



Canadian National
TRANSPLANT
Research Program

Programme national
de recherche en
TRANSPLANTATION
du Canada

YEAR 3 SCIENTIFIC PROGRESS REPORT

RESEARCH HIGHLIGHTS



Scientific Research Progress Summary from
November 2015 to November 2016

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CNTRP Year 3 Scientific Progress Report

PNRTC



CNTRP 3rd Annual Scientific Meeting
Quebec City - Oct 13-16, 2016

The burden of disease addressed effectively by transplantation encompasses tens of thousands of Canadians with organ failure (kidney, lung, heart, liver, pancreas/islet, bowel) and hematologic malignancies. Full realization of the benefits of transplantation, however, is limited by chronic complications including rejection, graft-versus-host disease (GVHD) and medication side-effects as well as disease recurrence. Moreover, the unremitting donor shortage means that many Canadians die waiting for life-saving transplants. There is no other field in medicine in which we are willing to accept that 65% of our sickest patients are denied a life-saving and cost-effective therapy.¹

The Canadian National Transplant Research Program (CNTRP), launched in 2013, is a world first. It is the only national research program worldwide that by design integrates researchers in organ/tissue donation, hematopoietic cell transplantation (HCT) and solid organ transplantation (SOT). Teams of basic and clinical scientists work with chemists, biomedical engineers, health economists, legal and ethics researchers, and policy experts at 30 sites across Canada. Through innovative strategies tightly integrated across all four health research pillars, with embedded participation of patients, families and donors, the CNTRP aims to increase access to transplantation and improve survival and quality of life of transplant recipients.²

www.cntrp.ca

In Year 3, the CNTRP strengthened existing partnerships across program components and across the country and developed new collaborations to support pioneering and paradigm-shifting research. In particular, by linking researchers in areas covered by all three of the tri-council agencies, breaking down traditional silos and enhancing trans-sector collaboration, we have created dynamic and rapidly productive synergies, including:

- Developing, building and testing novel perfusion machines for organ preservation and repair – allowing the safe use of organs that traditionally would never be considered for transplant
- Conducting the largest international clinical study in the world on circulatory death determination
- Defining novel causes and predictive biomarkers of rejection and GVHD in humans
- Describing new basic pathways regulating organ injury
- Testing novel methods for tolerance induction in transplantation
- Discovering the major discrepancy between law and health policy that exists in every Canadian province with regard to family veto of previously registered intent to donate
- Establishing the largest national collection of pediatric transplant bio-samples worldwide
- With partners in chemistry, creating and testing a new diagnostic to facilitate safe ABO-incompatible transplantation, and partnering with industry to move this technology toward commercialization and clinical use
- Launching an international multicentre industry-partnered clinical trial to guide treatment of CMV infection in transplant recipients
- Introducing novel ways to integrate patients and families as active participants in transplantation and donation research
- Bringing clinicians and scientists together to launch an entirely new national themed project investigating long-term complications and quality of life in transplant patients
- Developing national guidelines on the public solicitation of anonymous living donors

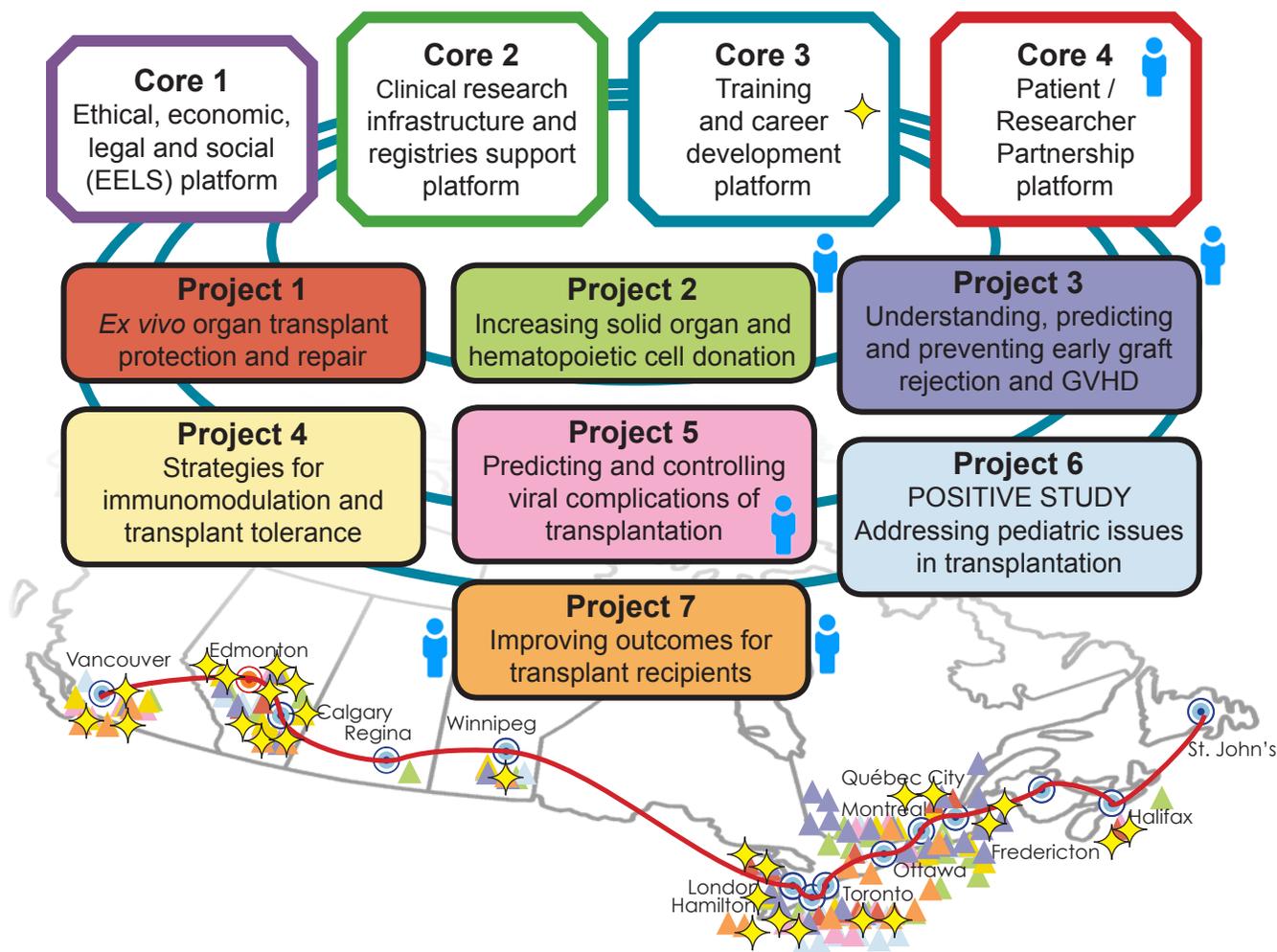
The program is led by **Dr. Lori West**, CNTRP Director at the University of Alberta, and **Dr. Marie-Josée Hébert**, CNTRP Co-Director at l'Université de Montréal, both clinician-scientists. Initial funding was provided through a peer-reviewed competition by the **Canadian Institutes of Health Research**, led by the **CIHR Institute of Infection and Immunity** in partnership with the **Institute of Circulatory and Respiratory Health**, the **Institute of Nutrition, Metabolism and Diabetes**, the **Institute of Cancer Research**, the **Institute of Gender and Health** and the **CIHR Ethics Office**. Additional founding partners included **Genome British Columbia**, the **Fonds de Recherche du Québec – Santé**, the **Canadian Liver Foundation**, the **Kidney Foundation of Canada**, **Canadian Blood Services** and **Cystic Fibrosis Canada**. *See our complete list of partners on page 12.*

To increase translation and clinical uptake, the CNTRP creates and fosters linkages with industry, health charities and provincial and federal governments, disseminating new knowledge (in both French and English) and addressing important policy issues and clinical gaps. These partnerships are taking place both nationally and internationally to enhance the impact of Canada's research community globally. To support this ongoing collaborative work, the CNTRP tripled the original investment in the program from \$13.8M to currently over **~\$37M** through creative leveraging strategies and newly funded grants. In Year 3 alone, CNTRP was successful in helping our researchers secure over \$7.7M in new funding and partnerships incorporated into and supported by our research structure. With CNTRP support and endorsement, grant applications to the recent CIHR Project

Scheme competition had a 44% (4 of 9) success rate (compared to only 13% overall success). This continued outreach and growth remains an integral feature of the CNTRP, driven by emerging opportunities, remaining knowledge gaps and understudied areas, encompassed in a framework of mutual benefit for all partners.

From the start, the CNTRP created a research environment fostering gender equity in its structure, ensuring leadership and funding opportunities for both male and female researchers and trainees. By the numbers, the CNTRP continues to represent a nearly 1:1 ratio of female:male leads, co-leads and trainees.

This report highlights examples of the research conducted across the CNTRP that is changing policy, clinical practice and societal impact, and improving the lives of patients.



The CNTRP is now comprised of seven projects and four core platforms integrating over 75 inter-related sub-projects and sub-aims.

Major accomplishments

Year 3 - Nov 2015 to Nov 2016

Increasing donor availability and access to transplants

This goal is being addressed primarily through the activities of Projects 1, 2 and 5, and Core 1.

To **increase donor organ utilization**, CNTRP Project 1 unites surgical and biomedical engineering expertise to advance studies of *ex vivo* organ perfusion strategies across the country. This collaboration brings new technology into the operating rooms, allowing surgeons to support and repair donor organs for transplantation that would otherwise be discarded.

Over the past year, Project 1 investigators published the first results of two pilot clinical trials of **normothermic *ex vivo* liver perfusion** led in Toronto by Dr. Marcus Selzner and in Edmonton by Dr. James Shapiro with a total of 22 patients, showing the safety and efficacy of the portable Metra device.^{3,4} These trials, in partnership with **Oxford University (UK)** and the spin-off company **OrganOx**, will now combine into one dual-centre trial to focus on the safe and expanded use of marginal donor livers; both centres will begin recruitment in early 2017.



Dr. Markus Selzner and the OrganOx Metra liver device in Toronto

For kidney transplantation, Project 1 investigators in London and Toronto continued to improve a new model of **normothermic *ex vivo* kidney perfusion**, having shown that prolonged perfusion can be performed without detectable kidney injury and with stable kidney function in a large animal model.⁵ The team received Health Canada approval to use the system in human transplantation and is currently developing a first-in-human clinical trial through the CNTRP. In heart transplantation, Project 1 investigators led by Dr. Darren Freed in Edmonton continue to develop our ***ex vivo* heart perfusion system** and recently launched a new spin-off company, **Tevosol**, that will promote development and commercialization of this new technology.⁶



Drs. Darren Freed, Jayan Nagendran and James Shapiro in Edmonton with the new heart perfusion system

Toward **increasing deceased donation** in Canada from the policy perspective, CNTRP Project 2, led by Dr. Greg Knoll (Ottawa), partnered with **Canadian Blood Services (CBS)** to identify and address barriers to donor identification and referral, and donation after circulatory death (DCD)

utilization across Canada. CNTRP and CBS co-hosted a workshop in Sept. 2016 in Ottawa that resulted in general agreement on a national definition of a potential organ donor, criteria for mandatory notification to the provincial organ donor organizations (ODO), options for early notification to the ODO, performance measures and strategies to improve donor intervention and referral practices in compliance with existing laws, policy and public health concerns.



DePPaRT team members Dr. Sonny Dhanani, Laura Hornby, Heather Talbot, and Amanda van Beinum at the CNTRP/CST in Quebec City.

Toward the goal of **improving the process of organ donation** in Canada, Project 2, in collaboration with the **Canadian Critical Care Trials Group**, continues to support the '*Death Prediction and Physiology after Removal of Therapy (DePPaRT)*' study.⁷ This groundbreaking research led by Dr. Sonny Dhanani in Ottawa involves the collection of real-time vital sign waveform data throughout the dying process, with the purpose of creating a clinical tool for time to death prediction in potential DCD donors and solidifying the criteria used to determine death. A nested qualitative study addresses knowledge gaps with respect to donor family perceptions of DCD. The DePPaRT study currently has 15 active sites

across Canada and three in Prague. At the time of writing it has enrolled 320 of a total 500 patients and continues to experience a 95% consent rate for study participation from surrogate decision-makers. Over the past year, the team built new collaborations with researchers internationally (**UK, Netherlands, Prague**) to expand the scope of the study, and established an ongoing research partnership with family members of a DCD donor. The team has received new CIHR funding to host an international deceased donation meeting in 2017 to showcase and expand Canada's leadership in donation research.

Project 2 expanded the 'Improving Neurological Death Determination (NDD) study' with new CIHR project scheme funding for Dr. Michaël Chassé to establish computerized tomography perfusion tests as reference standards for NDD. Led from l'Université de Montréal, this multi-site study investigates the accuracy of currently used ancillary tests for NDD, and examines also the satisfaction or dissatisfaction with the NDD process from the perspective of clinicians, families and caregivers.

For **translation and dissemination of research in donation**, in addition to several Café Scientifique events and other activities, the CNTRP has worked with award-winning independent filmmakers, producer **Rosvita Dransfeld** and director **Dr. Niobe Thompson**, on two documentary film projects and a national social media campaign aimed at increasing organ and tissue donation.⁸ **Memento Mori: Remember You Will Die** is a full-length feature documentary on organ donation

funded by the **National Film Board of Canada**. For the Canadian Broadcast Corporation science series **The Nature of Things**, **Vital Bonds** focuses on the science of transplantation and donation, featuring cutting-edge work underway by CNTRP researchers. Through international distribution, these films will reach an audience of millions to mobilize and transfer new knowledge on transplantation and the importance and impact of donation. Both films premiered in Nov 2016 in select cities across Canada and on CBC Television to critical and public acclaim.⁹



Coverage of the CST/CNTRP/CBS Guidelines in the Toronto Star on Sun, October 23, 2016

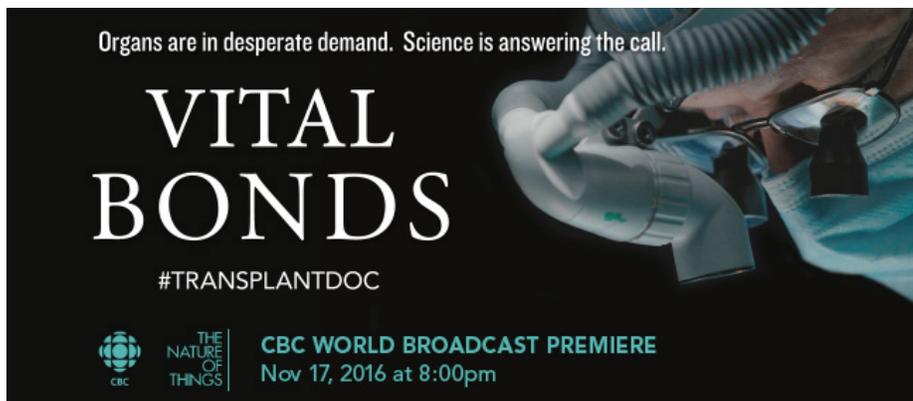
To explore defining **national strategies for recruitment of donors**, CNTRP Core 1 (Ethics, Economics, Legal and Social Issues), led by Prof. Timothy Caulfield (Edmonton) and Project 2, together with the **Canadian Society of Transplantation** and **CBS**, addressed the growing use of public solicitation for anonymous organ donors by collecting relevant evidence and publishing national guidelines.¹⁰ These widely publicized guidelines will help provide guidance for transplant centres and provincial ODOs to set local policies on how to accept and manage living donor requests from public solicitation.¹¹



CNTRP research on the issue of **family override of consent for deceased donation**, led by the Core 1 team in partnership with **CBS** and with data from the **Trillium Gift of Life Network** and **BC Transplant**, attracted much interest over the past year among the critical care research community and with the general public. In their study published in the Nov. 2016 issue of *Canadian Medical Association Journal*, Maeghan Toews and Prof. Timothy Caulfield at the Health Law Institute at the Univ. of Alberta showed that there is a clear disconnect between organ donation legislation and policy across Canada when it comes to respecting a family's objection to organ donation over a deceased individual's expressed wishes.¹² To understand how to address this pressing issue, the Core 1 and Project 2 teams are performing legal and policy analysis, media studies, a public opinion survey, a survey for the critical care and donation communities, and data collection on the occurrence of family override in the context of both NDD and DCD.

KEY POINTS FROM THE ARTICLE

- Under Canadian law, families have no legal authority to give or withhold consent for organ donation if the deceased person provided valid consent.
- Individual consent for donation provides the full legal authority necessary to proceed with organ procurement and is legally binding in most Canadian jurisdictions.
- Publicly available policy information from websites of organ donation organizations and government health authorities indicate that family wishes will be respected regardless of an individual's prior consent.
- Engagement with and understanding of the concerns of the donation community will be crucial to addressing the disconnect between organ donation legislation and policy in Canada.



Additional avenues to **increase access to transplantation and maximize effective use of valuable donor organs** include addressing biologic barriers once thought insurmountable or high risk, such as ABO blood group incompatibility between donors and recipients. CNTRP partnerships with non-medical basic science collaborators including carbohydrate chemists and nanotechnologists at the Alberta Glycomics Centre and the National Institute of Nanotechnology, together with the GlycoNet National Centre of Excellence, have resulted in creation of novel glyconanotechnology tools to study glycoimmunobiology. New insights into ABO-related immunology have been gleaned that will further expand the safe use of organs from ABO-incompatible donors.¹³



The Glyco-Nanomedicine in Transplantation Research Team at the University of Alberta - part of CNTRP Project 4

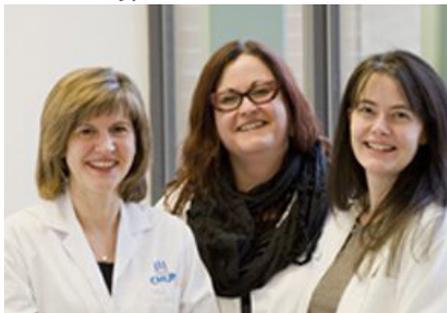
Led by Dr. Lori West's group at Univ. of Alberta, a CNTRP collaborative project has recently been funded through **GlycoNet** to study ABO-incompatibility in GVHD in HCT patients. These particular collaborations position CNTRP exceptionally well to lead studies in other emerging areas of glycobiology relevant to transplantation, including antimicrobial resistance and the impact of the microbiome on immune responses in transplantation. Toward this goal, mutual interest was explored through a joint **CNTRP-GlycoNet** workshop held in May 2016 at the Canadian Glycomics Symposium in Banff.

Through new funding received at **l'Université de Montréal** from the Canada Foundation for Research Excellence Fund (CFREF), the CNTRP built a partnership with research experts in mathematical modeling and machine learning to **improve organ allocation across Canada**. Over the coming year, this new team will begin fleshing out the many challenges associated with data science healthcare innovation – including issues of confidentiality, responsibility, privacy, public perception and social acceptability.

Extending graft longevity

This goal is being addressed primarily through the work of Projects 3 and 5.

In efforts to **understand, predict and prevent early transplant failure**, Project 3 led by Dr. Marie-Josée Hébert (l'Université de Montréal) identified novel causes of rejection, bringing together mechanisms, biomarker discovery and new targets of intervention for ameliorating the survival of transplanted organs and transplant patients in a uniquely translational approach.¹⁴⁻²³ The Project 3 team identified novel types of autoantibodies and demonstrated their central role in allograft dysfunction in humans. Using 'bedside-to-bench' strategies, Project 3 investigators were able to describe how these autoantibodies arise and, in doing so, discovered a novel type of membrane vesicles



Drs. Marie-Josée Hébert, Mélanie Dieudé and Héroïse Cardinal - Project 3 investigators in Montréal

released by dying vascular cells as inducers of allograft rejection and GVHD.^{14,15,16,18} The team also showed these antibodies to be of relevance to the donation field by describing their importance as aggravators of ischemia-reperfusion injury, both in animal models and in humans.¹⁶ Importantly, a new pharmacological target, the proteasome, was identified to block production of these autoantibodies. These findings were then explored in the bone marrow transplant field, again both in animal models and in humans,¹⁴ which highlighted some important differences between organ and bone marrow transplant patients.

Toward treating and preventing both organ transplant rejection and GVHD, these exciting results have identified more than ten new molecules that can potentially be targeted. These novel biomarkers will now be tested in adult and pediatric transplant patients and in perfusate from *ex vivo* perfused donor organs.¹⁴⁻²³



Drs. Atul Humar and Deepali Kumar - Project 5 lead investigators in Toronto

Toward improving prediction and prevention of common viral complications, basic and clinical research in Project 5 has investigated novel factors related to the pathogenesis of cytomegalovirus (CMV) reactivation, including viral miRNAs, using samples from cohorts across the country with or at risk of CMV reactivation, reported in three publications.^{24,25,26} To expand the CMV project, the CNTRP partnered with **QIAGEN** and the **Canadian Liver Foundation** to study a new approach to treating CMV infections in organ

transplant recipients. Through this partnership, we are able to support a new **\$1.5M multi-centre international clinical trial**, led by Drs. Atul Humar and Deepali Kumar at the University Health Network in Toronto, to use the QuantiFERON®-CMV assay to guide primary prophylaxis treatment for CMV infection in kidney and liver transplant recipients. This CNTRP trial is open and recruiting patients in several centres across Canada and will soon open at sites in the US and Spain.

The multi-center CIHR-funded 'BK Viremia: Kinase Inhibition to Decrease Nephropathy Intervention (BK:KIDNI)' trial, led by Dr. Lee Anne Tibbles at the University of Calgary, finished recruiting patients this year; data analysis is underway and is expected to yield important insights on the pathogenesis of BK reactivation. This Project 5 trial compares standard of care (reduced immunosuppression) to the intervention (change of immunosuppression to a combination of sirolimus and leflunomide), and provides biologic samples to Project 3 investigators to study mechanisms of viral transmission via nanoparticles.



Dr. Jean-Sébastien Delisle, Project 5 Co-Lead speaking at the CNTRP meeting in Quebec City, Oct 2016.

Exploring novel approaches to treating infection is also underway through Project 5; one of these is the development of a new adoptive **T-cell therapy for viral reactivation post-transplant**. Building on expertise generated through collaborations with Project 4, this sub-project is developing virus-specific T-cell lines from autologous virus-specific T-cell repertoires for eventual use in patients. Dr. Jean-Sébastien Delisle and his team at l'Université de Montréal are

generating T-cell lines from EBV and CMV seronegative patients who are at highest risk of developing complications related to these viruses. They will address a fundamental question for the future of anti-viral adoptive immunotherapy in renal transplant patients by aiming to determine the optimal timing for T-cell line preparation (pre- vs post-transplant). In addition, this team recently developed a clinical-scale protocol to generate BK virus-specific T-cell lines from actively viremic patients.

Improving long-term survival and quality of life of transplant patients

This goal is addressed mainly through the activities of Projects 4, 5, 6 and 7.

With the goal of **manipulating immune tolerance to improve outcomes in transplantation**, Project 4 is running a pan-Canadian clinical trial to treat chronic GVHD in HCT patients using extracorporeal photopheresis to deplete alloreactive T cells and expand regulatory T cells ('*Continuous Alloreactive T-cell Depletion and Regulatory T-cell Expansion [CARE]*' trial). This CNTRP trial led by Dr. Denis-Claude Roy (Montreal) officially opened in Dec. 2015 and is actively recruiting patients at all six centres. CNTRP is partnering on the CARE trial with **CellCAN** and **Kiadis Pharma** who provide photopheresis equipment in the three CNTRP cell-processing centres.

Project 4 is ahead of schedule on a unique approach to **non-pharmacologic immunosuppression** using newly characterized regulatory T cells (Tregs) derived from human thymus in cellular therapy trials. Recently published,²⁷ these CNTRP studies led by Drs. Megan Levings (UBC) and Lori West demonstrated that routinely discarded human thymuses



Dr. Megan Levings, Co-Lead of Project 4, and Dr. Lori West, Project 4 investigator and CNTRP Director

from children undergoing heart surgery are a superior source of abundant, stable and potentially suppressive therapeutic Tregs compared to peripheral blood, the current 'standard' source. GMP-applicable isolation and expansion protocols are now being tested in Vancouver and Edmonton in collaboration with StemCell Technologies, supported with new funds leveraged from **BioCanRx** and **StemCell Network**, in preparation for developing a Phase I clinical trial of thymus Tregs to prevent GVHD and/or transplant rejection. The CNTRP's work on this new source of Tregs for cellular therapies has generated considerable interest internationally as these cells are being explored also for use in autoimmune disorders including type 1 diabetes.

CNTRP Project 6 (POSITIVE Study) is focused on **improving pediatric outcomes in transplantation** through several sub-projects that utilize a precision medicine approach to incorporate biological, environmental and lifestyle factors towards individualized management strategies for children and young adults after transplantation. These include investigating age-appropriate calcineurin inhibitor dosing for pediatric transplant patients including newborns (led by Dr. Seema Mital at SickKids in Toronto), developing risk prediction tools (together with Project 5) based on viral-host interactions that predispose young organ transplant patients to EBV infection and post-transplant lymphoproliferative disease (PTLD) (led by Dr. Upton Allen at SickKids), and defining health care systems strategies to enhance medication adherence in adolescents and young adults (led by Dr. Beth Foster at McGill University).

Project 6 is unique through its establishment of a sub-network across 14 sites in Canada, the largest of its kind, spanning both pediatric and adult centres and including SOT and HCT. This allows the CNTRP to study and potentially to **improve outcomes throughout the lifetime of transplanted patients** beginning in infancy. Since the launch of the study, Project 6 has successfully recruited 640 of 800 transplant recipients of which 86 are incident patients. Project 6 has begun analyzing data from these patients to ascertain incidence of rejection, infections, PTLD and other outcomes during one-year post-transplant follow-up, and will publish the results over the coming year.

In collaboration with the international multicentre **iGENETRAIN** consortium and through supplementary funding from **SickKids Transplant Centre** and from **Astellas Canada**, Project 6 launched a new sub-study to investigate how genetic factors influence drug-drug interactions among pediatric transplant recipients typically managed with 'polypharmacy', and also to study how donor genotypes influence recipient outcomes. To date, the team has completed genotyping of 452 recipients and 244 donors to identify clinical, genetic and pharmacogenomic factors associated with tacrolimus concentrations and related outcomes across SOTs; these data are currently under analysis.



Dr. Sunita Mathur, Sandra Holdsworth and Dr. Maureen Meade - Project 7 Leads - speaking at the CNTRP meeting in Quebec City - Oct 2016

Over the past year, the CNTRP expanded the scope of the network and launched an entirely new project focused on **improving long-term outcomes and quality of life for**

transplant recipients. Our new CNTRP Project 7, led by Dr. Sunita Mathur (Toronto) and co-led with Dr. Maureen Meade (McMaster) and Sandra Holdsworth (patient co-lead), brings together under the CNTRP framework **19 researchers** from across the donation, SOT and HCT research communities, together with a strong patient partnership component, to focus on the following aims:

Project 7 - Improving long-term outcomes and quality of life for transplant patients

Aim 1: Evaluation of co-morbidities, disability and quality of life in transplant candidates and recipients

Aim 2: Effectiveness of interventions in donors, candidates and recipients to mitigate co-morbidities and improve long-term outcomes and quality of life after transplantation

Aim 3: Improving long-term organ function through innovations in assessments and novel interventions

Aim 4: Increasing knowledge uptake of Project 7 research findings by key stakeholders in transplantation (Knowledge Translation/ Knowledge to Action cycle)

Project 7 researchers are addressing these aims by bringing over **\$1.9M** of externally funded research into the CNTRP structure.

Expanding capacity: developing and enhancing the pool of talent in transplantation and donation research



Sylvain Bédard - CNTRP Patient Co-Lead and Dr. Marie-Chantal Fortin, CNTRP Research Co-Lead of the new Core 4 - speaking at the CNTRP meeting in Quebec City - Oct 2016

In April 2016, the CNTRP officially created the new CNTRP Patient Partnership Platform (Core 4), following more than 18 months of planning, preparation and consultation, and with new funding from **CIHR (ICRH)** and **Astellas Canada**. The purpose of the new Core 4 is to create a space for the patient's voice and to be a catalyst for cultural transformation in patient-researcher partnerships. The Core 4 team, co-led by Dr. Marie-Chantal Fortin (CRCHUM) and Sylvain Bédard (patient), will help align CNTRP's priorities and activities to ensure that the CNTRP remains relevant to the interests of patients and families, and



CNTRP Patients and Researchers participating in our first Patient Partnership Training Session during the CNTRP Annual Meeting in Quebec City - October 2016

that the core principles of partnership with patients in health research assist in defining CNTRP goals, objectives, projects and activities. In the pilot phase of implementing the patient partnership strategy, the CNTRP has incorporated one patient as Core 4 co-lead, three patients as project co-leads, and four patient researchers.

CNTRP research participants and promotion of gender equity

At the end of Year 3 (Nov 2016), there are 143 total funded and active CNTRP researchers, leads, patients and trainees, supported by an additional 377 individuals involved and associated with the CNTRP. CNTRP participants include:

- **17** Project & Core Leads (including the Directors and Committee Chairs) (**52%** female leads)
- **86** funded and active CNTRP researchers, including **13** Canada Research Chairs²⁸ (**40%** female researchers)
- **8** patient researchers or patient co-leads
- **32** trainees (**47%** female trainees)
- **15** program/project managers
- **205** collaborators
- **157** stakeholders (patients, partners, industry, health charities)

The CNTRP has proactively created a research environment fostering gender equity in its structure and ensuring opportunities for both male and female researchers and trainees. By the numbers, the CNTRP represents a nearly 1:1 ratio of female to male researchers, trainees and program leads/co-leads.

New research funding and recognition

The CNTRP was successful in helping our researchers secure new funding and new partnerships over the past year (**over \$7.7M**) that are incorporated into and supported by our research structure. CNTRP investigators received a number of awards and grants in Year 3, recognizing their contributions to the field of donation and transplantation. Some examples of these awards and recognitions include:

- Five CNTRP researchers received 2016 CIHR Foundation Grants (Garg, Hemmelgarn, Perreault, MacDonald, Wishart)
- Four CNTRP researchers received 2016 CIHR Project Grants for applications supported and/or endorsed by the CNTRP (Chassé, Hébert, Mathur, Ho)
- Six researchers received CNTRP Research Innovation Grants, funded through partnerships with Astellas Canada, the Alberta Transplant Institute (Edmonton), the CHUM (Montreal) and the UHN Multi-Organ Transplant Program (Toronto) (\$150,000 total)
- Three new industry-partnered clinical trial and research studies were initiated through the CNTRP (Humar, West, Mital; \$1,625,000 total) (Qiagen, BD, Astellas)
- One CNTRP researcher received a US NIH grant for a CNTRP-endorsed study (Foster; \$2,782,901)
- Three CNTRP operating grants were received from Canadian NCEs, including BioCanRx, GlycoNet, and StemCell Network (Levings, West; \$575,659 total)
- Dr. Marie-Josée Hébert received the Kidney Foundation of Canada 2016 Medal for Research Excellence
- Dr. Lori West received the 2016 Woman Leader in Transplantation Award from The Transplantation Society and the 'CP Has Heart' Award from the Heart and Stroke Foundation



Dr. Lori West (centre-right), receiving the 2016 Woman Leader in Transplantation Award in Hong Kong - Sept 2016

Research outputs

Research output from CNTRP investigators includes **151** peer-reviewed publications accepted, published or in press to date, **2** new national guidelines and **hundreds** of presentations at national and international conferences (*see attached list of CNTRP publications and presentations*).

To inform policy development and provide updated factual information on issues affecting organ donation and transplantation, Core 1 and Project 2 continue to produce, on an ongoing basis, a series of **Fast Facts**,²⁹ rapid review resources that provide evidence to inform policies and spark new questions and research on the topics of donation incentives, consent, ethical issues, death determination and deceased donation, public solicitation, living donation, and rights around human bodies and biological materials.

New opportunities

Through the CNTRP New Initiatives Committee (chaired by Dr. Tom Blydt-Hansen, UBC), three new research grant competitions were developed and launched in Year 3. In partnership with **Astellas Canada**, the **Alberta Transplant Institute**, the **University Health Network (Toronto)**, the **Centre Hospitalier de l'Université de Montréal** and the **University of Ottawa Heart Institute**, who together originally provided **\$325,000** in new funding, the CNTRP launched and completed the 3rd annual Research Innovation Grant Competition (review committee chaired by Dr. Upton Allen,

Sickkids). The CNTRP partnered with the **Transplant Research Foundation of BC**, the **Alberta Transplant Institute**, **Astellas Canada** and the **BC Children's Hospital Foundation** to develop and launch the National Child Health Transplant Team Grant Competition, providing **\$100,000** to support research to improve outcomes for pediatric organ transplant patients through cross-Canada, multi-disciplinary collaboration. With funding support from the **CIHR Institute of Circulatory and Respiratory Health**, the CNTRP participated in the **Heart and Stroke Foundation's** Emerging Research Leaders Initiative to support a new faculty member working to improve donation and/or cardiac transplantation (results to be announced in early 2017). To date, the CNTRP has funded **23** new pilot grants and four training awards to carry out work as part of the CNTRP.³⁰

New trainees

In 2016, the CNTRP Training and Career Development Platform (Core 3, led by Dr. Lee Anne Tibbles, Calgary) accepted **13 new trainees** into the program, which now includes **32** trainees across the country representing every CNTRP Project/ Core. Core 3 developed and launched a common web-based curriculum and organized 13 new training webinars (21 to-date), which are offered to all CNTRP members, recorded and made available on the internal website.

New international collaborations

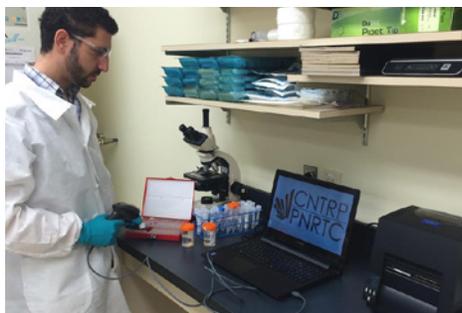
With support from the **Univ. of Alberta Faculty of Medicine and Dentistry**, the CNTRP hosted some of the world's top basic science transplant researchers in Edmonton on August 13-14, 2016 at the '**CNTRP International Summit: Emerging Biomedical Research in Transplantation**'. The goal of the workshop was to explore and plan international research collaborations to stimulate cutting-edge and emerging biomedical and translational research focused on rejection/cGVHD, tissue injury, allograft function and patient survival. In rapid follow-up to this exciting summit, a



Participants at the **CNTRP International Summit: Emerging areas of biomedical research in transplantation** that took place in Edmonton on August 13-14, 2016

CNTRP 'East Coast' International Workshop on 'Cell Death and Autoimmunity' has been organized for Dec. 2016 in Montreal, bringing together researchers from Boston, New York and Montreal to cement (mostly in French) additional collaborative studies. In October 2016, the CNTRP welcomed more than 100 participants to the 3rd Annual CNTRP Scientific Meeting in Quebec City, organized by Dr. Donna Wall (SickKids) and Dr. Mélanie Dieudé (UdeM), held jointly with the **Canadian Society of Transplantation** and the **Société Québécoise de Transplantation**.

In Year 3, the CNTRP Clinical Research Support Core (Core 2), led by Dr. Kirk Schultz (UBC), developed and launched the **CNTRP Patient Registration Database (PRD)** to help investigators across the program



The CNTRP Virtual Biorepository system being use in the Islet Lab at McGill University in Montreal.

capture all patients enrolled in CNTRP studies, clinical trials, translational research, and health services research projects. The PRD assigns each participant a unique CNTRP identification number that can be used to follow our research subjects through a link with administrative databases and to track enrolment rates. It will also be a key asset for correlative science through the tracking of all biological samples stored across CNTRP sites.

Together with **Beckman Coulter Life Sciences**, Core 2 is linking our national **Immune Monitoring Initiative** (led by Dr. Megan Levings, UBC), which provides standardized flow cytometry panels for pre- and post-transplant immune monitoring across Canada with the **Virtual Global Transplant Laboratory** (an initiative of **The Transplantation Society**) to make protocols for immune monitoring available to researchers internationally. Core 2 also expanded the CNTRP Virtual Biorepository platform to seven sites. The platform uses Canadian BioSample Repository inventory software and REDCap data management software, and allows CNTRP researchers to catalogue, manage and link research samples across Canada.³¹

Next Steps

In its first three years the CNTRP has effectively transformed the research landscape in transplantation and donation in Canada through creating a framework of inclusive trans-disciplinary collaboration. This has resulted in immediate impact for some of our most vulnerable citizens and a series of research 'firsts'. The CNTRP has swiftly demonstrated the effectiveness of a consolidated team structure in generating new knowledge to address complex health issues. The CNTRP is the first network worldwide to encompass donation, SOT and HCT researchers, and is now additionally integrating patients and citizens, not only within our governance and our research leadership team but also within basic science projects and other research pillars.

This innovative network of tightly integrated and collaborative partnerships allows for synergism leading to rapid impact:

- From mechanisms to clinical studies to therapy to policy
- Across SOT to donation to HCT
- From established to mid-career to junior investigator to patient researchers
- Across the age spectrum of our patients
- Across Canada's tri-council funding agencies, bringing together scientists from engineering, technology, social sciences and humanities and health
- Across Canada and internationally

As the CNTRP enters its 4th year, we will continue to build on these early accomplishments and integrate patients, stakeholders, governments and the general public to increase access to transplantation and to improve outcomes for transplant recipients.

The power of CNTRP integrated teamwork, an example of rapid translation led by the Project 3 team:

"Not only did we characterize a brand new type of autoantibodies, but within three years we demonstrated their predictive role in rejection of renal transplant patients. We were able to show that these antibodies are also of relevance to the donation field by describing their importance as aggravators of ischemia-reperfusion injury, both in animal models and in humans. Mechanistically we were able to identify how these autoantibodies are formed by describing a new structure altogether, tiny membrane-bound fragments of dying cells that are enzymatically active and foster autoantibody production. In doing so, we identified a new pharmacological target, the proteasome, to block the production of these autoantibodies. We were also able to explore these findings in the bone marrow transplantation field, again both in animal models and in humans. We are now poised to test these novel biomarkers and targets in pediatric patients, and during ex vivo organ perfusion. This was all made possible because of collaborations that span from Montreal to Quebec City, to Edmonton, Calgary and Vancouver. This was possible because of interactions between basic and clinical scientists, because of interactions between junior and senior investigators and because of the enthusiastic support of patients."



Participants at the CBS CNTRP Potential Donor Identification and System Accountability workshop in Ottawa (September 16-17, 2016)



Prof. Timothy Caulfield speaking at the CNTRP Core 1 Workshop on Research Ethics - Banff, AB Oct 2016



CNTRP Researchers participating in the Virtual Biorepository Training Workshop in Montreal, March 2016



Dr. David Suzuki moderating a discussion panel with Dr. Lori West and Dr. Niobe Thompson - Nov 2016.



Participants on the CNTRP International Summit discussing new collaborations - Edmonton, Aug 2016



Recipients, families, living donors, health care workers and researchers participating in the CNTRP Patient Partnership Workshop - Toronto, Nov 2015

CNTRP Founding Partners



CIHR IRSC

Canadian Institutes of Health Research

Instituts de recherche en santé du Canada

Institute of Infection and Immunity

Institute of Cancer Research

Institute of Circulatory and Respiratory Health

Institute of Gender and Health

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Institut des maladies infectieuses et immunitaires

Institut du cancer

Institut de la santé circulatoire et respiratoire

Institut de la santé des femmes et des hommes

Institut de la nutrition, du métabolisme et du diabète

Le Bureau de l'éthique des IRSC



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The CNTRP has received additional funding and research support from the following partners:



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29. www.cntrp.ca/fastfacts
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31. Video demonstration of the CNTRP Virtual Biorepository: <http://youtu.be/R91NHAuWDz4>