The Canadian Approach to Transdisciplinary Transplant Research: Structure of the Canadian National Transplant Research Program

The Canadian National Transplant Research Program (CNTRP) is a coalition of more than 300 scientists, students, collaborators, patient partners, and knowledge users at 29 sites throughout Canada who are actively engaged in the science of solid organ transplant, hematopoietic cell transplant, and organ donation. The goals of the CNTRP are to increase access to transplantation while improving outcomes and quality of life through innovative research strategies that cross the full spectrum of health research including biomedical, clinical, health systems/policy, and population health. At its inception, the CNTRP focused on 6 projects, each national in scope, tackling major challenges faced by transplantation and donation communities (Figure 1). These projects included: (1) developing and testing ex vivo organ perfusion strategies to enhance the number and quality of organs available for transplantation, (2) increasing the pool of organ, tissue and stem cell donors, (3) understanding and predicting rejection and graft-versus-host disease (GVHD), (4) inducing and maintaining immune tolerance, (5) predicting and preventing infectious complications, and (6) addressing specific needs of pediatric transplant patients. A seventh project focusing on chronic complications of transplantation is embedded within the CNTRP framework. Collectively, these projects harbor over 35 conceptually linked subprojects that cross-fertilize, and, by design, link not only with the cores but also with components of other projects; communications are in both French and English. This matrix-type structure aims to help research groups working collaboratively around research questions by providing a multifaceted yet integrated approach to knowledge generation (Figure 2).

Collaborations and effective communication among CNTRP investigators and projects are facilitated by a network management team that coordinates web-based meetings, training webinars, internal file/data sharing, living progress “wikis,” patient engagement, publication reports, social media output, in addition to regional and national meetings.

Three core platforms form the backbone of the network and help advance various aspects of the projects, fostering integration, and collaboration across the program and with partners. The Clinical Research Core tracks registration of all patients involved in CNTRP studies, coordinates development and management of CNTRP multicentre clinical trials, links patient samples and clinical data in existing biobanks, coordinates research ethics approvals, and develops and tests common and shared standardized operating procedures. The Training and Career Development Core is aimed at enhancing the capacity of trainees, CNTRP investigators, research associates, and research assistants to engage in transdisciplinary research.

Without attempting to transform scientists into “jacks-of-all-trades,” transdisciplinary research organizations need to develop training tools to help students and investigators acquire basic knowledge in relevant fields to engage and collaborate effectively with scientists from other research streams. The training core currently welcomes 43 graduate students, clinical and research fellows, each with a designated CNTRP mentor other than his/her primary supervisor. Monthly webinars take place, with 15 recorded sessions to date accessible on the CNTRP website (www.cntrp.ca). The Ethics, Economics, Legal and Social issues Core provides expertise in bioethics, health law, and health economy for all projects. This core also publishes easily accessible web-based resources and policy documents called “fast facts” on topics related to donation and transplantation intended for the general public and key policy stakeholders nationwide. The Ethics, Economics, Legal and Social Core also manages a comprehensive patient engagement strategy that integrates patients into the research and management structure of the CNTRP and works with patients and the public to define future research priorities.
Beyond building a structure based on collaborations amongst investigators and program elements, we strived from the beginning to engage and weave additional partners, decision-makers, and stakeholders into our evolving tapestry. These relationships vary in nature and are built on the fundamental premise that mutual benefit for all participants is essential. Partners include industry, health charities, various levels of provincial and federal government, research funding agencies, universities and research institutes, professional societies, donor procurement agencies, patients, and citizens.

**Early CNTRP Successes**

Although greater time investment and more substantive effort are usually expected for interdisciplinary research to get started compared with single stream investigations, our group has proven successful in rapidly generating new knowledge, guidelines, and additional partnerships in a number of key areas.

Since 2013, CNTRP investigators have developed, refined, and tested a number of devices for perfusion and repair of organs before transplantation. Ex vivo organ transplant protection and repair. Two prospective multisite clinical studies in organ donation (CNTRP Death Prediction and Physiology after Removal of Therapy, the DePPaRT study) and in GVHD treatment (CNTRP Continuous Alloreactive T cell Depletion and Regulatory T cell Expansion, the CARE trial) have been launched, whereas a third study on infectious complications in renal transplantation (BK Viremia: Kinase Inhibition to Decrease Nephropathy Intervention, the BK:KIDNI trial) that is independently funded, has joined the CNTRP to benefit from the transdisciplinary structure.

Canadian National Transplant Research Program teams characterized novel basic mechanisms of rejection, demonstrating the unexpected importance of an autoimmune component in shaping the severity of alloreactivity. We identified novel predictors of rejection and GVHD in humans. We developed an approach for generating abundant and potent regulatory T cells using discarded human thymuses. Incorporation of already-funded partners in glycomics and chemistry led to creation and testing of innovative glyconanotechnology tools, giving new insights in ABO immunobiology in transplantation. In addition to these successes, CNTRP partnered with key stakeholders (Canadian Blood Services, Canadian Society of Transplantation) to develop consensus guidelines for the safe use of increased infectious risk donors for organ transplantation. These national guidelines are a valuable tool for addressing the risk of infection transmission, providing both practitioners and organ procurement agencies with a sample standardized script for informed consent while aiding patient discussions. Canadian National Transplant Research Program members are also working with
award-winning independent documentary filmmakers\textsuperscript{10} on 2 donation and transplantation film projects through the National Film Board of Canada and the Canadian Broadcast Corporation’s science series *The Nature of Things* that will feature cutting-edge work undertaken by CNTRP researchers, and, with international distribution, are expected to reach an audience of millions.

Rapid success of our network can be attributed, at least in part, to the inherent multidisciplinary nature of donation and transplantation. Traditionally, knowledge transfer across health research pillars has been considered as a unidirectional linear pathway that moves from basic to clinical research and subsequently to health systems and population health.\textsuperscript{11} A brief glance into the history of transplantation (Figure 3), however, suggests that knowledge acquisition and translation can develop more efficiently in a stochastic fashion. Transplantation has evolved from the acquired capacity to connect suture blood vessels at the turn of the 20th century, subsequently applied in the first successful transplantation experiments in animals. This led to the concept of graft rejection, which in turn played a major role for the discovery of the major histocompatibility complex and the complexity of alloimmune responses. This progress translated then into the development of immunosuppressive agents and the capacity to perform increasing numbers of organ and hematopoietic cell transplants in humans. The increasing need for organs for transplantation prompted dialogue with ethicists and the public that had a major societal impact and changed the way modern societies define death, a fundamental concept that surpasses the fields of biomedical and clinical investigation by far.

Remarkable progress has been achieved in donation and transplantation in the past century by successfully engaging scientists, physicians, patients, ethicists, economists, psychologists, anthropologists, and the public around questions that were considered and debated in a collaborative and multifaceted discourse. This nonlinear and transdisciplinary problem-solving approach that seeks to gather expertise toward a common goal is by no means unique to the field of transplantation. In fact, a similar approach played a major role in the rapid progress accomplished over the past 3 decades in the fields of human immunodeficiency virus research\textsuperscript{12} and has parallels to approaches in oncology. Thus, nonlinear multidisciplinary processes are not new to medicine and, once established, are associated with rapid acquisition, validation, and application of new knowledge, clearly calling for revisiting the linear view of knowledge translation. Thus, a research framework similar to that developed by the CNTRP is likely valuable to other sciences and geographic areas.

Certain aspects of the Canadian research landscape are particularly well served by a structure, such as CNTRP. The relatively small population of Canada, and Canadian researchers, dispersed across a huge geographic area, are brought together effectively by the CNTRP structure in a bilingual communication. Moreover, the single-payer government-funded health care system of Canada, although administered at the level of individual provinces, tends to decrease the competitiveness that can impair truly collaborative health research. Nonetheless, it is likely that the tightly integrated nature of the CNTRP, linking the various elements at many

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\caption{Integrations and collaborations across the national program.}
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levels, would be universally advantageous in building a cohesive research enterprise from otherwise disparate and disconnected pieces. Indeed, such an organizational structure could provide a foundation upon which to build innovative and cost-effective research programs in countries with less well-developed research infrastructures.

Specific Challenges Associated With Transdisciplinary Research

Although transdisciplinary research has proven effective in a number of research fields, obstacles are important and worth considering. Transdisciplinary research asks for open-mindedness, a capacity to willingly wander through unknown territory and embracing of new perspectives into an ever-evolving research program. This demanding type of “contact sport” may not be for everyone, and the success fundamentally relies on the capacity to act as team players rather than self-promoters. Criteria used for promotion by academia and peer-review funding agencies, however, often value self-promotion above teamwork. Transdisciplinary research groups, to be successful, need extra time and energy toward creating a research “sandbox” equipped with a shared language, respect of discipline-related differences, and mutual trust that promotes and encourages exchange. Rules guiding academic promotion and peer review funding rarely recognize the time and energy required to build successful transdisciplinary programs. Authorships on publications that originate from large research groups are more likely to be middle rather than first or senior authorships, thus potentially undermining the recognition of everyone’s collective input. Indeed, individuals at the highest leadership positions of large research teams may not be authors on publication of discrete outputs at all. Although scientific journals increasingly value and publish transdisciplinary work, articles crossing scientific boundaries have traditionally been found to be more difficult to get reviewed and published.\textsuperscript{13} Moreover, transdisciplinary articles are usually less cited early after publication, however lead to more citations in the long-term, a citation profile that has not yet been favorably valued by either academia or funding agencies.\textsuperscript{13}

The importance of the network leadership team in promoting and nurturing exchanges, collaboration, and knowledge mobilization cannot be underestimated. The leaders play a pivotal role in articulating and promoting an interdisciplinary vision, supported by a governance structure that is in line with the vision and mission of the group as a whole. Although scientists may profess a desire to be involved in interdisciplinary networks, especially if there is a perceived funding advantage, the temptation may be great after funding has been secured to continue with a “take the money and run” attitude. Indeed, competitive if not outright “predatorial” behaviors sometimes valued in traditional research streams represent major barriers to interdisciplinary research. Thus, leaders must be extremely mindful and attentive to these types of behaviors, ready to reiterate and reinforce the collaborative vision of the group if these emerge.

Funding required to build sustainable core platforms to support transdisciplinary research groups is limited and often non-renewable. Access to highly qualified personnel at ease in crossing traditional scientific boundaries is also limited, and the ups and downs of peer-reviewed funding mechanisms impose further difficulties in maintaining strong and collaborative groups across disciplines. Although an increasing number of funding agencies and academic institutions worldwide are beginning to appreciate the value of transdisciplinary research beyond traditional models, major changes in funding and promotion mechanisms will be required to promote and sustain research endeavors that cross traditional scientific boundaries.

CONCLUSIONS

The CNTRP is, in itself, an experiment. Evaluating successes, challenges, and needs of such a national research structure is essential in gaining a better understanding of...
critical elements required to harvest the seeds of transdisciplinary research. Addressing complex issues associated with donation and transplantation, chronic complications of immunosuppression or the impact of donor management policy interventions, among others, necessitate coordinated long-term efforts that benefit from a sustained and structured transdisciplinary environment.

The CNTRP strives not only to generate new knowledge but also reassesses continuously its structure and impact, thus defining components that are successful and others that need recrafting. Moreover, the network addresses evolving research needs of the community on a regular basis. Meeting those goals, the scientific network will not only contribute to scientific discovery but also to a better understanding of how new innovative knowledge will come to full fruition, thus contributing to the transformation of the research community.

In building and launching the CNTRP, we have learned that enhanced interactions at the interface of various disciplines are a recipe for innovation. Sustaining these interactions as the research landscape evolves and new challenges arise is not an easy task, but who said research was easy?

Approaching the unknown with a well-developed support network and with versatile skill sets, in life as in science, is the best way to prepare for challenges to come.

REFERENCES


