grade anti-LG3 testing

Next Steps (Year 3 plan)

The major goals for the next period are essentially to further work already initiated and to evaluate the validity and clinical usefulness of putative biomarkers.

Specifically, with regards to the role of programmed cell death and inflammasome pathways in rejection/GVHD we plan:

- To further the evaluation of necroptosis, apoptosis and inflammasome activation in regulation of vascular, renal and heart rejection and GVHD in murine models.
- To further the characterization of immunogenic pathways triggered by apoptotic nanovesicles leading to acceleration of rejection/GVHD
- To assess the immune-modulating functions of pancreatic islet-derived microvesicles in models of islet transplantation and in models of type I diabetes in mice
- To further the characterization of tolerogenic pathways triggered by apoptotic bodies and inhibiting rejection in models of transplantation in mice
- To further the characterization of tolerogenic pathways triggered by apoptotic bodies and preventing the production of anti-LG3 antibodies in models of vascular transplantation and ischemia-reperfusion

With regards to identification of programmed cell death/inflammasome components as predictors/biomarkers of rejection/GVHD we plan:

- To characterize the proteomic signatures of necroptosis and inflammasome activation in renal epithelial cells
- To optimize epoxide-based cysteine protease probe proteomics as a new methodology to assess renal injury and cell death in transplant patients.
- To complete the characterization of the proteomic signatures of pancreatic islets apoptotic membrane vesicles
- To develop SOPs for the purification of islet-specific membrane vesicles in human serum/plasma samples from patients pre- & post-pancreas and islet transplantation
- To enhance biobanking of human islet-conditioned media, MVs and islet cell lysates from human pancreases.
- To characterize the RNA signature profile of endothelial membrane vesicles and to evaluate these signatures as putative biomarker/predictor of rejection/GVHD in mice and in serum samples from renal and bone marrow transplant patients
- To assess the validity and clinical usefulness of nanovesicle LG3, caspase-like activity and anti-LG3 as predictors of rejection/GVHD in renal, heart and bone marrow transplant patients.
- To launch two new sub-projects entitled «Urinary markers of intra-renal RAS activity in renal allograft recipient», by Drs Joe Kim, Ana Konvalinka, Eleftherios Diamandis, and Rohan John and the project «Non-invasive diagnosis of non-alcoholic steatohepatitis in liver transplant recipients: a prospective, longitudinal study employing serum cytokeratin 18 and transient elastography (Fibroscan)» by Drs Giada Sebastiani and Peter Metrakos, which

were recently funded through a peer-reviewed national competition launched by CNTRP in collaboration with Canadian Society of Transplantation
- To further collaborative work with **Projects 1, 2, 4, 5** and **6** aimed at evaluating previously mentioned putative biomarkers as predictors of allograft dysfunction or response to treatment.

Regarding the characterization of programmed cell death/inflammasome components as targets of pharmacological intervention we plan to:
- Pursue the characterization of NLRP3-modulating compounds
- Analyze the effect of pre- & post-isolation oxygenation on membrane vesicle production in human and murine islets (tying in **Project 1** to **Project 3**), as compared to the normoxic and anoxic states
- To assess the efficacy of proteasome inhibition with bortezomib in preventing the formation of autoantibodies (anti-LG3) in models of ischemia-reperfusion injury and in models of vascular, renal and heart rejection

Publications and Presentations

See attached list of publications and presentations.

Project 4 - Translating strategies for immunomodulation and transplantation tolerance

Leads: Dr. Megan Levings, University of British Columbia and Dr. Denis-Claude Roy, Hopital Maisonneuve Rosemout
Co-Leads: Dr. Lori West, University of British Columbia and Dr. Kirk Schultz, University of British Columbia

Original aims/sub-aims and changes

The overall goal of Project 4 is to combine our complementary expertise and translate strategies to induce tolerance to the clinical setting. The project includes approaches to target and monitor immunoregulatory cells in patients undergoing hematopoietic stem cell and/or solid organ transplantation. The original aims were:

Aim 1: Conduct phase I/II clinical trials using extracorporeal photopheresis to treat acute renal graft rejection and chronic GVHD and to promote immune regulation

Aim 1A. Conduct a phase I/II trial of TH9402 ECP in patients with refractory cGVHD (CARE Trial)
Aim 1B. Conduct a phase I/II trial of TH9402 ECP in patients with acute humoral and/or cellular kidney allograft rejection (ECP-kidney trial)
Aim 1C. Monitor changes in cells and biomarkers associated with tolerance in patients undergoing ECP for chronic GVHD or allograft rejection.

Aim 2: Conduct a phase I trial combining hematopoietic stem cell & kidney transplantation

Aim 2A. Conduct a phase I trial of haploidentical HSCT and kidney transplantation
Aim 2B. Monitor changes in immune cells and biomarkers associated with tolerance in patients undergoing dual transplantation

Aim 3: Develop methods to use thymically-derived regulatory T cells (Tregs) as a cellular therapy to induce transplantation tolerance

Aim 3A. Optimize expansion of thymus-derived Tregs
Aim 3B. Validate the phenotype & function of thymus-derived Tregs in humanized mice
Aim 3C. Develop and optimize GMP-based protocols to expand thymus-derived Tregs

Revisions made to Aim 1b and Aim 2.

Aim 1b: Discrepancies in the treatment approach of acute cellular kidney rejection across Canada prevented consensus on the protocol design of the ECP-kidney trial. We therefore re-allocated a portion of the budget to carry out new studies to better define the criteria, endpoints and sample size to design the clinical trial. The new goals are:

- To conduct a systematic review of the literature on treatment of acute cellular rejection in renal patients.
- To conduct a retrospective study on the treatment of acute cellular rejection in selected centers.

- To conduct a pan-Canadian survey to explore standard practice for the treatment of acute cellular kidney rejection.

Aim 2: Because of the increased budget for the projected clinical trials in Project 4 and the changes to the study design, the budget for this trial was re-allocated to the CARE trial (aim 1a). We are evaluating other possible funding sources and partners to pursue clinical trials involving combined hematopoietic stem cell transplantation and organ transplantation.

Major accomplishments

Aim 1a: The preparations for the CARE trial are nearing completion. The study was presented to Health Canada (HC) during a pre-Clinical Trial Application (CTA) meeting and well received. Ethical board approval was obtained from lead center (Hopital Maisonneuve Rosemount) and applications to ethical boards of other participating sites are submitted. Both Montreal and Vancouver are fully-equipped and two qualification runs were successfully conducted at HMR. The 3rd cell processing site in Winnipeg should be equipped in September. The CTA has been finalized (and will be submitted to HC). Legal contracts between the sites are being drafted.

Aim1c: Standard operating protocols have been established for the sample collection/storage and immune monitoring. Furthermore, logistics for sample collection/analysis have been implemented in the CARE trial.

Aim 3: This aim is ahead of schedule. Thymic and peripheral blood Tregs have been compared in *ex vivo* expansion protocols and analysed functionally both *in vitro* and *in vivo*. Data from these studies are described in a manuscript currently in press in the American Journal of Transplantation (Dijke *et al*, AJT 2015). The data demonstrate that thymic Tregs have the potential to be an excellent source of therapeutic Tregs. Currently, GMP-applicable expansion protocols are being tested in collaboration with Stem Cell Technologies. We also obtained a grant of the Canadian Foundation of Innovation to purchase equipment required for clinical grade expansion of thymic Tregs. We are pursuing multiple funding opportunities to perform a phase I clinical trial of 3rd party thymic Tregs to prevent graft-versus-host disease.

Interactions across the CNTRP

Project 4 is most closely linked with **Core 2** as both are involved in the design and execution of the CARE trial. Essential interactions with **Core 2** to develop the CARE trial have included:

- development of the clinical protocol
- logistics of site preparation
- logistics and budget allocation of cell processing and shipment
- ethical applications to local IRBs
- logistics of biosample collection, processing and storage
- development of standardized immune monitoring using the Navios flow cytometer

Other interactions include:

- with **Project 3** to collect urine from subjects in the CARE trial to test for exosomes and the presence of other biomarkers of rejection and/or cell death. Specifically Project 3 has demonstrated that endothelial-derived apoptotic nanoparticles can break tolerance to self and lead to the development of anti-LG3 antibodies (Abs). These nanovesicles have been shown to accelerate disease in a GvHD mouse model. As the PDT treatment induces apoptosis, bio-samples from the CARE trial will be used to: 1) evaluate the type of apoptotic vesicles produced by the PDT-treated PBMCs from GvHD patients and their proteomic

content; 2) monitor the presence of nanovesicles in the plasma by proteasome activity detection and anti-LG3 IgG levels; and 3) analyse urinary LG3 levels.

- with **Project 5** to monitor changes in anti-viral immunity longitudinally for subjects in the CARE trial. Specifically PBMCs will be sent to project 5 for evaluation of changes in the proportion and/or phenotype of T cells specific for CMV or EBV. In addition, for subjects who receive an annual anti-influenza vaccine, anti-flu specific T cell responses will also be evaluated. See more details below.
- with **Project 6** to implement similar standardized immune monitoring to that being used for the CARE trial. Specifically, the antibody panels and instrumentation developed by **Core 2** and **Project 4** will be used to evaluate longitudinal samples from children undergoing solid organ transplantation and enrolled in the POSITIVE study. The resulting data will be sent back to **Project 4** for analysis using the automated software that has been developed to analyze data from the CARE trial. In addition to intra-study analysis, this will also be a unique opportunity for inter-study analysis.

New research & collaborations

We have established significant collaborations with investigators in The ONE Study as well as Beckman Coulter to develop the immune monitoring platform for the CARE trial (see details in Core 2). We also developed a new collaboration with Dr. Ryan Brinkman at the BC Cancer Agency to develop an automated flow cytometry data analysis platform.

A new research collaboration is being established with project 5 to analyse cell-mediated immune responses to CMV and EBV on samples from the CARE trial, for those patients who were seropositive or received seropositive donor cells. As cGvHD suppresses immune responses, treating cGvHD may increase the response. Evaluations will be done on PBMCs pre- and post PDT collected at baseline, during and at the end of the treatment. The logistics of analyzing effects on the response to influenza antigen exposure are also being considered. We are also exploring the feasibility of using a novel flow cytometry apparatus (CyTOF) to analyze these samples.

For Aim 3, a new approach to develop antigen-specific Tregs using Chimeric Antigen Receptors has been developed using peripheral Tregs. This exciting technology will be transferred to the thymic Treg project and tested using *in vivo* models. The Chimeric Antigen Receptor technology is being developed with the Centre for Drug Research and Development at UBC. In addition, data revealed that thymic Tregs have a distinct profile of chemokine receptor expression and a new research aim to study how expression of cell homing receptors is underway. We will also work with Core 1 to study the legal and ethical considerations around using thymic Tregs from discarded human thymuses as a cellular therapy. Additionally, funding has been received from the Alberta Diabetes Institute was obtained for a pilot study to test the effectiveness of thymic Tregs in suppressing rejection of pig islet xenografts.

Next Steps (Year 3 plan)

Aim 1A.

- Open the CARE trial for recruitment
- Complete validation of assays to be used for immune monitoring to be done in the CARE trial
- Complete data analysis from the first patients of the CARE trial.

- Increase collaborations with Project 3 based on the new research plan on apoptotic vesicles.
- Explore collaborations with Project 5 to use CyTOF technology as part of the immune monitoring platform for the CARE trial

Aim 1B

- Complete systematic review and national survey
- Develop the protocol the ECP-kidney trial and seek funding for a pilot study

Aim 1C

- Define the SOPs and approaches to monitor the CARE trial.
- Begin the analysis of CARE trial samples

Aim 2

- Continue to seek alternate sources of funding and collaborations to enable this aim

Aim 3

- Develop GMP-compatible thymic Treg expansion protocols with STEMCELL Technologies and seek funding for a clinical trial
- Complete a study on chemokine receptors in thymic Tregs
- Test antigen-specific thymic Tregs using *in vivo* models of islet and skin transplantation
- Work with Core 1 to determine the ethical framework under which thymuses could be retrieved for a cell therapy application

Publications and Presentations

See attached list of publications and presentations.

Project 5 - Predicting and controlling viral complications of transplantation

Leads: Dr. Atul Humar, University Health Network – Toronto
Co-Leads: Dr. Lee Anne Tibbles, University of Calgary and Dr. Cindy Toze, University of British Columbia

Original aims/sub-aims and changes

Viral infections are common after transplant and are important contributors to post-transplant morbidity, mortality and graft loss. Viruses can be donor-derived, community acquired, or endogenous latent viruses that are reactivated post-transplant. Overall, numerous unanswered questions remain in all aspects of viral complications post-transplant. The opportunity to definitively answer these questions through the multi-centre framework of this program has numerous potential benefits including improved organ donor utilization, better prediction and prevention of common viral complications, and potential discovery of novel pathogens.

Project 5 focuses on viral complications from across the transplantation spectrum. The studies span several critical aspects of virology and encompass themes important to donation, SOT and HSCT. Project 5 started with 3 major sub-projects/aims and over the past two years has added a new clinical trial, one multicenter study to track incidence of PCP and a new EBV therapeutic subproject that addresses an unmet medical need for the SOT patients in Canada and tackle the issue of opportunistic infections following transplant (detailed below):

Aim 1: Our goal is to optimize and standardize utilization practices for high infectious risk organ donors (IRDs) across Canada i.e., those with behavioral risk factors for Human Immunodeficiency Virus (HIV), Hepatitis C virus (HCV) or Hepatitis B Virus (HBV). There is limited data in Canada on increased risk donors (IRDs) (defined as donor with behavioral practices that place them at increased risk for HIV, HBV, HCV. Epidemiologic data on the incidence and utilization practices for IRDs does not exist for Canada and will help inform strategies and policies for optimal utilization of these donors. Development of Canadian guidelines will allow engagement of utilizers and providers. It is also crucial to understand patient factors that play a role in acceptance or decline of IRD organs and the psychosocial impact use of these organs may have.

Aim 2: Our goal is to assess common infectious problems associated with SOT and HSCT, specifically cytomegalovirus (CMV), BK polyomavirus (BK) and Epstein Barr Virus (EBV).

- For CMV (**Aim 2a**), the goals are to 1) better understand the pathogenesis of CMV reactivation following transplantation, and 2) to develop and validate novel biomarkers that can predict reactivation of CMV.
- For BK (**Aim 2b**), the goals are to 1) determine how BK virus causes aberrant changes in expression of host proinflammatory and profibrotic genes and mediators leading to acute inflammation and interstitial fibrosis, and 2) to determine how BK virus controls host transcriptional regulatory machinery, therefore altering the expression of both inflammatory and fibrosis inducing genes. The BK:KIDNI Trial (BK Virus: Kinase Inhibition to Decrease Nephropathy Intervention Trial), the largest ongoing trial in the treatment of BKV viremia, was brought under **Aim 2b**. This CIHR funded multicentre trial is comparing the standard of

care (reduction of immunosuppression) with the intervention (change of immunosuppression to a combination of sirolimus and leflunomide).
- For EBV (**Aim 2c**), we are working closely with the Pediatric Study in Project 6 to study pathogenesis and outcomes related to EBV viremia and P6 Aim 2c is leading the adult cohort validation of the larger pediatric study.
- The new EBV therapy study (**Aim 2d**) was added in January 2015 to use cell therapy to prevent or treat opportunistic viral reactivation or disease following transplantation by generating autologous EBV-specific T-cell lines *in vitro* from prospective EBV seronegative organ recipients who are at high risk of developing EBV-related disease following their transplant.

Aim 3a: the goal is to discover novel viral agents in transplant patients who develop specific idiopathic disease syndromes using existing metagenomics-based pathogen discovery programs in Canada.
Aim 3b: the goal is to develop a viral immune cassette to evaluate immune competence against infectious agents in patients enrolled in tolerance induction trials in **Project 4.**

We have recently added a new **Aim 4** to study an increased incidence of late onset PCP identified in centres across Canada. To date, we performed a cross Canada survey to better understand the scope of the problem, and based on these results, we are starting a multi-center case control study looking at risk factors for development of late-onset PCP using funds identified within Project 5.

Major accomplishments

Aim 1
- The planned CNTRP IRD consensus conference was held and included representatives from all major transplant programs in Canada and multiple OPOs, as well as HC, CST. The consensus conference was published (Transplantation 2014).
- A standardized informed consent was developed for use by transplant programs. It has been widely distributed through OPOs, CST.
- Mathematical modeling of risk of transmission for IRDs (based on Canadian data) was performed and published (Transplantation 2014)
- A cross-Canada survey of transplant surgeons and physicians on utilization of IRDs was performed and presented at WTC 2014 and is accepted for publication in Transplantation.
- The Ontario OPO (TGLN) has developed a tool-kit for distribution to all Ontario transplant programs based on the CNTRP consensus guidelines. Other OPOs are looking at similar KT strategies.

Aim 2:
- Several samples were collected from clinical cohorts with or at-risk of CMV reactivation. (**Aim 2a**)
- Further basic and clinical work was performed assessing novel factors related to the pathogenesis of CMV reactivation. This includes the first assessment of viral miRNAs in the role of CMV reactivation post-transplant. This work includes two recent (2015) AJT publications. (**Aim 2a**)
- Further basic science work was performed to understand the pathogenesis of BK reactivation. (**Aim 2b**)
- The multicenter CIHR funded BK trial was formally included within the framework of Project 5. (**Aim 2b**)

- Further validation work has been performed related to the role of EBV viral heterogeneity in the pathogenesis of PTLD. We have done preliminary genotyping studies on selective major EBV latent and lytic genes where we have examined viral strains among patients with primary EBV infection after transplantation versus healthy subjects. (**Aim 2c**)
- A new project assessing *ex-vivo* development of EBV specific T-cells has been including in project 5. This received competitive funding through the CNTRP grant competition ($25K). (**Aim 2d**)

Aim 3:

- A novel retroviral retroviral pol gene has been detected in bile and stool samples from a patient with severe recurrent primary sclerosing cholangitis following liver transplantation. (**Aim 3a**)
- We are performing prevalence studies of viral infection and cloning more of the viral genome. We have incorporated the novel viral sequences into a Nanostring probe capture assay for detection of viral sequence in both paraffin embedded material as well as fresh/frozen biliary epithelium samples. (**Aim 3a**)
- We have optimized and validated methods for assessing viral host immune response to CMV, EBV and influenza antigens.(**Aim 3b**)
- This work led to two recent publication assessment influenza responses (Published in *J Infect Dis* and *Plos Pathogens*)
- Assessment of antiviral responses has now been incorporated into the clinical trial within **P4**.

Interactions within the project

The different sub-projects within Aim 1 are all complementary. For example knowledge gained from the consensus conference helped inform the developed of the cross country survey, which subsequently helped inform the knowledge translation plan.

Aim 2a, b, c, address different viruses but explore complementary aspects of pathogenesis. For example, the understanding of unique aspects to CMV viral pathogenesis can be adapted to BK and EBV pathogenesis. Recently we have been exploring the use of CMV viremic samples to look at reactivation of novel virus (Viral discovery aim).

Host immune response parameters developed for Aim 2 (CMV and EBV aim) are now being applied to Aim 3b looking at viral responses with the ultimate goal of evaluating these responses in the upcoming P4 tolerance trial.

Interactions across the CNTRP

- The **Aim 1** (utilization of IRDs) is closely linked to **Project 2** that is looking to assess the determinants of use or non-use of organs from deceased donors offered to Canadian transplant centres and evaluate the outcomes of organ transplants from deceased donors perceived to be at increased risk for graft failure or transmissible diseases. The standardized inform consent for IRDs has been developed in close collaboration with **Core1**. This IRD project unites the donation and transplantation communities and received very positive feedback from the ICU research community during our 2nd Annual CNTRP meeting.
- The recently added BK:KIDNI trial (**Aim2b**) is providing samples to **Project 3** to investigate the mechanism of viral transmission via nanoparticles. The BK:KIDNI is also collaborating with **Core2** to develop clinical trial management support through the Montreal Health &

Innovation Coordinating Centre (**MHICC**) and register patients in the **Core2** patient registration database.
- **P5 Aim2c** (EBV) closely aligns with Project 6 to establish the pediatric and adult cohort for the study.
- The collaboration between **Aim3b** and **Project 4** is now just beginning.
- A new collaboration with **P1** and **P5** involves the ex-vivo utilization of antiviral miRNA to prevent HCV reinfection of livers.

New research & collaborations

The CNTRP and Project 5 have established a strong collaboration with **Health Canada** (HC). This includes funding of the IRD consensus conference by HC and funding for establishment of a Canadian disease transmission advisory committee. The consensus guidelines for the use of IRDs have been distributed across all Canadian OPOs. TGLN has formed an "IRD toolkit" based on the consensus guidelines.

CNTRP has formed a collaboration with the **Swiss Cohort Study group** on the CMV project (Aim 2a), leading to a transfer of samples and co-funding from the Swiss Science Foundation. As previously mentioned, Project 5 is excited to have added the BK:KIDNI trial, the EBV therapeutic subproject and the multicenter PCP study.

Next Steps (Year 3 plan)

Aim 1: To continue develop the framework for prospective data collection among OPOs (in conjunction with **Project 2**). In the meantime, a retrospective evaluation of donors from TGLN will occur. The psychosocial substudy will commence. We will publish our cross Canada survey (done – recently accepted).

Aim2: We will continue with what has so far been highly successful analysis of factors that relate to the pathogenesis of BK, CMV and EBV reactivation post-transplant including assessment of potential biomarkers. We will continue to develop the two new projects that have been added to this aim (EBV CTL study and the BK randomized trial).

Aim 3: Identification and validation of novel viruses post-transplant will continue. We will ensure that MTA are completed for sample transfer. We will participate on the Tolerance Trial (**Project 4)** regarding assessment of viral response in patients undergoing tolerance related treatments.

Aim 4 (newly added): We will commence the cross Canada PCP case-control study at 10 centres across Canada.

Publications and Presentations

See attached list of publications and presentations.

Project 6 - Improving pediatric outcomes in transplantation (POSITIVE Study)

Leads: Dr. Seema Mital, Hospital for Sick Children
Co-Leads: Dr. Beth Foster, McGill University and Dr. Upton Allen, Hospital for Sick Children

Original aims/sub-aims and changes

Aim 1: Develop age-appropriate calcineurin inhibitor (CNI) dosing for pediatric SOT patients

- Create a personalized physiologically-based CNI dosing algorithm in SOT
- Validate pediatric sensitive immunosuppression monitoring tools and their therapeutic targets
- Validate immunologic assays for assessing age-specific immune responses.

Aim 2: Develop risk prediction tools based on viral-host interactions that predispose young SOT patients to EBV/PTLD

- Gain knowledge of EBV/PTLD host susceptibility factors (age and immune maturation) at the time of transplant.
- Develop an EBV genotype panel to be used as clinical tool for detecting high risk subtypes in patients with EBV

Aim 3: Develop health care systems strategies to enhance medication adherence in adolescents and young adults

- Characterize differences between Canadian solid organ transplant programs in potentially modifiable meso- and macro-level systems factors.
- Identify potentially modifiable meso- and macro-level factors that are determinants of adherence, adjusting for potential confounders.
- Compare the educational attainment and employment outcomes of kidney, liver, and heart transplant recipients with those of the general Canadian population in the same age group.

Major accomplishments

Study Design, Infrastructure & Launch:

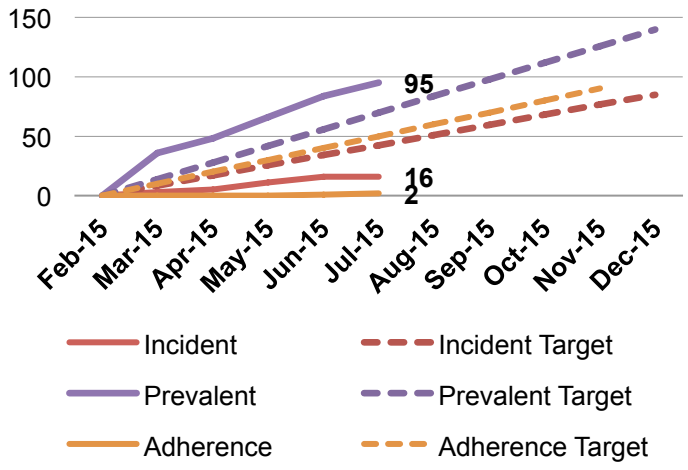
- The major achievement was to effectively develop the necessary infrastructure to run and operationalize this 14-site multicentre study. Not only are there 14 study sites, but even within some sites, there are up to 3 participating clinics (kidney, liver, heart).
- All of the study documents have been completed which include protocols, consents, questionnaires, manual of operations and study brochure.
- The study REDCap database is operational and all case report forms have been developed.
- CRFs have been piloted at multiple participating sites and finalized on April 2015.
- Research ethics applications and contracts have been submitted for the POSITIVE and POSITIVE-Adherence studies. In addition, research ethics applications and contracts have been submitted for the Transplant Biobank Registry, which existed at 5 centres prior to the inception of the CNTRP and has now been expanded to 7 centres (See table 1).
- With the assistance of Dr. Lacaze from MICYRN, we were able to obtain waiver of CTA by Health Canada for tacrolimus pharmacokinetics on December 24th 2014.

- Research personnel were hired and trained to support the aims of Project 6 and include a project manager (SickKids), a data coordinator (SickKids), a research assistant (SickKids), two research coordinators (1 at SickKids and 1 at McGill), a biobank lab technician (SickKids) with one lab technician pending recruitment in Stollery for the immune lab. Some of these staff are supported through institutional matching funds at SickKids. Research personnel have been involved with setting up study processes and procedures. These staff have since been involved in training research personnel at participating centres, to date 9 out of the 14 centres have been trained on study procedures.
- Recruitment for the POSITIVE study launched successfully at SickKids in March 2015 and has since enrolled 16 incident transplant patients and reconsented 95 prevalent transplant patients out of the total of 470 prevalent patients (425 SickKids, 18 Alberta Children's, 27 Winnipeg Children's) recruited previously in the transplant Biobank registry. The latter will provide a validation cohort for POSITIVE including linking to long term outcomes registries.
- The questionnaires and REDCAP data entries have been done in 100% of enrolled incident and 69% of prevalent patients.
- The POSITIVE-Adherence study launched at SickKids in July 2015 and CHUM in June 2015 has enrolled 2 participants to date. Currently for the POSITIVE Study we are at 50% of our target for year 1 for incident transplants and 150% for prevalent transplants (figure 1). Given that this is only with one site actively recruiting we expect to catch up quickly as additional sites launch recruitment. As POSITIVE-Adherence has just recently started recruiting it is still early to see recruitment trends.

Table 1: Study Site Ethics, Contract & Recruitment Status

SITE	REB	SERVICE AGREEMENT	RECRUITING
SickKids	Y	N/A	Y
Montreal Children's	Y	Y	N
Stollery	Y	Y	N
Alberta Children's	Under review	Under review	N
Winnipeg Children's	Under review	Y	N
CHU Sainte Justines	Under review	Under review	N
BC Children's	Submission Pending	Under review	N
Toronto General Hospital	Y	Under review	N
Vancouver General	Y	Y	N
St.Pauls Hospital	Y	Y	N
Royal Victoria Hospital	Y	Y	N
Centre Hospitalier Universitarie Montreal	Y	Y	Y
Foothills Medical Center	Under review	Under review	N
Ottawa Hospital	Y	Y	N

Figure 1: Year 1 Enrollment Status



Results & Impact: Results of the main study are pending completion of recruitment. Preliminary studies are currently ongoing that will contribute to the analysis of P6 aims, the status or results of these studies as they relate to each aim are as follows:

***Aim 1a**: Pharmacogenetics Aim (Mital):* A single centre pharmacogenetic trial of tacrolimus after solid organ transplantation is underway since 2013 and is anticipated to be completed in 2016. The results of this study will provide important data for **Aim 1** of the POSITIVE study (PI: Mital). Three abstracts related to pharmacogenetics of post-transplant immunosuppression from prevalent patients were presented at CST 2014 and related manuscripts are in various stages (1 under review, 1 being submitted, 1 in preparation) with a CNTRP trainee (Habbous).

***Aim 1c**: Immune phenotyping aim (Urschel):* In the past year, we have participated in a **Core 2** collaboration to perform standardized immune assessment of the lymphocyte phenotypes using identical samples, equipment, processing standards and joint analysis and comparing the results achieved in various centers across Canada. The results were orally presented at the World Transplant Congress and discussed within a report paper. A manuscript is in preparation and details of a follow-up study are being discussed. Urschel is part of the working group. The successful performance and achievement of comparable results across Canada will help facilitate future studies with less need for transport of samples improving sample quality and reducing cost. All assays are included in a SOP collection within **Core 2** to warrant CNTRP wide similar standards and proceeding and optimize quality, validity and comparability of the results. In regards to immune phenotyping and function for **Aims 1** & **2**, the Urschel lab has established additional techniques for assessment of pediatric post-transplant patients with a focus on viral infection (EBV/CMV). Results have been presented and publication is in preparation. Our group has further published a study on immune phenotype and interaction with the innate immune system in children after heart transplantation with emphasis on the particular aspects of blood group (ABO) incompatible transplantation. A second manuscript assessing the maturation and development of B-cell memory in children after heart transplantation, using the methods proposed for Project 6 is being submitted. The findings reveal new aspects of the immature immune system that will be assessed within the currently proposed approach.

***Aim 2**: EBV/PTLD aim:* We have done preliminary genotyping studies on selective major EBV latent and lytic genes where we have examined viral strains among patients with primary EBV infection after transplantation versus healthy subjects. The preliminary data provide further evidence that strengthens the rationale for this study.

Aim 3: In a truly unique model of collaboration, we have established a network of pediatric and adult transplant programs across Canada to study determinants of adherence. This ambitious effort reflects the strong collaborative partnerships enabled through the CNTRP.

Interactions within the project

Project 6 is unique through the establishment of a research network across 14 centres in Canada, the largest of its kind, which includes both pediatric and adult centres and spans solid organ and hematopoietic stem cell transplants. This is a major strength of our network that is allowing us to study and potentially improve outcomes throughout the lifetime of a transplanted patient. A Steering Committee for the POSITIVE Study is successfully established and meets via teleconference monthly to discuss project progress and direction. The POSITIVE-Adherence aim also holds regular monthly conference calls and has been since November 2013. Data

committee meetings are held every 2 weeks by conference call. We also have annual in person meetings in conjunction with the CST annual meeting to develop the project and engage members. Two such in person meetings have been held for the larger group and an in person meeting of the 3 co-leads took place in Toronto in December 2014 to develop and finalize the project SOPs and CRFs. Future standing meetings are also being planned with research coordinators as the study launches and expands recruitment. A number of P6 investigators serve as liaisons on other CNTRP project calls and likewise we have invited other Projects to provide liaisons to join the P6 calls. The leads and co-leads have also had calls with other Project leads to discuss integration and synergy. Agenda items and minutes are circulated to the members before and after each call.

Interactions across the CNTRP

We are participating in the standardized immune cassette development led by **Core 2** by providing samples from POSITIVE patients for immune phenotyping using the standardized platform. Simon (P4 project liaison) is on the working committee. Immunoassay SOPs are being sent to **Project 4** so as to align sample processing and storage procedures. P6 provides a novel component to this collaboration as duraclone tubes have never been tested in a pediatric population. Having samples run on the Navios platform will produce additional panels which extend beyond what we had originally proposed. Collections will begin in September when we are expected to receive the tubes from the Beckman.

We will collect data and samples for validation of inflammasome markers in a pediatric cohort associated with graft injury identified in adults in **Project 3** as well as interaction between inflammasome activation and immune maturity or viral infection. The amount of blood required for this is well within our planned collection of ~5-8 ml sample for biomarkers at enrollment, at 1-3 mos post transplant, and at 1 year post-transplant. As requested by **P3**, these samples will be annotated with data regarding rejection episodes and graft dysfunction episodes.

EBV genotypes associated with EBV disease identified in **Aim 2** of our project will be validated in adults with EBV through **Project 5**. Adult patients with EBV viremia and/or PTLD have been banked through UHN, these samples will be shared and used for validation. There have been two calls (Dec 2014, Jan 2015) to discuss project integration and ensure that common specimen time points and data required for project integration have been discussed. In order to support **P5** in their study of outcomes of SOT from high risk ID donors, we have included data on development of HIV and hepatitis B/C in pediatric SOT recipients during 1 year follow-up in our CRFs. This data will be shared with **P5**.

We are collaborating with **Core 1** to analyze cost-effectiveness of implementing healthcare system changes that can enhance medication adherence after transplant. In conference call with Scott Klarenbach (November 6th, 2014) from **Core 1**, it was determined that no additional data collection is needed at this time beyond the planned data collection for **Aim 3**. It is anticipated that analysis of **Aim 3** data will identify which healthcare system strategies are associated with improved medication adherence. These strategies will then be costed through **Core 1**. The potential impact of improved adherence on clinical outcomes of reduced rejection and improved graft longevity will be modeled to calculate impact on cost savings. This will provide us with cost-benefit analysis of healthcare system strategies for improving medication adherence.

Finally, we are working closely with **Project 2 & 5** in an effort to standardize the processes for access to data and samples for research from deceased donors from Trillium Gift of Life for CNTRP projects. The processes implemented in Ontario will be used to involve other OPOs in other provinces and provide a standardized national framework for these efforts.

New research & collaborations

Three new research studies have been initiated that leverage the infrastructure created for Project 6 through the CNTRP. Two of the studies have leveraged the network to successfully obtain external funds. These studies are as follows:

1) *Allergy and Immunity* (PI: Avitzur) – The POSITIVE study has incorporated family questionnaires at baseline and follow-up to assess incidence and type to assess incidence of allergic/immune conditions post transplant. This multi-centre effort will enable development of a future study exploring immune mechanism and predictors of allergy and immunity post transplant.
2) *Pharmacogenomic-guided immunosuppression in pediatric transplant recipients* (PI: Mital): **Aim 1** received funding through Astellas Pharma Canada Inc to collaborate with the iGeneTrain consortium, an international transplant consortium, to genotype POSITIVE study patients using a transplant-specific array (iGeneTrain) to study genetic determinants of multiple outcomes post-transplant not limited to pharmacogenetics. Plans to begin genotyping are underway.
3) *Extreme Phenotypes of PTLD* (PI: Allen): This ancillary project was funded by Enduring Hearts Inc. (USA) which will look at whole exome sequencing of Th1/Th2 / Th17 and Treg cyotokines in extreme phenotypes of PTLD. This study will synergize directly with **P6&5**. Another grant application related to extreme phenotypes of PTLD was submitted to CIHR which aims to address the relationship between genetic variations in cytokine genes mediating the immune responses associated with T helper cells and extreme clinical phenotypes of post-transplant lymphoproliferative disorder (PTLD).

Next Steps (Year 3 plan)

1. Finalize and execute Services Agreements and REB approvals at all pediatric and adult participating sites
2. Train all study coordinators at all participating pediatric and adult sites.
3. Have the developed REDCap database in active use at all participating centres recruiting subjects.
4. Finalize Manual of Operations
5. Recruitment of 80-100 incident SOT patients
6. Recruit/re-consent 100-150 prevalent SOT patients
7. Recruit ~20-40 new transplant recipients who develop EBV/PTLD post transplant
8. Launch POSITIVE-Adherence and recruit 100-120 participants
9. Launch HSCT arm of POSITIVE study

Publications and Presentations

See attached list of publications and presentations.

Core 1 Ethical, Economic, Legal and Social (EELS) Issues in Transplantation

Leads: Prof Timothy Caulfield, University of Alberta
Co-Leads: Prof Jennifer Chandler, University of Ottawa and Dr. Scott Klarenbach, University of Alberta

Original aims/sub-aims and changes

The overall objectives of Core 1 are to:

- Identify emerging EELS issues, including:
  - The relevance of existing legal frameworks and ethical norms;
  - Public perceptions/representations in relation to several issues central to public support of, or fears about donation;
  - The development and implementation of novel incentives and procurement initiatives
- Provide support on EELS issues for the science and policy work of all the relevant CNTRP Projects;
- Lead and facilitate policy translation and public engagement; and
- Create unique interdisciplinary EELS opportunities for training of highly qualified personnel and emerging scholars.

Specific objectives of Core 1 in relation to each of its Research Platforms:

Platform 1: Legal Frameworks and Ethical Norms

- Map relevant legal norms as they relate to concepts such as consent
- Explore the potential impact/benefit and legality of new incentives policies
- Examine the attitudes of families toward the decision for DCD
- Explore the relevance and evolution of ethical concerns such as commodification and exploitation
- Respond to legal/ethical needs of all CNTRP projects

Platform 2: Research Ethics Challenges

- Engage in mixed methods research (surveys, interviews, consensus workshops, and legal scholarship) exploring issues to do with consent, the right to withdraw, the control and management of tissue/health information and governance, and research ethics challenges associated with next generation genome sequencing technologies
- Will provide guidance based on research results to CNTRP projects on a range of practical research ethics challenges

Platform 3: Health Economics and Economic Evaluation

- Conduct contemporary high-quality health care costing, using a population-based provincial dataset;
- Conduct a high-level economic evaluation to determine the utility and scope of future investments in transplantation such as: novel strategies of organ perfusion and repair; increasing numbers of donors through strategies to recruit living donors, DCD and marginal

donors; use of novel biomarkers that may reduce rejection and ameliorate the consequences of graft-vs-host disease; interventions at the level of the health care system or patient that improve medication adherence

Platform 4: Public Representations and Engagement

- Examine how the popular press, including print and online media, as well as new media (e.g. blogs, social networking websites), represents 1) organ donation issues, 2) incentive policies, 3) our relationship with tissue/organs, and 4) developments in neuroscience that bear upon questions of awareness, prognosis and suffering in unconscious or dying patients, among other topics.

Major accomplishments

The Core 1 team has done considerable work exploring legal issues surrounding consent for organ donation; the potential benefits, impact and legality of incentive mechanisms; and issues of privacy, property and controls of genes and cells, work that has resulted in numerous presentations and publications (see below). In addition, a qualitative study of Canadian family decision making in the context of DCD is well underway, and a large public survey (n=1200) has been administered investigating the public's opinion of a range of organ donation and transplantation issues, including questions of research ethics. The Core 1 team has also completed a systematic review of the cost effectiveness of solid organ transplantation; a scoping review of strategies to increase organ transplantation, and de nova health care costing of organ transplantation. The members of the Core 1 team have also completed a study exploring public reactions to neuroscientific studies of disorders and consciousness, as well as one investigating newspaper portrayals of biobanking; and have produced a number of short "Fast Facts" policy documents exploring a range of issues (see below). Lastly, in conjunction with **Project 2** members, the Core 1 team developed and implemented the CNTRP's Patient Engagement Strategy, which to date has resulted in a workshop in Montreal, the development of a national survey that has been administered to health care practitioners, patients, families, researchers and the general public, and the organization of a national workshop, which is scheduled for November 25-26, 2015 in Toronto.

Interactions within the core

It is advantageous for each of the 4 Aims to be part of Core 1 because: (a) organ donation and transplantation raises many issues out-side the strictly medical and scientific disciplines and it is necessary to examine these social issues from the wide range of perspectives encompassed by the 4 Aims; (b) the different Aims are complementary in this regard (for example, exploring media representations and public opinion of donation issues under Aim 4 can inform suggestions for policy or legal reform under Aims 1 and 2) and there are many issues that cut across multiple Aims, allowing for a rich and nuanced analysis from multiple perspectives (for example, we are exploring issues associated with DCD from legal, ethical (Aim 1), and public perspectives (Aim 4); we are also exploring issues associated with consent under Aims 1, 2 and 4); (c) many of our team members have broad expertise and are able to contribute to multiple aims (specifically Aims 1, 2 and 4) which allows for flexibility in how Core 1 functions and valuable collaborations between team members (see list of outputs below); (d) the highly specified expertise in Aim 3 provides a unique perspective and enhances the depth of work being done under the other Aims (for example, work has been done exploring the law, ethics and public opinion associated with using financial incentives to increase donation which was

greatly enhanced by the economic analysis provided by Aim 3 demonstrating the feasibility of different incentive models).

Interactions across the CNTRP

Core 1 has worked with many team members across the CNTRP and sends out quarterly e-mail updates to the Project and Core leads to seek input/collaboration and to create opportunities for other CNTRP members to inform Core 1 of any EELS issues arising in their work.

Specifically, Core 1 members has collaborated with Greg Knoll, Linda Wright, Sam Shemie, Sonny Dhanani and Samantha Anthony from **Project 2** on a number of initiatives including several Fast Policy Facts documents, the development and implementation of the CNTRP's Patient Engagement Strategy, the development of a public survey that is currently being administered, the legal/ethical/social analysis of the "family veto" issue in organ donation; and family decision-making in the context of DCD in association with **Project 2's** DePPaRT study. Collaboration with John Gill (**Core 2**) and Greg Knoll (**Project 2**) has also resulted in a peer reviewed publication examining the potential use of financial incentives to increase donation in Canada as well as high profile public lecture where this work was presented to the public. Core 1 has also supported the work of James Shapiro (**Project 1**) by providing background work and the development of an integrated economic evaluation for an ex vivo liver perfusion study. Lori West and Denis-Claude Roy (**Project 4**) also participated in a workshop hosted by members of Core 1, which has resulted in a peer-reviewed publication providing policy recommendations to address privacy challenges in cell-based research. In addition, Core 1 participated in a Policy Advisory Group at the University of Alberta Hospital that resulted in a draft DCD policy for the NICU, which relates to and furthers the work being done under **Project 6** to improve pediatric outcomes in transplantation. Further, in response to requests by members of several CNTRP Projects, Core 1 is examining the rights and interests in human bodies and biological materials through a Fast Policy Facts document and academic publication that is in preparation.

New research & collaborations

Canadian Blood Services has been and continues to be an important collaborator by funding a Core 1 team member (Toews) through the James Kreppner Fellowship, establishing the Donation Legal Research and Health Policy Group with several members from Core 1 and **Project 2**, and by hosting a workshop on Effective Requesting that involved significant participation and contributions by Core 1 members. The Core 1 Leader, Timothy Caulfield, has also collaborated on an international scale through the European Commission's International Symposium in the Hague addressing organ trafficking and transplant tourism, where he chaired a session resulting in a paper that has been submitted to the conference organizers with plans for submission to a peer-reviewed journal. In addition, Core 1 is collaborating with a colleague from the University of Adelaide in Australia on legal issues associated with consent for donation, which will provide a valuable international perspective to this important issue. The CNTRP has benefitted from these collaborations by raising the CNTRP's profile through these significant events, by gaining access to the work that has been done by other collaborators and organizations on many issues relevant to Core 1's work, and by creating valuable partnerships that will continue into the future. Lastly, Fortin secured funding from CIHR ($25,000) to support the national workshop: *Patient Engagement in setting Research Priorities in Transplantation within the Canadian National Transplant Research Program.*

Next Steps (Year 3 plan)

Platform 1: Legal Frameworks and Ethical Norms

- Complete legal review and critique of the "family veto" issue
- Explore potential ethical and legal issues related to organ donation by individuals seeking physician-assisted death
- Engage in legal assessment of the inclusion or exclusion of non-Canadians from organ allocation waitlists
- Continue qualitative study of Canadian family decision-making in the context of DCD
- Continue exploration of ethical, legal issues related to organ transplant tourism
- Complete additional Fast Policy Facts documents on brain death, transplant tourism (and related paper), and other relevant topics that arise

Platform 2: Research Ethics Challenges

- Complete survey of Alberta public on research ethics and other donation/transplantation issues
- Host research ethics workshop

Platform 3: Health Economics and Economic Evaluation

- Continue de novo health care costing of organ transplantation
- Complete scoping review of strategies to increase organs for transplantation
- Complete systematic review of the cost-effectiveness of solid organ transplantation and disseminate in user-friendly format to CNTRP members

Platform 4: Public Representations and Engagement

- Complete media study examining the issue of presumed consent
- Complete media study examining how the "family veto" issue has been represented in the United States
- Complete survey of patients and healthcare workers under Patient Engagement Strategy
- Host the national Patient Engagement meeting

Publications and Presentations

See attached list of publications and presentations.

Core 2 - Research infrastructure and registries support platform

Leads: Dr. Kirk Schultz, University of British Columbia
Co-Leads: Dr. Donna Wall, University of Manitoba and Dr. Kristjan Paulson, University of Manitoba

Original aims/sub-aims and changes

1. Develop the foundation for national transplantation registries to evaluate transplant outcomes in Canada, starting with patients involved in CNTRP studies.
   - Aim 1A. Consensus building on Canada's future transplant registry
   - Aim 1B. CNTRP Outcomes Database (COD)
   - Aim 1C. Develop a biostatistical core for registry research in Canada

2. Create national methodology standards and standardized national 'core' resources and services for interventional clinical trials
   - Aim 2A. Develop national infrastructure strategies for the performance of large interventional clinical trials that involve multiple transplantation types and communities.
   - Aim 2B. Facilitate project development and performance by creating a national resource system for interventional clinical trials studies

3. Create national methodology standards and standardized national 'core' resources and services for biorepositories
   - Aim 3A. Build a national consensus regarding necessary methodologies and standard operating procedures for correlative biology studies in transplantation in Canada
   - Aim 3B. Develop a national virtual biorepository network of biological samples for transplant
   - research studies
   - Aim 3C. Evaluate the feasibility of using standardized biological cassettes in CNTRP research

4. Establish a training program for personnel essential to the future of transplantation in Canada. (***Moved to Core 3***)

The ambitious aims of Core 2 required the hiring of a 0.5 FTE manager to coordinate both the daily administrative activities of Core 2 as well as the development of the biorepository. Funding for this position came primarily out of the Biorepository (Aim 3AB), which had already budgeted a manager position.

Aim 1
There have been no changes in the aim's design or direction since the grant was awarded. However, in retrospect, we were too optimistic about the timeline in which these goals might be achieved. In particular, data custodians carefully safeguard data contained in administrative databases. We believe we have a model that will allow this data to be safely utilized for research goals with minimal risk to patient privacy.

Aim 2
A major restructuring of the three planned interventional trials was made to reduce them to one interventional trial and a literature review with national practice survey. Upon discussion, this consolidation of trials was recommended by the Executive Coucil and approved by Dr West, and the amended proposal for the Project 4 survey was recommended by the Evaluations Committee and approved by Dr. West. A major focus of Core 2 has been the first CNTRP multicentre trial (Project 4 CARE trial) that has informed the needs and complexities of the CNTRP core processes.

Aim 3
The biorepository efforts were delayed as the aim reorganized leadership; due to prior commitments, Dr. David Wishart and Dr. Bruce McManus stepped back from the development of this aim, and Dr. Kirk Schultz took on the Lead responsibilities of creating national methodology standards and biorepositories. Dr. Bruce Ritchie, of the Canadian Biosample Repository located at the University of Alberta, has also agreed to provide input and assistance into the development of the CNTRP Virtual Biorepository efforts, however prior commitments limit the amount of time he has available to dedicate to this project. Additionally, the Immune Monitoring portion of this aim was originally going to be completed within FY2, however they will be completed over FY1-2.

Aim 4
The training components outlined in Aim 4 were moved to a dedicated training core (**Core 3**) under Drs. Lee Anne Tibbles, Silvy Lachance and Sonny Dhanani.

Major accomplishments

Core 2 was able to make progress across all Aims. Core 2 contacted and evaluated all the Provincial/Regional academic research organizations (AROs) across Canada that could support the clinical study activities of the CNTRP. At the end of this vetting process, we were pleased to announce a collaborative partnership with the Montreal Health Innovations Coordinating Centre (MHICC) to assist in the development and management of all clinical studies taking place after the Project 4 CARE Trial (under agreement with the Hematology Research and Clinical Trials Unit at the Vancouver General Hospital (HRCTU/VGH). The MHICC has already begun to work with Dr. Kristjan Paulson, Core 2, Aim 1, to develop and operate the *CNTRP Patient Registration Database* (now undergoing final contracts review) to track all trial patients within the CNTRP.

Core 2 also successfully facilitated the integration of the *BK Viremia: Kinase Inhibition to Decrease Nephropathy Intervention Trial*, a pre-existing project run by Dr. Lee Anne Tibbles, into the CNTRP, **Project 5**, under MHICC management. Core 2 also assisted the **Project 1** *OrganOx Metra Liver Ex Vivo Perfusion Trial* grant preparation and submission process in collaboration with the MHICC. Contracts for sponsor/ARO are currently under review for the management of the *Continuous Alloreactive T cell depletion and Regulatory T cell Expansion (CARE) trial* (detailed in the **Project 4** report), with the anticipation that the CARE trial will open in fall 2015 for accrual.

The *CNTRP National Virtual Biorepository* released its start-up kit for pilot testing with **Project 3**, and has linked the CNTRP server for the Canadian BioSample Repository inventory software, as well as a training server for clinical data collection in REDCap. It is expected to attract wide

interest from other projects and groups affiliated with the CNTRP based on its simplicity and low operational cost. Core 2 and the Biorepository working group are currently in discussions with the Canadian Society of Nephrology to share our platform with their regional members to create a parallel repository of prospective specimen collection, as well as long-term inventory of pathology samples.

The *CNTRP Immune Monitoring Aim* initiated and completed a Phase I study to test the implementation of standardized flow cytometry using Duraclone tubes at 5 sites across Canada; three CNTRP research sites have machines provided through in-kind lease by Beckman-Coulter, and two clinical labs with access to Navios flow cytometers have also been included. Results were presented at the World Transplant Congress in June 2015.

Interactions across the CNTRP

Interactions within Core 2 and across the CNTRP are effectively one and the same. Core 2 aims to facilitate networking and provide services that allow for 'plug and play' integration into projects while providing value through economy of scale and generating cross-project interactions with projects that might otherwise remain silo'ed within their immediate group. To this end Core 2 is achieving this through direct involvement with all CNTRP projects such as attendance at all project teleconferences, pan-CNTRP working groups to tackle specific issues arising, and providing processes and infrastructure such as the Virtual Biorepository, Patient Registration Database, and larger collaborative agreements with providers such as the MHICC and Beckman-Coulter. Core 2 is also able to provide assistance with financial and contractual facilitation and oversight where desired to assist projects in meeting their objectives. The Patient Registration Database, and standard consent, should be implemented across all projects within the CNTRP, allowing researchers to follow subjects across provinces and track long-term outcome data. As well, the Biorepository has started piloting at three different sites, and will be expanding to a fourth very shortly. We have already received significant interest in the system from various provincial transplant and medical organizations, which will be expected to attract development of new partnerships.

New research & collaborations

As described within the major accomplishments, Core 2 contacted and evaluated all the Provincial/Regional SPOR support units, as well as other academic research organizations (AROs) that could support the clinical study activities of the CNTRP. It became apparent that the Montreal Health Innovations Coordinating Centre (MHICC) offered a tremendously valuable collaborative partner for the group and was contracted to partner in future trials and to manage the CNTRP registration process – a key tool in the development of interoperability between the projects and across the CIHR pillars. Core 2 also successfully facilitated the integration of the *BK Viremia: Kinase Inhibition to Decrease Nephropathy Intervention Trial*, run by Dr. Lee Anne Tibbles, into the CNTRP, Project 5, under MHICC management.

The Immune Monitoring Initiative group developed a cassette for flow cytometry in collaboration with Beckman-Coulter, who has recently standardized a set of flow cytometry panels for pre- and post-transplant immune monitoring as part of the ONE Study (http://www.onestudy.org/), a European Union initiative. Beckman-Coulter provided an in-kind lease (valued at $725,000) of 3 NAVIOS flow cytometers to CNTRP research sites in Vancouver (Levings lab), Edmonton (West lab) and Montreal (Deslisle lab) as well as 100 sets of Duraclone panels (worth about $25,000). Research labs were trained quickly and effectively to use the NAVIOS/Duraclone system by

Beckman application specialists, and will be become part of the CARE Trial biology.

Core 2 and the Biorepository working group are currently in discussions with the Canadian Society of Nephrology to share our platform with their regional members to create a parallel repository of prospective specimen collection, as well as long-term inventory of pathology samples. There is also interest being shown by several agencies of Alberta Health Services to use the biorepository system. Development of CNTRP Standard Operating Procedures (SOPs) will be an important aspect of these interactions.

Additionally, Dr. Kirk Schultz and Dr. Marie-Josée Hébert are collaborating on biomarker validation studies using an anti-LG3 ELISA developed by Dr. Hébert's lab.

Next Steps (Year 3 plan)

Aim 1

The Patient Registration Database (PRD) will be implemented into all CNTRP studies consenting patients, and will collect basic information on patients with the goal of linking patient data held in different locations with data captured in CNTRP clinical studies. This database will be actively managed the MHICC.

Two draft protocols have been developed to link data contained in the CBMTG Registry (maintained and developed by the Canadian Blood and Marrow Transplant Group) with the Canadian Organ Replacement Registry (CORR) and administrative databases held by Canadian Institute for Health Information (CIHI). The first protocol looks to understand how access to transplant might vary across Canada by a number of sociodemographic variables (rural location, poverty, education, income). We hypothesize that access to both SOT and HCT would be inferior in disadvantaged populations. The second project reviews the development of chronic diseases following transplant, using administrative databases to review the incidence of chronic diseases (heart disease, diabetes, chronic lung disease, etc) in transplant recipients, and would be linked to a future Project 7 on improving outcomes for transplant patients.

Aim 2

We aim to finalize and implement the CNTRP interventional trial Manual of Procedures, and leading to the creation of the Clinical Trials Operations Committee. This also involves the creation of a Data Safety Monitoring Board (DSMB) (for which Dr. Paul J. Martin at the University of Washington has been recently recruited as a Chair), protocol working groups, templates for standard operating procedures, consents, clinical trial data collection, organization, reporting forms, procedures for submitting clinical trial applications to Health Canada, and audit preparedness. These will be tested and refined with subsequent studies. This process will involve significant mentorship of the junior clinical principal investigator currently co-leading the CARE trial and the establishment of trial timelines and deliverables that will be critical for future CNTRP studies. Starting in year 3 we also plan to develop web-based training for investigators designing trials.

Aim 3

The Biorepository will complete its pilot phase at the end of year 2 and enter the full distribution and support phase. Based on the experience of the pilot sites, a start-up guide and manual will be developed, along with training videos, to help new sites operate the Biorepository system. 'Biorepository in a box' kits will be available for purchase at around $3000 and will include all hardware (computer, scanner, flatbed, overhead camera, and label printer with 5000 labels)

necessary to start banking samples. The system is geared towards prospective sample collections, however recent hardware changes and upcoming software updates will allow it also to index existing sample collections efficiently. An oversight committee will be established to review access requests to already banked samples across the CNTRP National Virtual Biorepository.

The Immune Monitoring group will perform a phase II study involving patient samples that is being planned and will be completed in the next half year. This data is expected to lead to a publication in late 2015 or early 2016. More importantly, we are using the experience gained in the phase I study to set up similar immune monitoring procedures for the CARE trial in Project 4.

Publications and Presentations

See attached list of publications and presentations.

Core 3 - Academic and Career Training Platform

Leads: Dr. Lee Anne Tibbles, University of Calgary
Co-Leads: Dr. Silvy Lachance, Université de Montréal and Dr. Sonny Dhanani, Children's Hospital of Eastern Ontario

Original aims/sub-aims and changes

CNTRP, spanning the breadth of investigation from basic biology through health systems, economics and policies, offers the ideal training environment for cross-pollination of clinical and basic science trainees on a national basis, together with all CNTRP investigators and participants. A variety of comprehensive training initiatives across the program serve to develop a new generation of highly qualified personnel for the transplantation field, from physicians and surgeons, Masters & PhD scientists, allied health and technical personnel to trainees in ethics and law. The CNTRP Core 3 Academic and Career Training Platform consists of two aims:

Aim 1: The Academic Training Program (Curriculum and Mentoring)
Aim 2: The Professional and Technical Development Program.

Academic Training Program

Over the first two years, the objectives of the CNTRP Academic Training Program were to set standards for admission to the program, select appropriate candidates, provide each trainee with an individual training plan with requirements and timelines, ensure mentorship relationships are set up and effective, and provide web-based modular learning, professional development and networking opportunities.

Professional and Technical Development Program

The goal of this aim was to provide all members of the CNTRP with educational modules to ensure development of a common language and scientific understanding amongst the diverse participants from the three research communities (SOT, BMT, Donation). Additionally we sought to ensure common approaches to biobanking of samples, clinical trial case report forms, common data management protocols, and standard operating procedures for technology used throughout the CNTRP.

Changes: Originally conceived as part of Core 2, the Training Program became an independent entity in March 2013 under the leadership of Drs. Tibbles, Dhanani and Lachance (SOT, Donation and BMT leads)

Major accomplishments

Academic Training Program

- Established entry criteria for trainees (Sept 2013)
- Developed application form (Sept. 2013)
- Established website (www.cntrp.ca/training) (Sept 2013)

- Recruited trainees (18 Trainees entered Jan. 2014; 9 entered December 2014; call for next round of applicants is currently underway)
    - These trainees represented a broad range of expertise, education and geographic distribution. (8 Masters of Science, 9 PhD Students, 9 Postdoctoral Fellows, 1 Research Associate; from Halifax, Montreal, Toronto, London, Winnipeg, Calgary, Edmonton and Vancouver)
    - Trainees involved with Projects 1,2,3,4, 5 and 6.
- Initiated web module development
- Defined core content for all trainees (see appendix 3)
- Produced live Webinars geared to core curriculum content (10 sessions, see appendix 1)
- Amalgamated existing web modules and recorded sessions from several Transplant Training Programs across the country (see appendix 2)
- Recruited mentors and developed mentorship section of website (20 mentors volunteered to advise trainees)
- Developed Individual Training Curriculum template
- Supported travel to national and international scientific meetings for trainees to present their work
- Fostered Professional Development with sessions on:
    - Manuscript Writing (interactive in person group process with Drs. Roslyn Mannon and Kathryn Wood) – June 2014
    - Pecha Kucha Presentation format, (theory, group work and presentation at 2015 CNTRP Annual Meeting) – June 2015
    - Peer review of abstracts for national and international scientific meetings (group and individual work with feedback) – March 2015
- Hosted networking sessions between trainees and Investigators across the CNTRP
    - In person "speed dating" with participation of all trainees and 15 Leads/Co-leads of Projects/Cores - June 2014
    - Trainee networking events at annual meetings – June 2015
- Partnered with Astellas Canada to develop the CNTRP Astellas Training Award Competition, Two grants, maximally $50,000 over two years (peer review currently ongoing). (www.cntrp.ca/training_award)
    - to support the training and development of future researchers in the field of organ and cell donation and transplantation
    - to advance CNTRP's objective to increase organ and tissue donation in Canada and enhance the survival and quality of life of Canadians who receive transplants with the ultimate goal of improving patient care

Professional and Technical Development Program

- Established website
- Initiated web module development
- Amalgamated existing web modules
- Defined core content for common platforms (see appendix 3 below)
- Collaborated with **Project 3** to develop module on Methods for Biobanking Samples across the CNTRP
- Collaborated with **Core 2** to develop module on Virtual Repository for Biobanked Samples across the CNTRP
- Collaborated with **Core 2** to develop module on Common Information Platform for Patient Information in the CNTRP

Interactions within the core

The Core 3 team meets on average twice a month to develop and plan the academic training program. All trainees also meet twice per month on the live webinars. All trainees participate in the Annual CNTRP Meeting for in-person sessions. There are opportunities at every live webinar for questions regarding the presentation, the Training Program, and any obstacles to advancement of their learning.

Interactions across the CNTRP

Trainees are participating from all CNTRP Projects.

For the 2015 Annual CNTRP Meeting, all of the trainees participated in learning the Aims of all of the different Projects, as part of their 'Pecha Kucha' presentations. This presentation style (20 slides, each displayed for 20 seconds automatically progressing) was introduced in a webinar by one of the trainees who had prior experience with the format. The trainees were formed into groups including students from 2-4 projects. They were assigned to develop and present actual and potential interactions between projects, from the point of view of a Project that was not their own. To accomplish this they were required to contact the Leads of the Project, understand the interactions between this project and all others, and construct and present at a plenary session their Pecha Kucha presentation.

Next Steps (Year 3 plan)

- Continue development of live and archived webinars
- Increase partnerships with industry, professional associations, public to provide support to more trainees
- Liaise with Royal College of Physicians and Surgeons of Canada to develop some of the topics in the Focussed area of Competence in Transplantation as joint webinars in the CNTRP; develop similar approach for BMT and Donation topics
- Assess mentorship meetings and increase the participation of mentors in the trainees' development
- Assess individual curricula for all trainees
- Liaise with the Canadian Society of Transplantation "Research Fellows in Transplantation" sessions (next session on developing your CV and getting your first job); develop similar liaisons with training aspects of the Canadian Blood and Marrow Transplant Group and the Critical Care Clinical Trials Group
- Substantially increase the number and scope of the technical and professional webinars to cover many more aspects of best practices across the CNTRP
- Encourage more participation from CNTRP investigators to partake of the live and archived webinar series.

Appendix 1 – CNTRP Produced live Webinars

Organs, Tissues and Ethical Issues
Linda Wright - Project 2 Co-Lead
https://cntrp.adobeconnect.com/p5fppn3rera/

Living Kidney Donation
Dr. Amit Garg - Project 2 member
https://cntrp.adobeconnect.com/p3buv1ihxq4/

Is necroptosis the missing link to graft rejection?
Dr. Zhu-Xu Zhang - Project 3 member
https://cntrp.adobeconnect.com/p3424bzqbn2/

Transplant Tolerance
Dr. Megan Levings - Project 4 Co-Lead
https://cntrp.adobeconnect.com/p4iqxf73vln/

Consent, Incentives and Transplantation in Canada: What Does the Law Say?
Prof. Tim Caulfield - Core 1 Lead
https://cntrp.adobeconnect.com/p2k7hmpaj8c/

Cell Therapy Research: Exciting opportunities across Canada - Depletion of Alloreactive T cells
Dr. Denis Claude Roy - Project 4 Co-Lead
https://cntrp.adobeconnect.com/p2ceqkpnl0z/

Indications and Outcomes of Clinical Islet Transplantation, and Future Plans for Stem Cell Transplantation in Type 1 Diabetes
Dr. James Shapiro - Project 1 Lead
https://cntrp.adobeconnect.com/p6ipdpze7kl/

Surgical Innovation in Kidney Donation and Transplantation
Dr. Ian Alwayn – Project 1 member
https://cntrp.adobeconnect.com/p4lxt35qse4/

Trainee Session – Pecha Kucha Training
Dr Esmé Dijke – Project 4 Trainee

Evolution of Deceased Donation Research, Practice and Policy in Canada
Dr. Sam Shemie – Project 2 Co-Lead
https://cntrp.adobeconnect.com/p8pr4tadmhh/

Appendix 2 –Webinars from Partner Training Programs Supported by Core 3

Brining the Luster Back to Transplantation: Developing organs & tissues for patients in need
Dr Jason Wertheim - Northwestern University, Feinberg School of Medicine

http://phsa.mediasite.com/mediasite/Play/5152b479f9d0400eb4d77ebbb1338bb81d?catalog=6f044f49-fce4-47b6-bf22-b200c9ee32a3

A Non Conventional Organ Donor: Ethical issues in Xenotransplantation
Dr Lainie Friedman Ross - Carolyn and Matthew Bucksbaum Professor of Clinical Ethics, University of Chicago
http://phsa.mediasite.com/mediasite/Play/341d45e1caa64765b390f2087b1df4fd1d?catalog=6f044f49-fce4-47b6-bf22-b200c9ee32a3

Kidney and Pancreas Transplantation in BC
Dr RJ Shapiro – UBC
http://www.cesei.org/transplant/2013.09.27/2013.09.27.html

Lung Transplantation Overview in BC and around the world
Dr. John Yee – UBC
http://www.cesei.org/transplant/2013.09.27_2/2013.09.27_2.html

History and current practice of Immunosuppression
Dr. David Landsberg - UBC
http://www.cesei.org/transplant/2013.10.04/2013.10.04.html

The Promise of Stem Cells in Transplantation
Dr. Christopher Ong - UBC
http://www.cesei.org/transplant/2013.10.11/2013.10.11.html

Psychological Impact of Transplantation
Dr Melody Preece – UBC
http://www.cesei.org/transplant/2013.10.11_2/2013.10.11_2.html

Islet Cell Transplantation: A Model for cellular transplantation
Dr Garth Warnock – UBC
http://www.cesei.org/transplant/2013.10.18/2013.10.18.html

Heart Transplantation and Mechanical Circulatory Support
Dr Anson Cheung - UBC
http://www.cesei.org/transplant/2013.10.25/2013.10.25.html

Appendix 3 – Core 3 Curriculum

Roles for Canadian National Transplant Research Program Trainee Curriculum for Organ, Tissue, Bone Marrow Donation and Transplantation

CNTRP trainees must demonstrate the requisite knowledge, skills, and behaviours for effective patient-centred care through clinical and research service to a diverse population. Trainees within the CNTRP are expected to be members of the Academic Training Program and to fulfill GENERAL objectives of the training program. Once accepted into the program, an INDIVIDUAL training plan will be designed for each trainee, in collaboration with their primary supervisor, their mentor, and the Lead of their Project or

Core. All academic trainees within the CNTRP are required to have a mentorship plan for achieving their personal goals. Each trainee will identify a supervisor and **mentor** who will provide ongoing guidance and develop INDIVIDUAL objectives for their field of interest. Mentorship is a key component in the development of technical, clinical, ethical and scientific knowledge and competence needed to fulfill the aims of the CNTRP.

The training program will consist of the scientific, clinical, legal and ethical content that the trainee is expected to master during their training. Some of this content will be accessed through web-based modules, some through live webinars, and some in person at the CNTRP Annual meeting, or the specialty society meetings of the solid organ, stem cell transplant or donation communities. The CNTRP has a web-based interface for educational content that will benefit the training program by allowing access to a wide variety of educational modules. These sessions, developed for specific training programs across the country, will be open for all our trainees regardless of funding source, organ group, CIHR theme or training level. The CNTRP will provide recording and webcasting for certain seminars in participating centers, ensuring that the curriculum remains up to date and increases in number and variety over time, and therefore access will be provided to seminars that would otherwise be unavailable. Faculty within the CNRTP will develop new web-based seminars specifically related to the 6 projects which will become widely available, and a real-time research in progress component for CNTRP trainees will be facilitated.

Timelines will be defined, and ongoing participation in the program will be determined by annual reporting. Salary support (up to one half salary) may be provided by the specific Project or Core in which the trainee is associated. Many institutions throughout Canada have committed matching funds for trainees at their institutions. Trainees with external support (CIHR, Kidney Foundation etc) may also participate in the Core III activities and apply for travel support to national and international meetings.

The GENERAL curriculum is designed to provide trainees with a broad overview of issues related to organ donation, stem cell and organ transplantation including scientific, clinical, legal, and ethics, and to encourage them to think about their own particular focus as it applies to problems in donation and transplantation. As well, the aim is to foster innovative research and strengthen the donation and transplant research community through participation in collaborative opportunities and to provide trainees and the transplantation research community with opportunities to participate in knowledge translation and public education activities. Because of the diversity of backgrounds, experience, and interests of trainees, INDIVIDUAL objectives developed by each trainee and their supervisor, and designated mentor rely on more developed and specific domains depending on clinical or laboratory focus on donation and transplantation. Trainees will have acquired advanced knowledge and skills in broader donation and transplantation principles as well as specific objectives pertaining to organ donation, or solid organ, tissue, and hematopoetic cell transplantation.

Roles and objectives

CNTRP trainees must integrate medical and scientific knowledge, clinical skills, and professional attitudes in their provision of research to enhance clinical care and/or research in donation and transplantation. *Medical and Scientific Expert* is the central role in the curriculum framework but only part of the CNTRP GENERAL objectives. The CNTRP trainee must acquire a working knowledge of the theoretical basis of this discipline, including its foundations in science and research in the following domains: Medical and Scientific Expert, Communicator, Collaborator, Manager, Health Advocate, Scholar, Professional

Roles	Key Competencies	Methods to achieve competencies
1. Medical and	a. To be aware of the advancing science of ex-vivo transplant	• Online live Webinars

Scientific expert	protection and repair b. To be aware of the novel methods of increasing solid organ and hematopeitic cell donation c. To be aware of the emerging knowledge of predicting and preventing early graft rejection and GVHD d. To be aware of strategies for immunomodulation and transplant tolerance e. To be aware of methods for predicting and controlling viral complications of transplantation f. To be aware of research improving pediatric outcomes in transplantation g. To be aware of existing legislation and ethical norms to developing and implementing new donation and transplant initiatives	• Archived Lectures from Training Website • State of the Art Lectures recorded at various transplant centres • In person attendance at CNTRP Annual Meeting (required for all trainees) • Travel funds to travel to National and International Conferences (when presenting abstracts) • Stipends to visit CNTRP laboratories for one on one training in advanced techniques
2. Communicator	a. Establish relationships of trust and ethical respect with transplant patients and their families, colleagues, co-workers and fellow scientists. b. Gather and effectively summarize information relevant to patients' conditions, as well as the opinions, hopes and fears expressed by them and their families. c. Gather and synthesize relevant facts and experimental observations, formulate hypotheses and test them, present scientific findings to colleagues and the public. d. Accurately convey relevant information and necessary explanations to donation and transplant patients, their friends and families, referring physicians, colleagues and other professionals. e. Develop a common understanding of the risks and benefits related to organ donation and transplantation procedures, and be able to discuss these with patients, their friends and families, colleagues and other professionals. f. Present oral and written information effectively. g. Deliver clear, thorough explanations of diagnosis, investigations and management with patients, families and the health care team h. Use appropriate language to impart information i. Communicate professionally (accurately, respectfully and in timely fashion) with patients, families, the medical team, colleagues, co-workers and the public	• Participation in Patient Engagement Strategy (Core 1) • Presentations at National and International Conferences and CNTRP Annual Meeting (travel funds provided by Core III • In Person professional training at CNTRP Annual Meeting (Manuscript Writing, New Presentation Techniques)
3. Collaborator	a. Participate effectively and appropriately in the activities of a multidisciplinary team. b. Be familiar with individual roles and collaborate effectively with other professionals in order to prevent interprofessional conflicts and, if necessary, negotiate and resolve them. c. Be familiar and work with community organizations and other professionals which can provide support for transplant patients and their friends and families. d. Work in partnership with fellow learners across all disciplines e. Recognize the importance of interdisciplinary teamwork and respect the diversity of roles, responsibilities, knowledge and skills of other professionals	• Participation in live online Webinar Series • Peer review of abstracts of fellow colleagues prior to submission • Peer review of Pecha Kucha presentations with feedback for improvement • Responsibility for arranging meetings with Mentors, Supervisors and Project Leads for

	f. Demonstrate respectful attitude towards other colleagues and members of the interprofessional team g. Demonstrate medical and scientific expertise in situations other than patient care, such as advising governments, as needed h. Refine and utilize conflict resolution skills when required	Individual Curriculum Development
4. Manager	a. Effectively balance time between research, learning and stress management b. Participate in activities that contribute to the organizational effectiveness of the CNTRP (multidisciplinary meetings, committee work, and conflict resolution). c. Manage research project and career effectively. d. Make judicious use of limited resources. e. Serve in administrative and leadership roles, as required.	• Sharing of Best Practices for work-life balance at CNTRP Annual Meeting (Networking events) • Regular meetings with Mentor to manage Career trajectory • Assume leadership roles in group projects such as presentations at CNTRP Annual Meeting
5. Health Advocate	a. Demonstrate an appreciation of the possibility of competing interests between individual advocacy issues and the community at large b. Identify opportunities for advocacy, health promotion, and disease prevention, and respond appropriately c. Promote organ donation and tranplantion, deceased and living donation, as appropriate d. Identify the determinants of health of the population, including barriers to access to care and resources e. Describe challenges in equitable access to organ transplantation, including but not limited to cost and geography f. Identify vulnerable or marginalized populations within those served and respond appropriately g. Describe how public policy impacts on the health of the populations served h. Describe policies that promote access to organs for donation, including but not limited to Funding for living donors and Legislation that regulates deceased donor organ donation, including but not limited to NDD, DCD, and exceptional distribution i. Appreciate the possibility of conflict inherent in their role as a health advocate for a patient or community with that of manager or gatekeeper j. Appreciate patient safety and the responsiveness of healthcare to patient needs	• Participation in Patient Engagement sessions (Core 1) • Live online Webinars Series • In Person professional development sessions at CNTRP Annual Meeting
6. Scholar	a. Contribute to the development, dissemination, and translation of new knowledge and practices b. Apply lifelong learning skills of the Scholar Role to implement a personal program to keep up to date, and enhance areas of professional competence c. Integrate the available best evidence and best practices to enhance the quality of care and patient safety in Organ Donation and Transplantation d. Critically evaluate medical information and its sources, and apply this appropriately to practice-related decisions,	• Individual Curriculum Goals and Achievements • Presentation at National and International Conferences of individual research outcomes (travel funds provided by Core III

	particularly in relation to transplant patient care. e. Facilitate knowledge acquisition for patients, their friends and families, students, residents, other health professionals, the public at large and other stakeholders (continuous medical education sessions). f. Contribute to the creation, dissemination, application and use of expert, innovative medical knowledge and practices. g. Lead formal and informal teaching sessions on scientific topics	• Participation in Patient Involvement in Research Sessions • Presenting research, journal analysis or techniques to other Trainees and the entire CNTRP community via live Online Webinar Series
7. Professional	a. Demonstrate a commitment to patients and their families, profession and society through ethical practice and professional self-regulation b. Seek feedback from all members of the multi-disciplinary team regarding progress and performance c. Demonstrate recognition of personal limitations and seek help from supervisors and mentors when appropriate d. Demonstrate integrity and a reliable, responsible and respectful attitude e. Demonstrate a commitment to patients, profession, and society through ethical science and practice	• Participation at in person professional development sessions at CNTRP Annual Meeting • Live Online Webinar Series sessions on Ethics and Law