Research Manitoba

Kidney Transplant Research

An Impact Narrative

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List of Acronyms

CA	Contribution analysis
CBS	Canadian Blood Services
CCDT	Canadian Council for Donation and Transplantation
CFI	Canada Foundation for Innovation
CIHR	Canadian Institutes of Health Research
CNTRP	Canadian National Transplant Research Program
CTOT	Clinical Trials in Organ Transplantation
ESRD	End stage renal disease
HLA	Human leukocyte antigen
HSP	Highly Sensitized Program
KPD	Kidney Paired Donation

LDPD	Living Donor Paired Exchange Program
NIH	National Institutes of Health
NOW	National Organ Waitlist
OTDT	Organ and tissue donation and transplantation
PI	Principal investigator
RCT	Randomized control trial
UNOS	United Network of Organ Sharing

Key Terms

Antibodies	Proteins in the blood produced in reaction to foreign substances, such as bacteria and viruses, that cause infection.
Antigens	Any substance that causes an immune system to produce antibodies against it.
Biopsies	The process of verifying the proper functioning of an organ transplant after the surgery.
Dialysis	A medical therapy for the loss of kidney function. The treatment is an artificial replacement for lost kidney functions, cleaning the blood and removing waste and excess water.
dnDSA	An antibody that was not apparent prior to a transplant but became apparent after the transplant.
End stage renal disease (ESRD)	A state of irreversible kidney failure.
Flow cross-matching	The process for ensuring the compatibility between a donor and recipient.
Flow cytometery	An electronic biotechnology tool that uses lasers to analyze blood cells to identify the compatibility between a donor and a recipient i.e. flow cross-matching.
Graft	Living tissue that is transplanted.
Human leukocyte antigen (HLA)	Protein makers that let your body know which cells are yours and which cells are not. HLA antibodies are specific cells that lead to the rejection of a kidney transplant since the individual's body thinks the new kidney is a foreign entity that must be attacking their immune system.
Pathogen	A type of microorganism e.g. a virus that can cause a disease.
Randomized control trial (RCT)	A type of experiment that allows a researcher to conclude a causal relationship between variables.
Renal disease	Refers to the deterioration of your kidney function.
Subclinical rejection	The existence of rejected tissue from an organ transplant that cannot be identified utilizing clinical techniques for monitoring rejection.
Sensitized	Prior exposure to donor tissue antigens from transfusions, prior transplants, or pregnancy and make it more difficult to find a compatible match for a kidney transplant.

EXECUTIVE SUMMARY

The purpose of Research Manitoba's impact narrative is to document the outcomes and impacts of research in the province. The goal of the impact narrative is two-fold: 1. to communicate the impacts of research to a wide variety of audiences such as academics, industry, community groups, the public, and other users of research findings, and 2. to link outcomes and impacts to the original research.

Interview guides were developed to capture the impacts from the work of the Kidney transplant team in Manitoba and across Canada. For this report Dr. Rush and Dr. Nickerson were interviewed from the kidney research team. Additionally, secondary data sources were utilized e.g. government reports and other publicly available resources to augment the findings of the interviews.

Starting in 1998, Manitoba's research on end stage renal disease (ESRD) and subclinical rejection has led to

- Lower rates of hospitalization,
- Lower rates of renal transplant rejection,
- Increase cost savings for the Canadian healthcare system, and
- longer life expectancy of ESRD patients.

The Manitoba kidney transplant research program has accomplished these goals, amongst others that will be discussed in detail below, by: 1. creating novel methods as well as national standards for pre-and post-transplant screening/monitoring of ESRD patients; 2. creating the kidney paired partnership (KPP) program and the highly-sensitized patient registry. In total, these improvements took more than 15 years to be realized and are still being developed today. Below are the impacts of the kidney research program organized into Research Manitoba's five impact categories:

Advancing knowledge: In total the research team has been published 373 times and been cited over 18,000 times by their national and international peers. Four publications have been referenced in the change of national clinical practice changes in Canada. Additionally, advancements include: 1. Dr. David Rush in the early 90s utilizing a surveillance biopsies method that identified the rejection of a kidney transplant before it became clinically apparent; 2. The development of non-invasive urine tests in 2004 by Dr. Peter Nickerson to help identify and prolong the life of transplanted kidney's; 3. Dr. Rush also began research into utilized serologic cross-matching in the early 1990s that led to the rate of graft survival improving from 90% to 98%.

Building capacity: Beginning in 1998 Dr. Rush and Dr. Nickerson have been able to recruit and train 6 students, 4 of which have remained in Manitoba and established their own kidney transplant research programs. Furthermore, the research team has constructed the most prominent biobank in the world that has continued to be utilized for health-related research projects in Manitoba.

Informing decision making: In 2001, the federal and provincial governments established the Canadian Council for Donation and Transplantation (CCDT), which was comprised of members of government, provincial leaders, and ministries. In 2005, the CCDT asked Dr. Nickerson to chair the first workshop/consensus conference in Montreal that focused on results of the flow-based technological study in 2000 and the standardized use of this technology by 2010 across Canada. Another consensus conference in 2005 held in Toronto was co-led by Dr. Nickerson to establish a national kidney paired system to address the problem of matching difficult to match patients.

Applications and Changes: Based on the consensus conference in 2005, the federal, provincial, and territorial governments across Canada recognized the need for a national transplant program in 2008. As a part of the national program, Dr. Nickerson helped to establish the kidney paired donation (KPD) program that facilitates living donor transplantation in ESRD patients with a blood group or human leukocyte antigen (HLA) incompatible living donor. The KPD program has resulted in 271 transplants from 2013 until 2016. In addition to the KPD the National Organ Waitlist (NOW) and highly sensitized patient registry (HSP) have been established since 2012 and 2013 respectively.

Broad economic and social impacts: For patients, the research team has been able to facilitate 271 kidney transplants as a result of establishing the kidney paired system in 2013. Additionally, patients are more likely to have successful transplants as well as improved health after a transplant due to the creation and development of pre-and post-biopsies procedures. These are important developments for ESRD patients because transplants prolong patient survival, improves their quality of life e.g. ability to spend time with family and find gainful employment, and is more affordable compared to dialysis, which 58% of ESRD patients were on in 2000 i.e. savings of $33,000 to $84,000 a year beginning in the 2nd year post-transplant.

Part I: Introduction

1. Background

Between 1981 and 1999, the number of new patients with end-stage renal disease (ESRD) in Canada increased at 7.3% per year. By the end of 2000, 24,921 Canadians received treatment for ESRD, 58% of whom were on dialysis and the rest with a functioning kidney transplant. Not all with ESRD proceed with kidney transplantation despite the fact that this is the treatment of choice as it prolongs survival, improves quality of life and is more affordable than dialysis.[1] Among ESRD patients, 30% on the wait-list had become "sensitized" i.e. had prior exposure to donor tissue antigens (HLA) from pregnancy, transfusions or prior transplants, resulting in preformed HLA antibodies, which make it very difficult to find a compatible match. Sensitized ESRD patients had prolonged wait-times compared to non-sensitized patients as kidneys were not shared between provinces. At that time, 7.2 % of all deceased donor transplants and 3.9% of all living donor transplants failed in the first post-transplant year, obliging the patient to revert to dialysis. Early graft loss commonly occurred due to undetected donor specific HLA antibodies.[2]

Research on end stage renal disease (ESRD) and subclinical rejection in Winnipeg, which started in 1982, has made a huge contribution in transforming the access to kidney transplants and improving the health outcomes of ESRD patients in Canada and globally.

2. About the topic

Kidneys are the main component of the urinary system and are essential to overall health and wellbeing. Humans typically have two kidneys located below the ribs. The nephrons located within the kidneys are "filtering units that filter the blood flowing through your kidneys, removing toxins and producing urine that is then drained into your bladder."[3] Kidneys serve vital roles in filtering out waste products, balancing minerals, secreting hormones and helping to control blood pressure.[4]

Image Credit → City of Hope: Breakthroughs. Retrieved from: http://breakthroughs.cityofhope.org/kidney-cancer-awareness-treatments

When renal disease develops there is a progressive loss of function over time, or the kidneys fail completely. Renal replacement therapies include dialysis and transplants.

Dialysis is a medical therapy for the loss of kidney function. The treatment is an artificial replacement for lost kidney functions, cleaning the blood and removing waste and excess water. There are two types: hemodialysis (removal of waste when kidneys are in failure) or peritoneal dialysis (treatment for severe

kidney disease). When kidney dysfunction is permanent, dialysis becomes a regular routine, or a transplant is needed for a patient to stay alive.[5]

Renal transplant is the transplant of a healthy kidney from a living or deceased donor. Before the transplant can occur, measures of compatibility must be met including 1. blood group compatibility and 2. cross match compatibility (HLA antigens).[6] Kidney transplants are a lifelong procedure and complications such as infection, bleeding, urinary complications, inflammation or rejection may transpire post-transplant at any time. Four forms of rejection can take place:[7]

- **Hyper-acute rejection** happens within minutes of the transplant and takes the shape of rapid clumping of red blood cells; it rarely occurs due to cross match testing prior to surgery.
- **Acute rejection** (cellular immunity) typically occurs six months after the transplant. Regular blood samples are drawn, checking for levels of creatinine, a protein released into the bloodstream as a waste material from muscles. Higher levels of creatinine indicate that the kidney is not doing a good job flushing out the waste material, which could lead to rejection.
- **Sub-clinical rejection** is detected with a kidney biopsy before there is enough damage to cause the creatinine in in the bloodstream to increase. Early treatment for this condition can improve the chance of keeping the new kidney long-term.
- **Chronic rejection** is a long-term loss of function in transplanted organs and happens slowly over time. In this case, the kidney develops a lot of scar tissue, which is the result of repetitive injury from the immune system's response over a long period.

3. About kidney transplant research

Kidney transplant research in the province has been unfolding since the early 1980s and has developed substantially within the past decade. For the purpose of this narrative, kidney transplant research is confined to the period between the 1990s to 2015 and divided into three areas:

- Subclinical rejection and non-invasive diagnostic urine testing,
- Pre-transplant assessment: HLA cross- matching antibodies/flow cytometery, and
- Post-transplant outcome studies.

Each research areas is affiliated with numerous projects, studies, and publications, collaboration with many researchers, and are intertwined to some degree.

a. Subclinical rejection and non-invasive diagnostic urine testing

Once a kidney transplant occurs, monitoring is crucial to detect rejection as early as possible. Biopsies, which are done post-transplant to determine what is taking place at a microscopic level, can identify early scarring that can happen with chronic rejection, injury to the kidney from medications, or silent rejection that can occur without the levels of creatinine increasing.[8] Creatinine levels are monitored

within the kidneys which help identify the functioning levels. However, sometimes problems arise before the creatinine levels rise, so biopsies are crucial for post-transplant treatment.[9]

In the early 1990s, Dr. David Rush, one of the early researchers in kidney disease in Winnipeg, pioneered the use of surveillance biopsies (performed with a special needle that removes tiny pieces of the kidney guided by ultrasound pictures) in kidney transplantation and reported high prevalence (30%) of subclinical rejection in renal transplant recipients even though clinically they were functioning normally.[10] When present it was noted to be linked to early chronic pathologic changes and long-term graft survival. This approach was a revolutionary and novel way of determining the causes of graft rejection. Dr. Rush initiated research in rejection when there was no apparent reason to think of graft failure occurring.

In 1998, Dr. Rush conducted a randomized control trial (RCT) and his team found that treatment of subclinical rejection as detected in the surveillance biopsies led to better outcomes. This led to patients in Winnipeg being routinely treated for rejection before it became clinically apparent. The 1998 research project was a major contribution to the field, and received 275 citations, indicating the level of interest it created.

In 2004, Dr. Rush led a multicenter Canadian RCT and found that new, more potent immunosuppressive drugs could diminish the levels of subclinical rejection. This resulted in reducing the need for doing as many protocol biopsies. Nevertheless, there was still ongoing inflammation. The research showed that subclinical inflammation was leading to scarring from the biopsies, and was associated with premature graft loss.

The research team realized that for transplants to succeed, frequent and non-invasive diagnostics were needed, leading to research on subclinical rejection and the development of non-invasive urine tests by Dr. Peter Nickerson, another leading researcher in kidney disease with the University of Manitoba. Dr. Juliet Ho, one of Dr. Nickerson's trainees, has taken over the lead in this research area since 2008/2009 when she completed her degree. She has developed additional urine tests that detect kidney transplant inflammation and scarring so they are diagnosed early and effective treatment can be started.[11]

From 2009-2014, the research team completed clinical trials aimed at drug minimization to avoid toxicity while preventing subclinical rejection. Going forward, the research project will implement another phase of clinical trials, looking to minimize kidney inflammation from the time of transplant, in order to reduce overall subclinical rejection and its resultant injury.

b. Pre-transplant assessment: HLA cross-matching antibodies/flow cytometer

At the same time as research on subclinical rejection and non-invasive diagnostic tests was taking place in the early 1990s, the research team recognized that the graft survival one-year post-transplant was 90% using serologic cross-matching.[12] "We knew grafts were being lost early to antibodies, which were

forming in the patient's blood. When the patient received a transplant, they would lose the graft within a couple of weeks. The tools we had in the lab were insufficient", according to Dr. Nickerson.

The research team observed that a flow cytometer cross-matching technique was an innovative method, however there were no high quality clinical studies utilizing it to prevent early graft loss.[13] This laser-based technique simultaneously does cell counting, cell sorting, and biomarker detection by suspending cells in a stream of fluid and passing them by an electronic detection apparatus. [14] In 2000, a flow cytometer was purchased and the Winnipeg research team conducted retrospective analyses to show that had flow-cross matching been done, many grafts would not have been rejected/lost. Based on the study's findings, the use of the flow cytometer was implemented, and the rate of graft survival improved from 90% to 98%. Winnipeg became the first Canadian center to implement and standardize flow cytometer cross-matching pre-transplant. This eventually became the national standard of care – transplants in Canada now occur without flow cross-matching.

c. Post-transplant studies

The research team started routinely screening patients for the development of antibodies post-transplant. With funding from Canadian Institutes of Health Research (CIHR), the team was able to return to previously stored samples in the biobank and showed that de novo (i.e. newly formed) donor specific antibodies–dnDSA had bad outcomes. Specifically, the 2012 study found that 47 out of 315 (15%) patients developed dnDSA and no patients had the donor specific antibody prior to 6 months post–transplant. The 10-year graft survival with patients with dnDSA was lower than the no dnDSA group (59% vs. 96%, $p < 0.0001$) and the results are statistically significant.[15] The principal findings were:

- The dnDNA antibody onset may be overlooked without post-transplant routine monitoring of stable grafts. The routine monitoring for dnDSA identifies patients for early interventional studies in an attempt to define effective therapies to alter their prognosis.
- The importance of cellular rejection should be recognized and treated aggressively given that it frequently precedes dnDSA and the induction of dnDSA.
- When cellular rejection coincides with dnDSA and antibody mediated microvascular injury, it may accelerate the time to graft dysfunction/loss.[16]

The 2012 study became recognized as a landmark study, with over 200 citations internationally. In 2013, the research team studied why patients were forming antibodies and a companion paper on antibodies about the rates of progression once the antibody is present and the determinants of those outcomes was published in 2015. The research team remains a leader on post-transplant research.

4. About the principal investigators (PIs)

Dr. Peter Nickerson of Winnipeg, Manitoba, has conducted leading and world recognized kidney transplant research. His career began at the University of Manitoba with a Bachelor of Science degree in biochemistry and a degree in Medicine (MD). Shortly thereafter, he was awarded a Nephrology

Fellowship in 1990 from the University of Manitoba and a Transplant Research Fellowship at Harvard Medical School in 1991.

Since Dr. Nickerson's return to Winnipeg in 1995, he has held numerous positions including clinician, teacher, scientist, researcher, editor, and director. He has received local, national and international awards, fellowships and grants and is recognized internationally for his contributions to kidney transplant research. Additionally, he has over a hundred peer-reviewed publications in recognized journals featuring research about subclinical rejection and non-invasive biopsy tools, and pre-transplant and post-transplant assessment. He has upwards of two dozen completed reviews and several editorials with accompanied peer reviewed publications. Finally, Dr. Nickerson co-authored a chapter on subclinical rejection of the 4th edition of the Oxford Textbook of Clinical Rejection, published in October 2015.

Dr. David Rush received his MD degree from the National University of Tucumán, Argentina in 1972. From 1974 to 1981, Dr. Rush pursued his post-graduate training in Internal Medicine and Nephrology at the University of Western Ontario in London, Canada. In 1982, he was recruited to the University of Manitoba in Winnipeg. He is currently Professor, Faculty of Health Sciences, University of Manitoba (1996-present), Director, Transplant Manitoba – Adult Kidney Program (2004-present) and Nephrologist, Department of Internal Medicine, College of Medicine, Faculty of Health Sciences, University of Manitoba (1982-present).

Dr. Rush is a researcher, clinician, teacher and editor. Dr Rush has received multiple national and international awards, served as a visiting professor and invited speaker in Canada and in other countries, has over a hundred peer reviewed publications, and has published many reviews, editorials, and commentaries. His research interests include clinical renal transplantation, subclinical rejection, transplant pathology focusing on acute and chronic rejection, protocol biopsies particularly subclinical cellular and vascular rejection, and proteomics and metabolomics of non-invasive biomarkers in kidney transplantation. Dr. Rush is the author of the chapter on subclinical rejection of the 4th edition of the Oxford Textbook of Clinical Rejection that was published in October 2015.

5. Impact narrative approach/methodology

Research Manitoba develops impact narratives to document the outcomes and impacts of research in the province. The goal of the impact narrative is two-fold: a) to link outcomes and impacts to the original research, and b) to communicate the impacts of research to a wide variety of audiences such as academics, industry, community groups, the public and other users of research findings. The narrative also contributes to the following goals of Research Manitoba's in measuring impacts:

- Determine the return on investment of Research Manitoba's funded programs and projects;
- Inform Research Manitoba's decision making, planning and programming;

- Record accountability and transparency (a reporting tool to the Government of Manitoba – Jobs and the Economy);
- Encourage a proactive and prospective measurement and monitoring of research impacts among researchers, funders and users of knowledge; and,
- Contribute to the growing practice of research impact assessment in Canada and globally.

Outputs, outcomes and impacts are examined through the lens of the Research Manitoba impact framework, which is divided into five categories:

- **Advancing knowledge** involves creation/co-creation of knowledge, leading to new discoveries and breakthroughs, and contributing to the knowledge pool.
- **Building capacity** refers to the development and enhancement of the ability of individuals and teams to conduct and sustain research.
- **Influence and effects** on perceptions, thinking, awareness and decision making because of research activities/findings can take numerous forms. This category largely refers to the influence and effects on government; industry; the research enterprise; not for profit organizations; individuals, groups and communities; educational institutions; and the public.
- **Applications and changes** are the outcomes and impacts that result from research in health, social sciences and humanities, and natural sciences and engineering disciplines.
- **Broad benefits** include economic, technological, environmental, social/societal, and cultural benefits impacts such as wellbeing and prosperity**.**

This impact narrative will discuss the development of kidney transplant research in Manitoba and the effects that the research results have had on health interventions and policy in Canada and internationally. In Winnipeg, the standards of care on renal disease or kidney failure now involve flow based cross-match testing prior to transplant surgery, and changes in protocol for monitoring post-transplant. Pioneered by researchers in Winnipeg, the standards of care have been adopted nationally and by many countries all over the world.

To collect data, a questionnaire was developed (Appendix 1), based on the protocol developed for Project Retrosight, a study that assessed the returns from cardiovascular and stroke research.[17]

Two interviews were carried out with a principal investigator (PI), Dr. Peter Nickerson. Additional information was gathered from documents provided by Dr. Nickerson such as his curriculum vitae (CV), the CV of another PI, Dr. David Rush, PowerPoint presentations, published articles, policy related documents, and from the Internet.

The results of the interview and the analysis of secondary data was complemented with bibliometric analysis using data from Scival[18] and the Web of Science. Count of publications, citation counts and distributions, as well as collaboration rates were presented. Citations and collaborations, together with funding support, provide a good indicator at the level of interest in the research that took place.

A part-time person (Ashley Pearson, M.A.) was recruited for the project and worked with Ambrosio Catalla, Evaluation & Policy Analyst at Research Manitoba from August to October 2015. Mr. Ryan Catte, M.A., Evaluation Assistant, contributed to the report.

PART II: Findings

1. Inputs into kidney transplant research

Kidney transplant research in Manitoba has involved different types and levels of inputs: funding from provincial, national and international sources; a core research team led by Dr. Rush and Dr. Nickerson together with trainees and many collaborators in and outside of Canada; study recruits and tissue samples, and research infrastructure. This section will take a closer look at these.

a. Funding

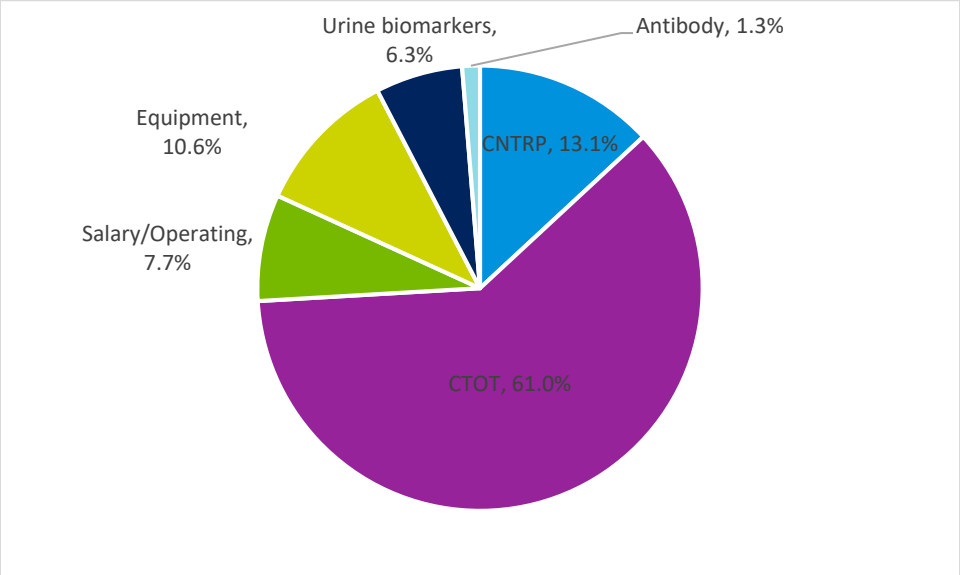
Beginning in 1997, a total of $85.8 million from provincial, national, and international sources have been invested in kidney transplant research and its translation to policy and practice (Table 1). The National Institutes of Health (NIH) has contributed 61% of total funding to kidney transplant research followed by the Canadian Institutes of Health Research (CIHR) and the Canada Foundation for Innovation (CFI). By type of support, the bulk of funding has gone to operating costs. Of the total investments, three quarters have been spent on translation and networks, mostly outside Manitoba. Manitoba's past and ongoing support of $4.1 million has seen an additional investment of $18.1 in research, leveraging $4.4 for every Manitoba dollar invested in kidney transplant research.

Table 1. Funding of kidney transplant research in Manitoba by source, type and amount

Source of funding	Type of support	Value ($)	%
University of Manitoba	Salary and operating	4,000,000	4.7
MHRC (now Research Manitoba)	Operating and establishment grants	135,000	0.2
CIHR/MRC	Operating grants	20,443,024	23.8
CFI	Research infrastructure	8,927,949	10.4
NIH	Operating grant	52,355,221	61.0
Total		85,861,194	100.0

Kidney transplant research in Manitoba has had huge investments between 1997 and 2016, which reflects the great interest in this area of research within and outside Canada. By project, the Clinical Trials in Organ Transplantation (CTOT) accounts for 61% ($52.4 million) of total funding (Figure 1). Research on allograft/urine biomarkers comprised 6% of the total ($5.4 million), 13% or $11.3 million was used by the Canadian National Transplant Research Program (CNTRP) while antibody mediated rejection research accounted for 1.3% (see Appendix 2 for details).

Figure 1. Research support by project



b. The kidney transplant research team

Winnipeg, Manitoba is home to a team of innovative researchers that continues to contribute to kidney disease research and transplantation. Collectively the kidney transplant research team in Winnipeg has extensive knowledge and expertise that ranges from clinical experience, research capacity, teaching, knowledge translation, and the ability to secure funding.

In 1982, Dr. Rush was recruited to and retained in Winnipeg in the area of renal transplantation and rejection. By the mid-1980s, he had established bio-banks, biopsy protocols and initiated research in subclinical rejection. In 1986 Dr. Nickerson met Dr. Rush at the University of Manitoba and was drawn to the innovative work being done around transplants, immunology and kidney disease. He was presented with a "huge opportunity because of the way the program had been set up and the innovative protocol biopsies and development of biobanks."[19]

Since 1998, six trainees have been mentored under Dr. Rush and Dr. Nickerson, three of whom were recruited from outside the province and three trainees who were Winnipeg residents (Table 2). Upon completion of their studies/ training three have remained, gaining enough experience and knowledge to become experts in their own right and developing kidney transplant related research programs. Dr. Kathryn Tinckam and Dr. Stefan Schaub, although no longer based in Winnipeg, remain close collaborators.[20]

Table 2. Composition of the kidney transplant research team

Researchers	From Winnipeg	Recruited to Winnipeg	Retained in Winnipeg	Collaborators
Dr. David Rush		X	X	
Dr. Peter Nickerson	X		X	

Dr. Juliet Ho		X	X	
Dr. Martin Karpinski	X		X	
Dr. Chris Wiebe	X		X	
Dr. Ian Gibson		X	X	
Dr. Stefan Schaub		X		In Switzerland
Dr. Kathryn Tinckam	X			In Toronto

Kathryn Tinckam was an internal medicine resident in transplant immunology (1998-2000), mentored by Dr. Nickerson, and obtained additional training at University of British Columbia (UBC) and Harvard. She was recruited from the USA to Toronto and now works with the Canadian Blood Services (CBS).[21] She is also an assistant professor at the University of Toronto and runs the laboratory at the Toronto General Hospital/Research Institute.[22] Her primary research area is infectious diseases and immunopathology and her secondary research area is genetics, genomics, and proteomics. "My main research interest is in the standardization of clinical immunologic assays utilized in transplantation and studying the impact of alloantibody before, during and after solid organ transplantation."[23]

Martin Karpinski was an early nephrology research fellow at University of Manitoba (1999-2001), and supervised by Dr. Nickerson. His research focus was "clinical renal transplantation Anti-HLA antibodies, allo-sensitization non-invasive diagnosis of rejection".[24] He currently holds an Assistant Professorship of Internal Medicine and does not currently have a major research focus. He is involved in clinical care in Manitoba and as a transplant physician with Transplant Manitoba.

Stefan Schaub. Attracted to the University of Manitoba from Switzerland, he was a trainee and nephrology fellow from 2002 to 2004 under Dr. Nickerson. After graduation, he returned to Switzerland, has been funded by the Swiss National Foundation and is affiliated with the Division of Transplantation Immunology and Nephrology, University Hospital Basel and is also the vice president of the Swiss Transplantation Society. He has continued his collaboration with Dr. Nickerson and the University of Manitoba since return to Switzerland.

Juliet (Julie) Ho. Originally from Ontario, she completed her undergraduate studies in internal medicine. Dr. Ho was attracted to the University of Manitoba as a nephrology fellow (2006-2008) and was one of the top trainees of nephrology in Winnipeg, supervised by Dr. Nickerson. Dr. Ho has helped move the urinary protein biomarkers project forward (early predictors of eventual scarring and dysfunction in renal transplant patients), and has worked on an evaluation of iron and stress in end stage renal disease patients and acute kidney injury in cardiopulmonary bypass patients.[25] Currently, she is a transplant physician with Transplant Manitoba, holds a position of Associate Professor of Internal Medicine at the University of Manitoba and is funded by the Canadian Institutes of Health Research.

Christopher Wiebe. Originally from Winnipeg, he was a nephrology fellow (2010-2014) within the Department of Immunology at the University of Manitoba. Mentored by Dr. Rush and Dr. Nickerson, he assisted the antibody research project and has helped move the project forward in the past five years.

Dr. Wiebe's project focused on discovering specific targets that most likely initiate an immune attack against a donor's kidney by comparing the targets of transplant patients who developed antibodies with patients who did not develop antibodies. His findings allowed doctors to avoid these targets, resulting in a better and longer lasting kidney transplants, and understanding which patients are likely to benefit from a reduction of their immune suppressing medications.[26] Currently, he is a transplant physician with Transplant Manitoba, an Assistant Professor of Internal Medicine at the University of Manitoba and funded by the Crescent Kidney Foundation (partner with CIHR) as a research fellow.[27]

2. Resource: tissue samples/study recruits

Winnipeg has one of the "most prominent" biobanks in the world[28] and has the ability to collect, store and do a complete retroactive analysis of the samples.

Patients that received renal transplants in Winnipeg, Manitoba have provided tissue samples for subsequent research projects.[29] For instance in one recent publication, Wiebe at al. (2015) discuss the sample obtained between January 1999 and July 2012 from 560 adult and pediatric patients with renal transplants in Winnipeg. Some attrition occurred with the sample, thus 508 recipients were examined for analysis, inclusive of adults (n=459), and pediatrics (n=49).

3. Outputs of kidney transplant research

a. Publications

Between 1996 and 2015, the kidney transplant research team had 373 publications (Table 3). Not surprisingly, Dr. Nickerson and Dr. Rush had the highest number of publications, citations and h-indices. Dr. Rush had his first publication in 1978 and had 22 publications before 1996. Among the former trainees, Dr. Schaub and Dr. Tinckam produced the greater number of publications.

Table 3. Publications by research team members, 1996 to 2015

	Publications	**Citations**	**h-index**[30]
Ho, Julie	24	567	10
Karpinski, Martin	29	1,018	16
Nickerson, Peter	115	7,148	38
Rush, David	95	6,379	37
Schaub, Stefan	63	1,727	19
Tinckam, Kathryn	44	810	14
Wiebe, Christopher	12	228	6
Ian Gibson	31	875	19

Source: Scival (http://scival.com/home)

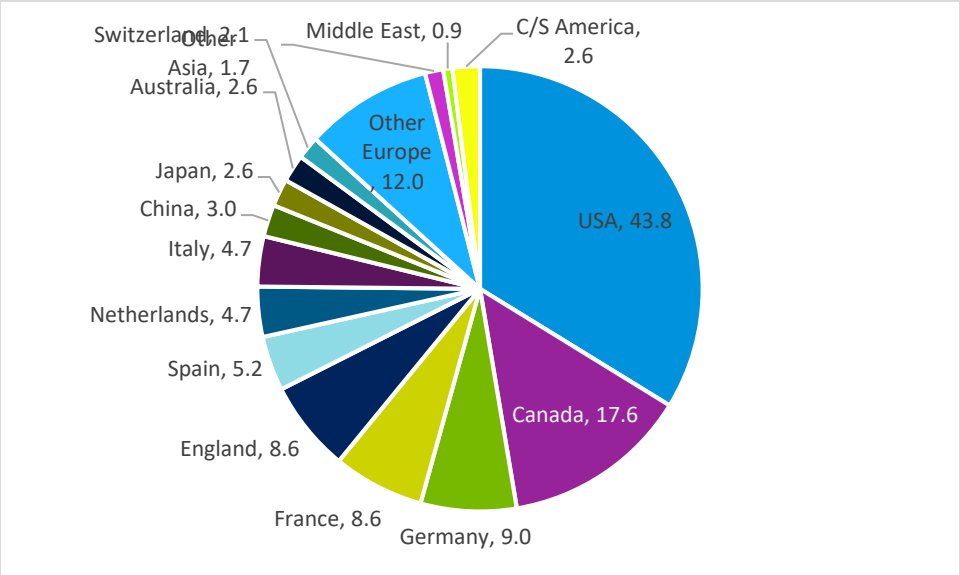
b. Citations

There are several key publications on kidney transplant research. Among them, four articles were chosen to highlight in this impact narrative based on their level of contribution and impact that was partial measured by citations. Using the 'analyze results' feature on the citing articles page of the Web of Science, the citation counts that the article has had based on countries were determined. This illustrates the impact that these papers have had in Canada and globally. [31]

Evolution and Clinical Pathologic Correlations of De Novo Donor Specific HLA Antibody Post Kidney Transplant[32]

Published in 2012, this has become a benchmark for post-transplant research, garnering more than 230 citations since it was published. This research project has been recognized internationally and Dr. Nickerson has been invited to many conferences and universities to discuss the findings. Two companion papers have since been published in 2013 and 2015. As of July/August 2016, this highly cited paper received enough citations to place it in the top 1% of the academic field of Clinical Medicine based on a highly cited threshold for the field and publication year. More than two of five citations originate from the US (Figure 2).

Figure 2. Distribution of citations from 2012 De Novo donor specific HLA antibody post kidney transplant paper, by country (%)

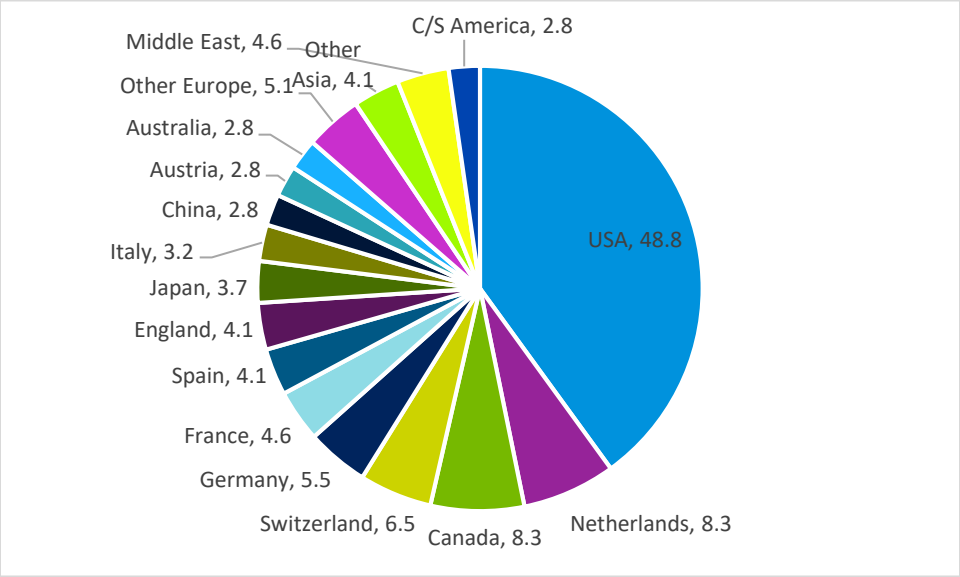


Pre-transplant assessment of donor-reactive, HLA-specific antibodies in renal transplantation

Published in 2003, the paper received a total of 217 citations. This is referred to as the "white paper" and was an evaluation/systematic review of literature.[33] This article was a 'pre-meeting reading' in a consensus workshop in 2005 that led to changes in the national standards of care.

USA and several European countries account for much of the citations (Figure 3). Several researchers based in Asia have cited this paper including Japan and China.

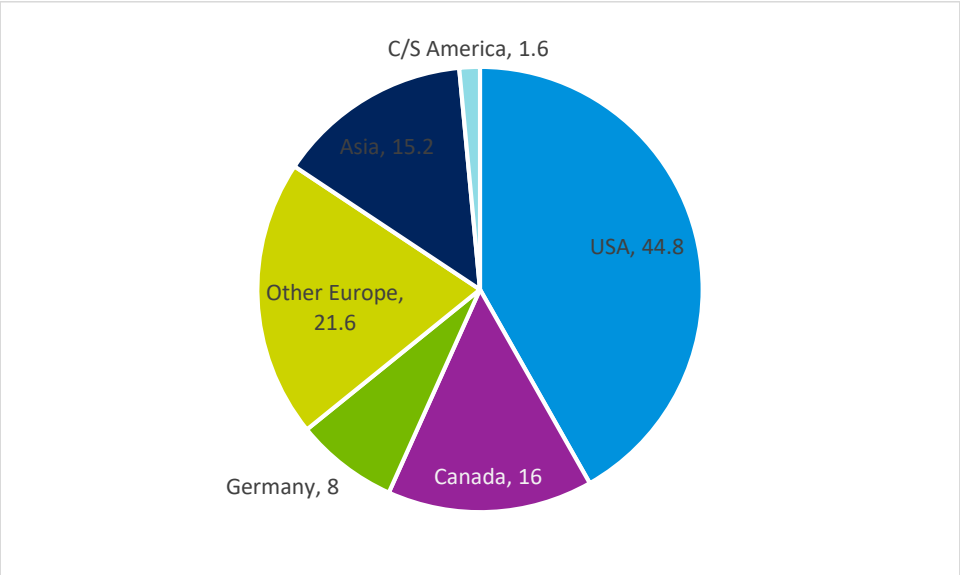
Figure 3. Distribution of citations from the 2003 systematic review paper, by country (%)



<u>Flow cytometric cross-matching in primary renal transplant recipients with a negative anti-human globulin enhanced cytotoxicity crossmatch</u>

Cited 125 times, this was an innovative publication in 2001 that led to changes in the national standards of care for pre-assessment kidney transplantation.[34] Researchers from the USA have cited the paper the most (Figure 4).

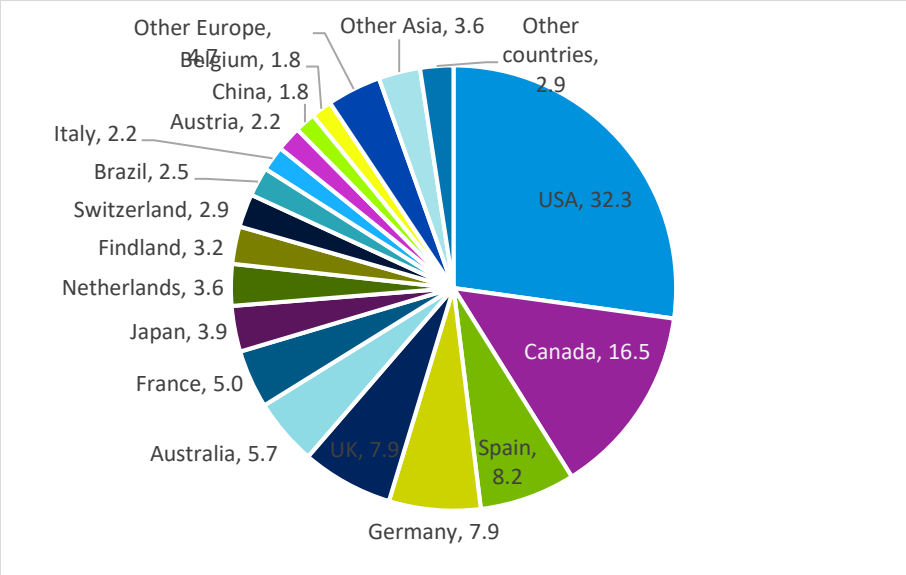
Figure 4. Distribution of citations from 2001 flow cytometer pre-transplant paper, by country (%)



Beneficial effects of treatment of early subclinical rejections

Cited 279 times, this 1998 paper helped to change perspectives and treatment of graft rejections. Researchers from the USA and European countries have cited the paper the most (Figure 5).

Figure 5. Distribution of citations from 1998 flow cytometer pre-transplant publication, by country (%)

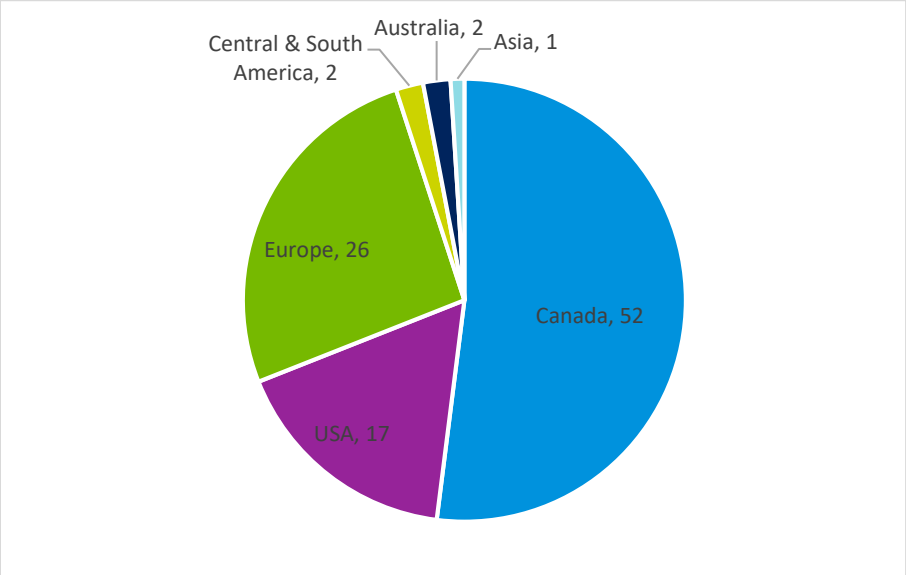


c. Collaborations

Scival was used to determine the levels of collaboration of the research team at the national and international levels. Publications from 1996 through 2015 were used for this analysis. Each team member was assessed individually on Scival and then combined with other team members to present the extent of the collaboration. Researchers from countries that collaborated with the research team less than five times were grouped as 'other countries'. This included Argentina, Belgium, Colombia, Czech Republic, Denmark, Finland, Italy, Japan, Mexico, Norway, Portugal, Sweden, Thailand, and Turkey.

More than half of the collaborations undertaken by the research team have been in Canada (52%) (Figure 5). Other collaborative activities have been with researchers in the USA (17%) and European countries (26%).

Figure 6. Research team collaboration levels, 1996-2015 (%)



4. Outcomes: from evidence to policy and interventions

a. Impact on decision making

Findings from kidney transplant research in Manitoba has had a profound influence on policy, programs and practice relating to kidney disease in Canada. Specifically, it has contributed greatly to a Canada wide policy on standards of care, the development of the national kidney paired program, and the provision of care to persons with renal transplants.

Prior to the development of a national policy and the introduction of these programs, pre-transplant immunologic evaluation was not standardized and did not allow for optimal patient risk assessment or for optimal organ allocation.[35]

Introduction of a national policy on standards of care

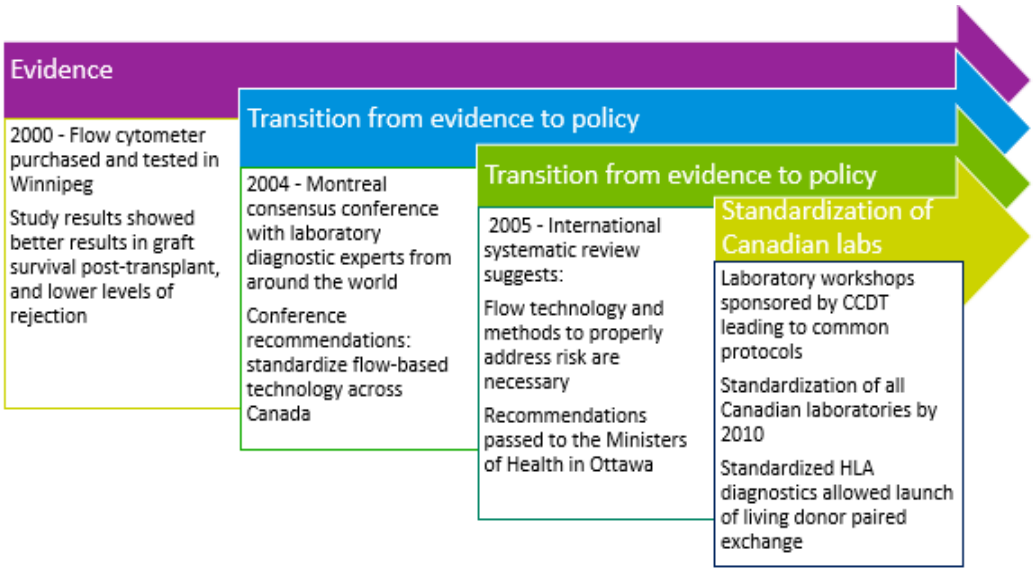
Kidney transplant research has resulted in major shifts in the care of kidney disease. One significant impact is its influence on policy. Over the last 30 years various provincial and federal government reports have stated the need to enhance organ and tissue transplants in Canada. In 2001, the federal and provincial governments formed the Canadian Council for Donation and Transplantation (CCDT). The Board, comprised of members of government, provincial leaders, and ministries (including Manitoba's Deputy Minister of Health), worked collaboratively to discover leading practices and make recommendations about the leading research in the area of organ donation and transplantation.[36]

CCDT asked Dr. Nickerson to chair the first workshop/consensus conference in Montreal in 2005, based on the kidney transplant research he was involved in, including the retrospective analyses on previous samples stored in the biobank that showed better outcomes with the use of flow-based technology.[37]

The consensus conference in Montreal brought together laboratory diagnostic experts from around the world. All of the literature on the topic was reviewed (including Winnipeg's research) and the experts concluded that the leading practice was to move to flow-based technology. A report from the conference was released titled, "Assessing and Management of Immunologic Risk in Transplantation: A CCDT Consensus Forum".[38] Simultaneously a background/systematic review on the international literature i.e. the "white paper", was written on behalf of the American Society of Histocompatibility and Immunogenetics.[39] This publication made a series of recommendations to properly address risk and reiterated that flow-based technology was necessary.

Post workshop and release of the CCDT report, recommendations were made to the ministers of health that all laboratories needed to adopt flow-based technology.[40] Canadian laboratory and transplant specialists came to a consensus on the required changes for the 15 laboratories across the country. With Winnipeg acting as a reference laboratory, CCDT sponsored a series of workshops with the laboratories and hired an objective analyst from Atlanta to provide the laboratories with blind samples, ensuring accuracy.[41] Proficiency workshops were developed and monitored to see the degree of variation between each of the laboratories. From that data, common protocols were developed for how the testing would be completed showing minimal variations, i.e. Winnipeg and Vancouver should produce the same results. "Because HLA diagnostics and antibody assessment are so complex, it took a lot of effort to come to a common standardization of the laboratories. All laboratories across Canada were standardized by 2010," according to Dr. Nickerson. At that point, Winnipeg no longer acted as a reference laboratory. Standardization directly impacted on improving clinical outcomes, that is, renal transplant patients experienced longer survival rates. Figure 7 illustrates the process through which findings from kidney transplant research have been used and served as the basis for a Canada wide policy on standards of care and as a driver for changing diagnostics and treatment of persons with renal transplants.

Figure 7. Evidence to policy and practice: adoption of flow-based technology and standardization of Canadian laboratories



Implementation of the national paired kidney program

Health care in Canada is a provincial jurisdiction; few programs are run inter-provincially. Before the national paired kidney program, the Canadian Blood Services (CBS) was the only agency that operated inter-provincially (excluding Quebec). Board members were appointed by the provincial ministers of health to deliver a blood service and supply in Canada. This became problematic because an informal list of registrants was maintained; a national program and an IT system was lacking. It became evident that correlated systems that worked cross provincially were necessary for best practice.

In October 2005, co-led by Dr. Nickerson, another consensus conference was held in Toronto looking at setting up a National Kidney Paired System, and a Highly Sensitized Donor Program. A report was developed to look at the need for creating the registries and for getting difficult to match patients with a transplant.[42]

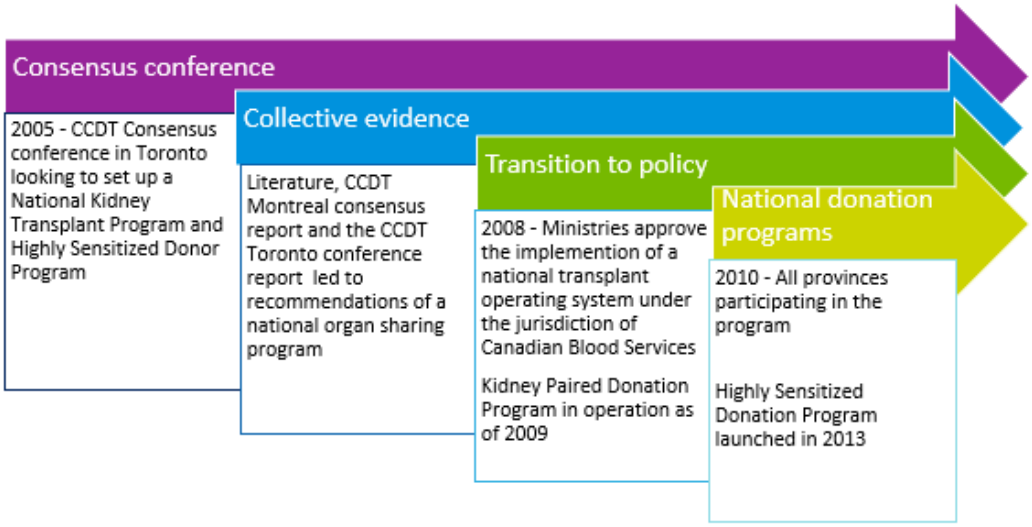
In 2008, the federal, provincial, and territorial ministries of health (except Québec) recognized the need for a national strategy to address the problems with organ and tissue donation and transplantation (OTDT) in Canada and directed CBS to work with the OTDT community to develop a plan that better served Canadian patients and significantly improved on past performance. In the same year, CBS was given the green light by the Conference of Deputy Ministers to create the national transplant program to begin development of the Living Donor Paired Exchange Program (LDPD), and to test it as a pilot program.[43] [44] The kidney paired donation (KPD) facilitates living donor transplantation in end stage renal disease patients with a blood group or human leukocyte antigen (HLA) incompatible living donor.[45] Kidney paired donation programs are a relatively new practice as a possible solution to the shortage of kidneys. Important aspects of the Canadian system are standardized patient pre-transplant procedures and HLA laboratory practices across all transplant centers. The KPD has dedicated staff that coordinates transplants and an advisory committee of transplant professionals to address logistical and medical issues that arise.[46]

In 2009, the program was launched in three provinces (British Columbia, Alberta, and Ontario) and by 2010 all provinces and territories were participating in the program. The first transplants were performed in June 2009. As of September 2013, the program had enrolled 468 patient-donor couples and had performed 271 transplants. New results from 2013 through 2015 will be released in September 2015 from CBS.[47] Two other registries were launched - the National Organ Waitlist (NOW) in June 2012, and the Highly Sensitized Patient (HSP) registry, which began accepting donor data entry and donor organ allocation for highly sensitized kidney patients in the fall of 2013.[48]

The Highly Sensitized Program (HSP) is a kidney registry for patients who are more difficult to match because they have increased antibodies, commonly because of blood transfusions, previous transplants and pregnancies.[49] [50]

The KPD and HSP is the result of research, collaboration, a global literature review, a consensus among experts agreeing that the technology was required, and a national consensus in Canada to transition to these standards of care. Through a series of workshops, the clinical process was standardized, and national registries were created and successfully implemented (Figure 8). According to Dr. Nickerson, "This has been an incredible 15-year journey."

Figure 8. Evidence to interventions - implementation of a National Organ Sharing Program



b. Changes in health care delivery

Winnipeg led the way in developing and adopting protocol biopsies. Several institutions followed suit including the Mayo Clinic, Johns Hopkins, and hospitals in Switzerland. There are a number of programs that now do routine protocol biopsies including Neckar Hospital in Paris, France and Sydney, Australia. However, many places still do not follow these measures as their standards of care.[51]

For some time, Winnipeg was ahead of Canada in terms of delivering the new standards of care. There was much support within Manitoba from Dr. Brian Postl, Dean, College of Medicine, Faculty of Health Sciences at University of Manitoba, Chair of the Canadian Institute for Health Information (CIHI), and at that time the head of WRHA to implement the technology, as well as support from the leaders and executives of WRHA and Manitoba Health to move the evidence and policy into practice.[52] To have a national policy that can be applied in all jurisdictions, an advisory panel met while the registries were being developed. CBS had experts that took policy ideas back to their jurisdictions, tested them and brought them back with adjustments before they were enacted.[53]

c. Other impacts

<u>On government</u>

Two major bodies that oversee accreditation of laboratories of transplantation in North America are the American Board of Histocompatibility and Immunogenetics (ASHI) and the College of American

Pathologist's (CAP). Dr. Nickerson became president of the society (ASHI), which led to being on the board of United Network of Organ Sharing (UNOS). UNOS is the organization contracted by the US Federal government to deliver the inter-state organ sharing. UNOS stipulated if an organ transplant were to occur, it had to go through the organization. Dr. Nickerson served on their board from 2003 to 2005, which provided understanding of how a national system was working and how the board was operating.

On education

Teaching materials on kidney transplants that are in use have been based on the standards of care.

Other research

As evident in numerous citations that originate from multiple locations, kidney transplant research in Manitoba has impacted the work of other researchers around the world.

International impact

Since the implementation of Canada's KPD, several countries have sought the assistance of CBS on setting up and operating their national programs. Countries with a national sharing program include: USA, South Korea, Holland, UK, Netherlands, Spain and Australia.[54] There have been successful international efforts with breakthrough collaborations for organ donation in Australia and the United States. [55] [56] [57]

The most current area in kidney transplant research in Winnipeg is routine post-transplant monitoring for patients with antibodies. This has become the new standard of care in Winnipeg and becoming adopted by more institutions of care around the world. Post-transplant research being conducted in Winnipeg is approximately 10 years in advance of similar research in other countries. Consequently, Dr. Nickerson has taken part of an international consensus report (2013) on behalf of the World Transplant Society. [58] This is a consensus document on laboratory diagnostics; one of the sections is based on pre- and post-transplant antibody work.

5. Health impacts

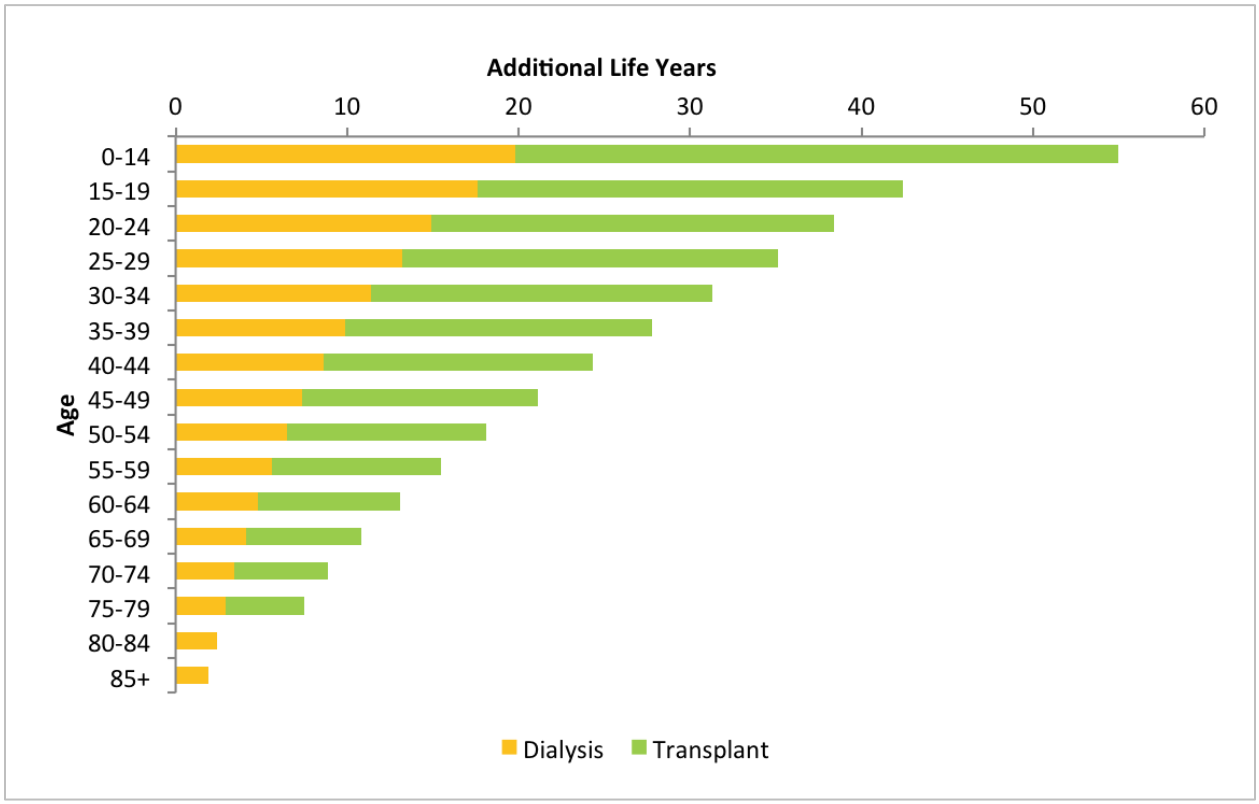
Kidney transplant research has had a positive change in the health sector. As stated elsewhere in this report, data from the research showed significant health impacts for patients and their families, including:

- Pre-transplant assessment of antibodies improved survival rates for patients post -transplant from 89% to 98% one year after
- Going into the transplant with a better understanding of what the risks are
- Post-transplant, better monitoring with improved outcomes
- Increase in 10-year kidney graft survival rate from 60% to 90%
- Living donors that were denied can now donate (KPD)

When asked how many people have benefited from the kidney transplant research, Dr. Nickerson responded, “It’s impossible for me to know how many people we have affected, but through standardization, we have most definitely impacted thousands of patients across Canada.”

Collaborations, new diagnostics and new drug therapies have helped lead to changes in health outcomes. Once the evidence led to national standards of care, there were lower rates of hospitalization, lower rates of renal transplant rejection, increased cost savings for the health industry, and longer life expectancy, depending on age at transplantation and co-morbidities (Figure 9). An individual with ESRD between the ages of 20-24 years could be expected to survive an additional 38.4 years with a transplant compared to 14.9 years on dialysis.[59]

Figure 9. Life Years: remaining on dialysis vs. receiving a transplant (Estimated based on age of onset of end-stage kidney disease)[60]



6. Socioeconomic impacts

a. Cost savings

Economically, renal transplants are a more viable option than dialysis. The cost of a renal transplant including care and medication is about $66,400 in the first year and $23,000 per year thereafter. In comparison, dialysis costs $56,000 to $107,000 annually.[61] With a transplant, the health care systems

can realize a saving of about $33,000 to $84,000 per year starting with the second-year post-transplant. In Canada, a health intervention is considered to be cost-effective if it costs less than approximately $40,000-$50,000 per quality adjusted life years (QALYs).[62] There have been attempts from the research team to persuade government officials that renal transplants are a much more cost-effective health procedure. According to Dr. Nickerson, "the need for dialysis has been reduced, but there are an increasing number of people with kidney diseases from diabetes, obesity etc...what we have done is mitigated the rate of rise, but we have not stopped the rate of rise."

The KPD program provides cost effective, lifesaving therapy to patients. Increased access to a lifesaving therapy for hard to transplant patients has resulted in cost savings of approximately $250,000 by decreasing the total cost of renal replacement therapy.

b. Improved productivity

Patients with a renal transplant show increased levels of individual productivity as they are more likely to go back to work with a transplant.[63] When a patient is on dialysis, usually three to four times a week and may take up to six hours per day,[64] they may feel tired and are less likely to work. Thus, the number of people with renal transplants that remain active in the workforce for a longer period are able to contribute to broader economic benefits.

PART III: Discussion

1. Impacts and attribution

An important issue that needs to be addressed in impact narratives is the extent to which outcomes can be attributed to previously supported research (or programs or any intervention). Establishing these links highlight the value of the work of researchers to funders, stakeholders, the public, and researchers themselves.

Contribution analysis (CA), an approach to exploring cause and effect,[65] will be used to frame the discussion around attribution. It is based on generative frameworks, a process view of causation that identifies the causal links and 'mechanisms' that explain effects.[66] This approach involves identifying the attribution problem, developing a theory of change, collecting evidence, and assembling a strong contribution story. Utilizing a results chain, it assembles the different pieces of evidence that illustrate the process by which outcomes have been achieved. It addresses the difference i.e. impact, that the research has made, and how much of that impact has been contributed by the research.

Using this approach facilitates the establishment of the direct connection between the changes in the standards of care in Canada for persons with kidney transplants and the kidney transplant research conducted in Winnipeg that started in the 1980s and continues until the present. Specifically, the theory of change that is being addressed is that kidney transplant research in Winnipeg from the early 1990s to

2014 has, to a large extent, a) led to better access to kidney transplants, and b) improved the survival rates of persons with kidney grafts.

As Figure 10 illustrates, there is clear evidence that research around kidney transplantation carried out in Winnipeg beginning in the early 1990s by a core group of researchers has impacted the access to kidney transplants, opening up the possibility of transplant to more people, and improved the survival rates of persons with kidney grafts. Pre-transplant and post-transplant research has uncovered:

- Subclinical rejection,
- The causes of rejection,
- The use of drugs to minimize rejection,
- The development of non-invasive biopsies that can be done frequently, and
- The discovery of antibodies that could adversely affect kidney grafts.

These research findings were integrated so that standards of care in Winnipeg were years ahead of the other provinces in Canada. Research findings and the experience in Winnipeg has provided a large and significant contribution to two consensus workshops held in Montreal and Toronto in 2005, leading to national standards of care. After the consensus workshop in Montreal, Winnipeg acted as a reference laboratory for all diagnostic laboratories in Canada until 2010, when all provinces provided the same standards of care to all kidney transplant patients.

Even as the local kidney transplant research unfolded and developed in the recent decades, it has regularly drawn from, and has been influenced by research carried out elsewhere in Canada and the world. The growth and the importance of the research on kidney transplants in Winnipeg has been validated by the investments that has increased over time and sustained until 2021.

Several reasons can be ascribed to the “success” i.e. the extent of the impact, of the kidney transplant research in Winnipeg. First, kidney transplant research in Winnipeg in the past decade has taken a trajectory that has directly responded to the needs of people who needed and who had kidney transplants. At the time when kidney transplant research was growing in Winnipeg, incident cases of ESRD were increasing and dialysis was the major approach to treatment. Second, the type of research carried out over time has produced results that improved graft survival. Changes in methods to match pre-transplant has increased survival rates one-year post-transplant. This was made possible by the presence of a biobank that enabled a retrospective analysis leading to the adoption of cross flow matching prior to transplant. Monitoring of the kidney graft post-transplant has also changed from surveillance biopsies to non-invasive biopsies, and from monitoring creatinine levels to examining de Novo donor specific antibodies. Research currently being undertaken locally after transplantation is ten years ahead relative to similar research in other countries. Lastly, a core team of researchers, largely unchanged since the 1990s that has built on their preceding discoveries and enhanced their expertise, has not only undertaken research but also participated in the translation of the findings in practice and the development of provincial and national guidelines, policies and programs.

2. Knowledge translation and impacts

Knowledge translation (KT) is defined by CIHR as a "dynamic and iterative process that includes synthesis, dissemination, exchange, and ethically-sound application of knowledge to improve the quality of life of Canadians and provide more effective services and products and strengthen the health care system". CIHR makes a distinction between integrated knowledge translation (iKT) and end of grant knowledge translation. In iKT, key stakeholders/intended knowledge users are included during some portion or all of the research process. End of grant KT on the other hand, are activities "aimed at diffusing, disseminating or applying the results of a research project".[67] For the purposes of this document, KT is the umbrella term for all activities involved in moving research from the research space (e.g. laboratory) into the hands of people, groups, and organizations who can put it to practical use, eventually leading to impacts. KT is not an action, but a spectrum of activities that change according to the type of research (i.e. pure or applied), the funds/time allotted for disseminating research findings, and the audience being targeted.

Understanding and optimizing how research is translated is critical to identifying and improving the outcomes that arise from research – including commercialization activities and broad social, environmental, and economic benefits to Manitoba and those that are non-commercial in nature such as behavior change interventions, policy changes and the like. Grimshaw et al. (2012) note that one of the most consistent findings in research is its failure to translate into meaningful changes in practice and policy.[68] Billions of dollars are invested every year into research that is meant to address problems and issues facing all facets of modern society. The aim of this section is to determine and analyze the activities that led to the impacts that kidney transplant research has had and contemporaneously contribute to the understanding of how knowledge translation activities lead to impacts.

Research on end stage renal disease (ESRD) and subclinical rejection in Winnipeg began in 1982 and has led to significant impacts that include: lower rates of hospitalization, lower rates of renal transplant rejection, increased cost savings for the Canadian healthcare system, and longer life expectancy/ improved quality of life for ESRD patients. Over the past 35 years, ESRD research in Manitoba is best broken into three key areas: subclinical rejection and non-invasive diagnostic urine testing; pre-transplant assessment; and, post-transplant outcome studies. The kidney transplant research team in Manitoba played a significant role in facilitating the transition from research activities to impacts by establishing and modifying programs and policies in Manitoba eventually across Canada including. Specific activities in achieving these goals include:

a. Proof of concept

In trying to understand subclinical rejection, Manitoba investigators explored the use of a flow cytometry in a retrospective study. This study was able to ascertain that the use of flow-cross matching would have prevented the loss of many grafts had it been used prior to previous completed transplants. Based on the results of this study, the use of the flow cytometry was implemented in the Manitoba

Transplant Program and resulted in an 8% increase in graft survival from 90% to 98%. The resulting increase in graft survival has led to an adoption of the practice across Canada. The primary benefit has been a decrease in subclinical rejection from kidney transplants in Canada. However, these benefits would not have been realized if it was not for the work kidney research team taking the necessary steps to validate their hypothesis.

b. Engaging end users

In Manitoba, clinician-researchers engaged key decision makers at two levels: first, provincial support was obtained from Dr. Postl, formerly the head of the WRHA, who was open to and understood the value of flow-cross matching technology. The support from Dr. Postl in partnership with Manitoba Health led to the development in new standards for kidney transplant procedures and policies across the province; second, on a national level, Manitoba investigators participated in two federal consensus conferences that were attended by all key stakeholders in transplant care and research across Canada. Specifically, in 2004 the CCDT asked Dr. Nickerson to chair a consensus conference in Montreal that examined the assessment and management of immunologic risk in transplantation. The proof of concept on the use of a flow cytometry demonstrated by the Manitoba Transplant Program was a key consideration that made Winnipeg a reference lab by 2005 in the national effort to standardize the practice across Canada. A second consensus conference held In Toronto in 2005, was co-led by Dr. Nickerson to establish a National Kidney Paired System and a Highly Sensitized Donor Program. In both conferences, recommendations were made to provincial and federal decision makers which have, over time, standardized laboratory diagnostics in all provinces and led to the creation of national programs that have provided greater access to kidney transplants and addressed the needs of highly sensitized patients.

c. Dissemination of research findings and discoveries

The kidney transplant research team has a total of 373 publications that have been cited 18,752 times. Many of these papers were written in collaboration with other Canadian researchers 52% of the time, European researchers 26% of the time, US researchers 17% of time, and researchers from other countries that include Colombia, Turkey, and Japan 5% of the time. Additionally, some of the most prominent publications have been instrumental in changing national standards of care in Canada, have reached the top 1% in citations amongst the academic field of Clinical Medicine, and led to invitations to many national and international conferences. As knowledge of Winnipeg's research and innovations spread, many institutions in the US, Switzerland, France and Australia have followed suit. This was the case for the development and adoption of protocol biopsies as well as routine post-transplant monitoring.

d. Creating a core team of researchers

The creation of a small and long-standing research team around ESRD has ensured continuity in the understanding of the determinants of (non) graft rejection and how better to mitigate them. The

mentoring of researchers new to the team has allowed junior members to make contributions on discoveries more senior members have uncovered. For instance, Dr. Juliet Ho has taken over for Dr. Nickerson and continued to develop additional non-intrusive urine tests that detect kidney transplant inflammation and scarring to increase the time to diagnose rejection of a transplant kidney. The Rh research team members are highly regarded and have become productive and collaborative investigators, authors, speakers and presenters in many meetings and conferences around the world facilitating the translation of knowledge about kidney transplant research.

e. Acting as champion of the research

Dr. Rush and Dr. Nickerson, two of Winnipeg's leading investigators on kidney transplant research, knew their pioneering work on subclinical rejection of kidney grafts could have a significant effect on the high prevalence of ESRD in Manitoba. Their work around protocol biopsies with the help of the research team led to: the use of more sensitive diagnostic technologies, use immunosuppressive drugs, non-invasive biomarkers, and post-transplant monitoring has improved graft survival rates. A key discovery was the use of cross flow matching pre-transplant which, through in-person engagement, convinced provincial and federal decision makers that there was a need for new standards of care.

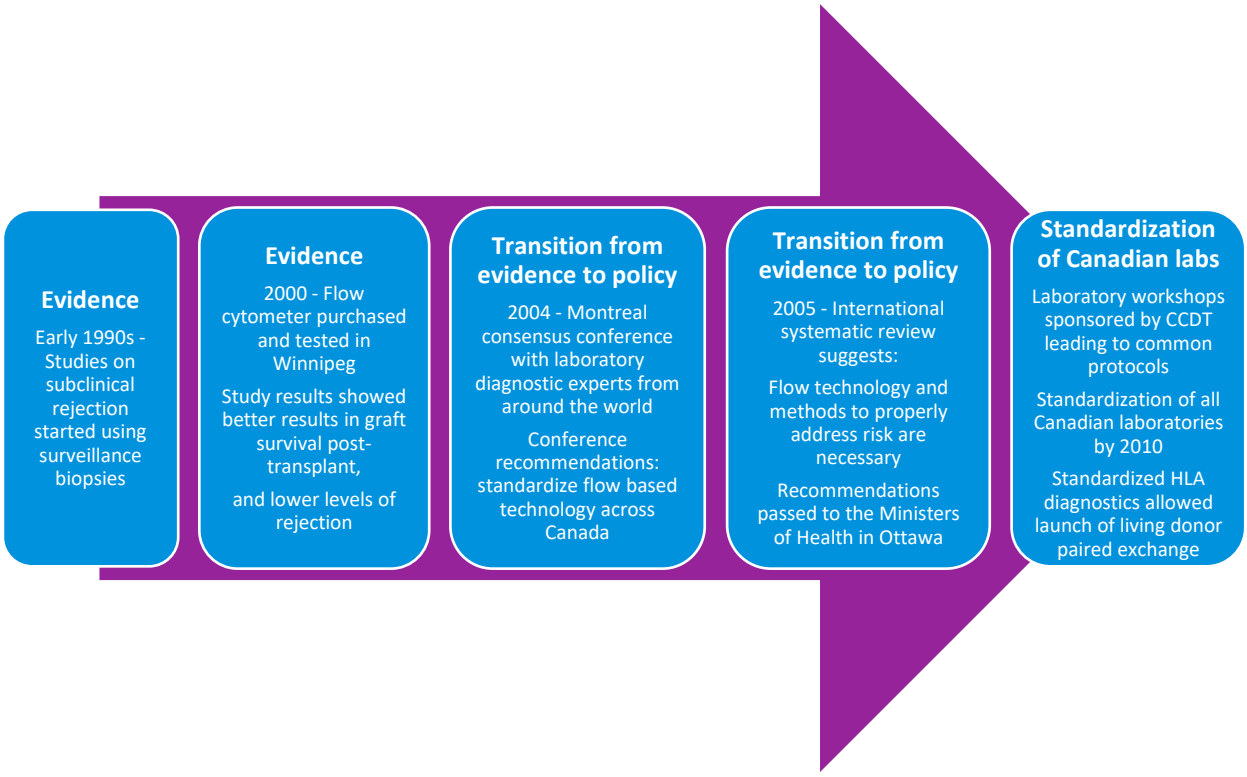
Individually, Dr. Rush was a visionary in his approach to understand the reasons why transplant failure was happening even as patients were passing clinical criteria. Specifically, the use of surveillance biopsies was revolutionary and novel. After becoming aware of Dr. Rush's innovative research, Dr. Nickerson has complemented the research results by Dr. Rush on transplant immunology and non-invasive diagnostics. As a team, Dr. Rush and Dr. Nickerson have written multiple academic peers in prominent journal publications and presented their work to key Canadian public health policy and decision makers at the provincial and federal level.

As the preceding discussion illustrates, the health and socio-economic impacts that are being realized in Canada and around the world from kidney transplant research in Winnipeg has come about due to certain knowledge translation activities. The success of the kidney transplant research program was the result of a series of innovative ideas, the development of an effective research team, dissemination of research results, and effective engagement with key public stakeholders to influence change in policy, program, and practice. Key among these is the willingness of investigators to engage with stakeholders and advocate for the uptake of their research finding in policy and practice. As champions of their research, they have maintained the visibility of an issue (i.e. the high prevalence of ESRD in Manitoba), and more importantly, the solution that has been developed from their discoveries. Overall, the development of the ESRD research program has led to an increase in the quality of life for Canadians as well as more cost-effective treatment programs for health policy/program decision makers across Canada.

3. Time to impacts

In the early 1900s, Dr. Rush pioneered the use of surveillance biopsies to determine the causes of graft rejection even as graft recipients were functioning normally clinically. By treating subclinical rejection starting in 1998, outcomes for graft recipients became better. Acting on the results of a retrospective analysis carried out in 2000, Winnipeg implemented and standardized flow cytometer cross matching pre-transplant. This improved survival rate from 90% to 98%. In 2005, a national consensus workshop recommended that flow cross matching pre-transplant should be an integral part of the standards of care across Canada. Winnipeg served as a reference laboratory when Canadian diagnostics labs were being standardized in 2006. From this partial timeline, it took around 15 years from the initial research on subclinical rejection of kidney grafts to having a substantial effect on survival rates of kidney transplants.

Figure 11. Time to impacts



Part IV: Conclusion

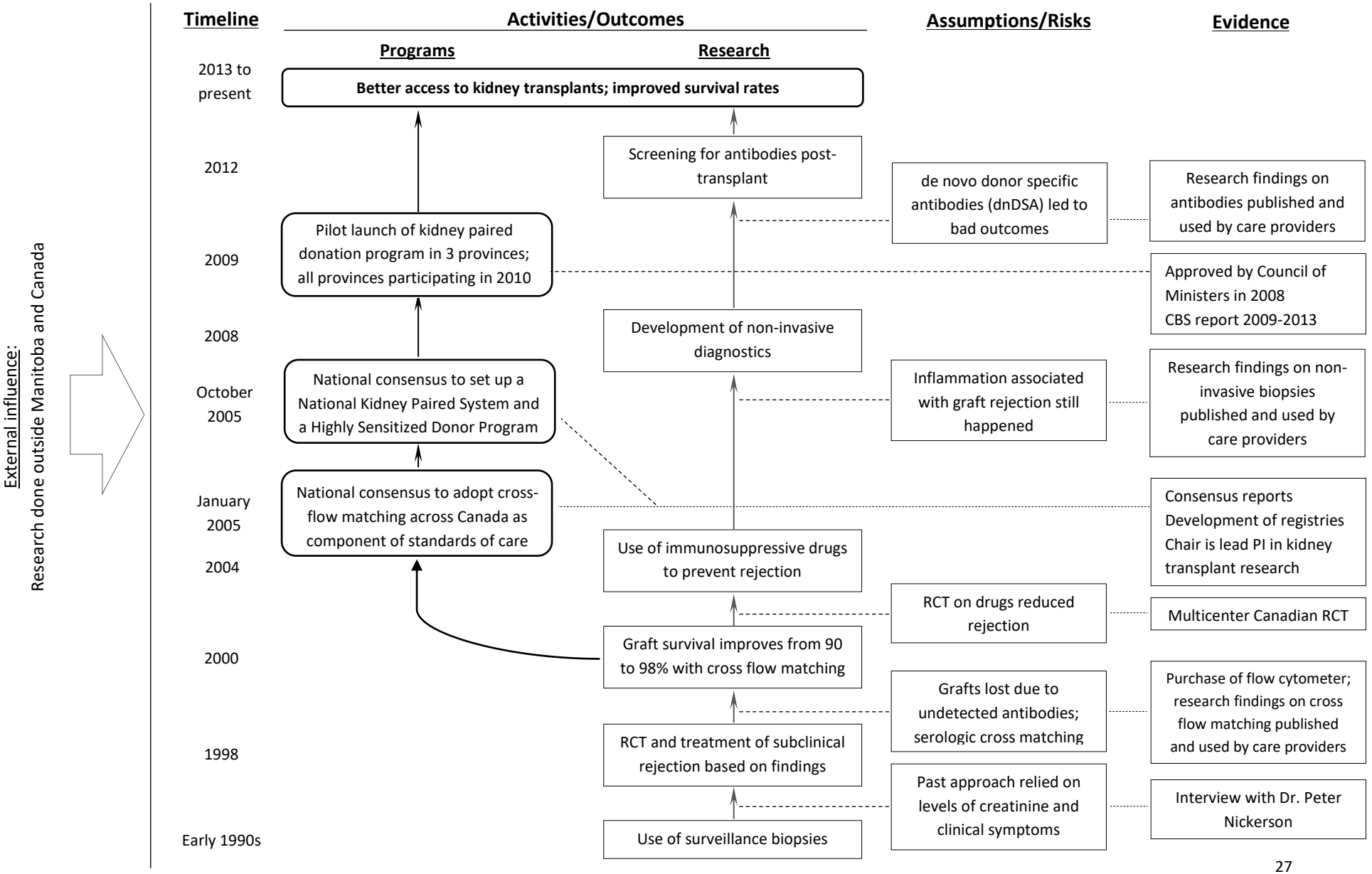
Kidney transplant research in Winnipeg has come a long way and has impacted the provision of care for ESRD patients and people with kidney transplants in many ways. The use of surveillance biopsies in the early 1990s led to the discovery and treatment of subclinical rejection, reducing the likelihood of rejection. The subsequent application of flow cross-matching technique pre-transplant introduced a

major shift in the standards of care. Further research has involved the use of drugs to reduce rejection, developed non-invasive and frequent biopsies, and the discovery of antibodies that may accelerate the time to graft dysfunction/loss. The growth in understanding on the causes of rejection and its mitigation has benefited patients with kidney transplant, translating into longer life spans, increased productivity and improved quality of life.

These findings and their adoption into practice also significantly contributed to the development of two key programs: the Kidney Paired Donation Program and the Highly Sensitized Program. These national programs have enabled greater access to kidney transplants and responded to the needs of patients that are highly sensitized.

Clearly, the translation of the discoveries in kidney transplant research conducted in Winnipeg since the early 1990s has made a great contribution to the improvement in the health of people with kidney transplants not only in Canada but globally.

Figure 10. Theory of change for kidney transplant research in Winnipeg



Appendix 1. Interview Questionnaire, Kidney Transplant Research

INTRODUCTION

1. Introduce self
2. Present Research Manitoba's objectives:
   - Determine the return on investment of Research Manitoba's funded programs and projects.
   - Communicate value and benefit of research to funders, stakeholders and public
3. Define impact narratives:
   - A story of an impact(s)
   - Examining the performance of a project(s) on the delivery of research activity, inputs, outputs and impacts generated.
   - Completed report will be validated with interviewee, and others as may be the case
4. Seek agreement/clarification about projects and impacts that are linked to it (present and review the logic model)

RESEARCH ACTIVITY

1. Outline career in terms of research for kidney transplant
   - What year did you start working on kidney transplant research in Winnipeg?
   - How did you decide to enter into this field of research?
2. How many research projects were responsible for the impacts?
   - For each of these research projects identified, request for project documents

INPUTS

A. FUNDING

1. Obtain a complete picture of funding of the research
   - Get complete list of grants received
   - Determine/verity funding amounts by source and year
   - Identify projects and links to the funding
   - Identify the projects that are related to impacts
2. Request for related project documents
3. What was the institutional support provided?

B. PROJECT(S)

1. What type of research was taking place from the beginning – biomedical, clinical research, etc.?
2. Who was involved in the research project(s)?
   - Were you the lead PI? Who were the main researchers?
3. How many trainees and research assistants/associates were involved?
4. What was their level of research experience/ seniority at the time, had they worked in this particular area?
5. Did the research project attract research talent to Winnipeg?

- How many students were attracted to this field of study due to your research?
- How many researchers were attracted to this field of study due to your research?
- Did it make any impact on the career of any of the research team?
- Did this enable the researchers in gaining further funding and/or other spin-off projects?

OUTPUTS

A. PUBLICATIONS/ CITATIONS

1. How many publications (in your CV) are related to these research project(s)?
2. In what way has the research been cited? (Funding applications, curriculum changes, guidelines, policies, academic articles, citations, and other research?)

B. TRANSLATION OF RESEARCH RESULTS

1. What impacts can be directly attributed to your research?
2. If cannot be attributed, to what extent has your research contributed to impacts?
3. Was there any interaction with potential users during the research process/ activities (or when research was happening?) that led to the impacts?
4. Who did the research team interact with to lead to the impact? Identify year/ timeline.
   - Were there any pilot programs?
   - Who or what positions were involved leading up to the impact?
5. How was the research disseminated to particular audiences (such as policy briefs for policymakers)?
6. Has your research led to an impact in teaching, or any advisory role to government, hospitals, industry or other?
7. Has your research led to an impact on guidelines, programs and/or policy?
8. Has any impact been local, regional, national or international?

C. HEALTH IMPACTS

1. What specific health impacts are related to your research project(s)?

D. BROAD SOCIO-ECONOMIC IMPACTS

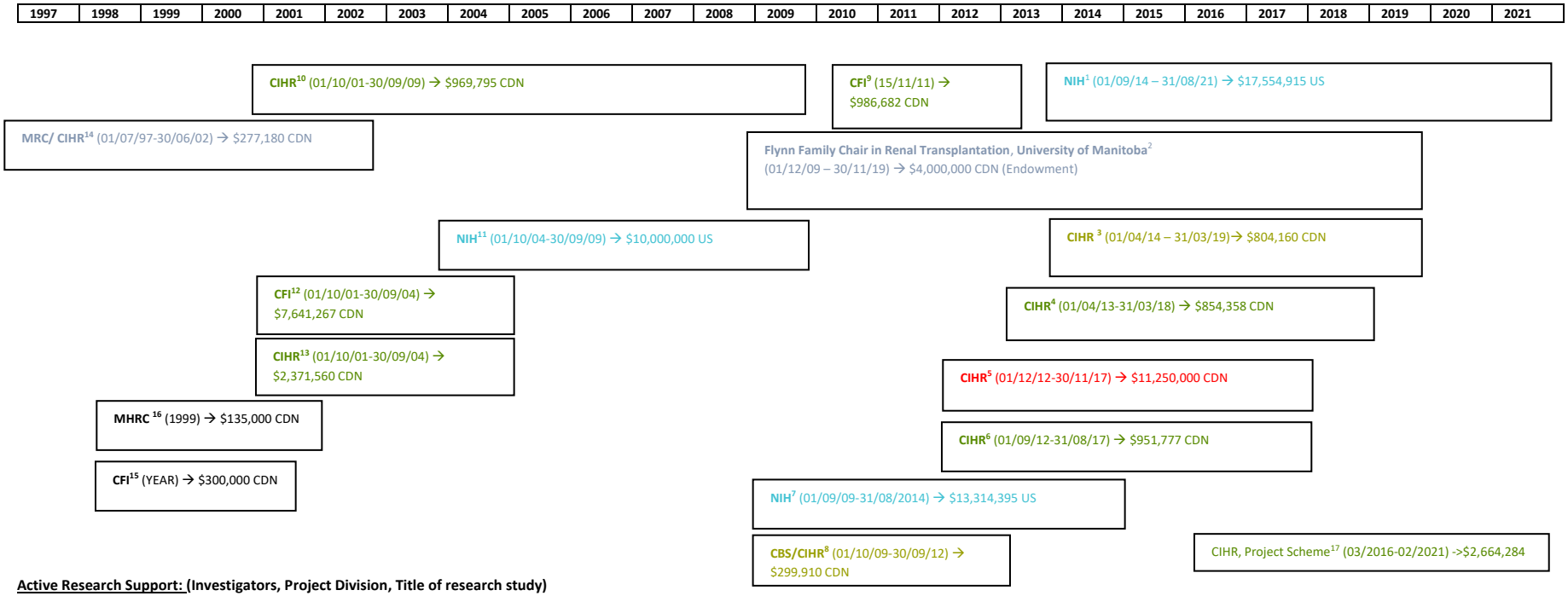
1. What are some of the impacts of your research in terms of improvements in quality of life, economics e.g. cost savings, productivity etc.? Are there studies that have measured/quantified these benefits? Ask for copies of studies.
2. Approximately how many patients have benefitted from your research and how many might benefit in the future?

OTHER QUESTIONS:

1. Who else should we speak to in regards to your research and the impacts of the research?
2. Are there other materials we should review to aid in in telling the impacts of your research?
3. Would you like to add anything else?

Thank you very much for your time.

Appendix 2. Prior and ongoing support for kidney transplant research



Active Research Support: (Investigators, Project Division, Title of research study)

1 Heeger (PI), Hricik, Nickerson, Rush, Formica & Poggio: CTOT→ Effects of inhibiting early inflammation in kidney transplant patients
2 Nickerson (PI): Salary and Operating Grant → Improving Access and Outcomes in Renal Transplantation
3 Nickerson (PI), Gibson, Ho, Rush & Wilkins: ANTIBODY→ Chronic Antibody – mediated rejection: identification of mechanisms and diagnostic proteins
4 Ho (PI), Gibson, Nickerson, Rigatto, Rush & Wilkins: URINE/ BIOMARKERS → Identification of novel proteins as diagnostic or mechanistic targets for renal allograft inflammation
5 West (PI) for the national transplant program: Canadian Network → The Canadian National Transplant Research Program (CNTRP)
6 Byldt-Hansen (PI), Gibson, Ho, Mital, Nickerson, Wishart: BIOMARKERS → Non-invasive monitoring of pediatric kidney allograft injury to improve diagnosis and patient outcome

Prior Research Support:

7 Heeger (PI), Nickerson, Rush, Hricik, Formica: CTOT→ Individualizing Therapy for Kidney and Heart Transplant Recipients (CTOT)
8 Nickerson (PI), Saw, Wilkins: ANTIBODY → Identification of Pathogenic Antibodies in Canadian Cases of Transfusion Related Lung Injury
9 Wilkins (PI), Nickerson, Levin: BIOMARKERS EQUIPMENT → Integrating mass spectroscopy and protein functionality in biology and medicine
10 Nickerson (PI), Gibson, Rush, Wilkins: URINE/ BIOMARKERS/ ANTIBODY) → Proteomic approaches to identify novel pathways associated with renal allograft rejection
11 Heeger (PI), Nickerson, Hricik, Newell, Formica & Goldfard: CTOT → Non-invasive methods to predict outcome in human transplantation
12 Wilkins (PI), Beavis, Coombs, Ens & Nickerson: BIOMARKERS EQUIPMENT → Program in Systems Biology
13 Wilkins (PI), Beavis, Coombs, Ens & Nickerson: BIOMARKERS SALARY → Biomedical proteomics program: Approaches to the analysis of disease progression and pathogenesis
14 Nickerson (PI): RESEARCH SALARY → Mechanisms of tolerance induction to islet allograft in normal and autoimmune mice
15 Nickerson (PI): LAB EQUIPMENT
16 Nickerson (PI): LAB EQUIPMENT for FLOW
17 Ho, Gibson, Hirt-Minkowski, Nickerson, Rush, Sharma, Atul, Wiebe: URINE BIOMARKERS -> A randomized controlled effectiveness trial of urine CXCL10 chemokine monitoring post-renal transplant

Appendix 3. About the primary investigators

Dr. Peter Nickerson of Winnipeg, MB, has conducted leading and world recognized kidney transplant research. His career began at the University of Manitoba with a Bachelor of Science degree in biochemistry and a Medicine degree (MD). Shortly thereafter, he was awarded a Nephrology Fellowship in 1990 from the University of Manitoba and a Transplant Research Fellowship at Harvard Medical School in 1991.
Dr. Nickerson was trained in basic research in Harvard. He has since practiced translational research, which is taking basic research and applying it to human research. He has used clinical research to evolve health policy and translate it into clinical practice and system design. Therefore, getting patients access to clinical care that they otherwise would not have received.[69]

Since Dr. Nickerson returned to Winnipeg in 1995, he has held numerous positions including clinician, teacher, scientist, researcher, editor, and director. He has been awarded local, national and international awards, fellowships and grants and is recognized internationally for his contribution to the field. He has greater than one hundred peer reviewed scholarly publications in various recognized journals featuring research about subclinical rejection and non-invasive biopsy tools, pre-transplant and post- transplant assessment. He has upwards of two dozen completed reviews and several editorials with accompanied peer reviewed publications.

Dr. Nickerson is an active member of many societies (Canadian Academy of Health Sciences, Canadian Society of Clinical Investigation, Transplantation Society, International Society of Nephrology, American Society of Transplantation, American Society of Histocompatibility and Immunogenetics, American Society of Nephrology, Canadian Society of Transplantation, Royal College of Physicians and Surgeons of Canada and Canadian Medical Association/Manitoba Medical Association) and committees at provincial, national and international levels.[4] He has chaired four conferences, been part of editorial boards and journal review panels and has been a visiting professor and invited guest speaker to well over one hundred conferences and universities internationally.

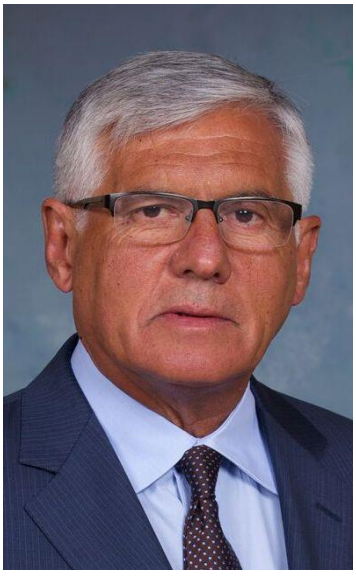
Dr Nickerson currently holds the following positions:

- Vice Dean (Research), Faculty of Health Sciences, University of Manitoba
- Medical Director (Transplant Manitoba), Winnipeg Regional Health Authority
- Medical Advisor (Organ Transplantation), Canadian Blood Services
- Professor of Internal Medicine, College of Medicine, University of Manitoba
- Professor of Immunology, College of Medicine, University of Manitoba

- Medical Director, Platelet Immunology Laboratory, Canadian Blood Services
- Medical Consultant, Transplant Immunology Laboratory, Diagnostic Services Manitoba
- Clinical Nephrologist, Winnipeg Regional Health Authority

His current areas of research focus include:

Transplant Immunology:
Focus on the role of HLA antibody as a principal determinant of both acute and chronic rejection.
Evaluation of clinical and pre-transplant factors that determine clinical outcome in renal transplantation.
Clinical trials to assess mechanisms of renal allograft cellular and antibody mediated rejection.
Non-invasive Diagnostics:
As a founding member of the Manitoba Centre for Proteomics studies are being conducted to identify urine and serum proteins unique to renal allograft rejection. These studies may reveal novel therapeutic targets for drug design, in addition to providing a non-invasive diagnostic tool.
First Nations Susceptibility and Resistance to Infectious Pathogens:
Focus on the role of genetic polymorphisms in promoting host resistance or susceptibility to environmental pathogens.
Health Care System Design:
Using business and engineering tools (Strategy Maps and Balance Scorecards, Process Mapping) to develop novel solutions to enhancing access to transplant and improve outcomes for patients with end-organ failure.
Development of organ allocation policy based on translational research to enhance equitable access to organ transplants.
Standardization of laboratory diagnostics policy in Canada to enhance transplant outcomes.



Dr. David Rush received his MD degree from the National University of Tucumán, Argentina in 1972.[70] From 1974 to 1981, Dr. Rush pursued his post-graduate training in Internal Medicine and Nephrology at the University of Western Ontario in London, Canada. In 1982, he was recruited to the University of Manitoba in Winnipeg. He is currently Professor, Faculty of Health Sciences, University of Manitoba (1996-present), Director, Transplant Manitoba – Adult Kidney Program (2004-present) and Nephrologist, Department of Internal Medicine, College of Medicine, Faculty of Health Sciences, University of Manitoba (1982-present).

Dr. Rush is an active member and fellow of many professional societies including:

- Fellow, Royal College of Physicians & Surgeons of Canada, 1978
- Member, Manitoba Medical Association/Canadian Medical Association, 1984

- Member, Canadian Society of Nephrology, 1993
- Member, Canadian Society of Transplantation (formerly Canadian Transplantation Society), 1990
- Member, American Society of Nephrology, 1993
- Fellow, American Society of Nephrology, 2004
- Member, American Society of Transplant Physicians, 1997
- Member, International Society of Nephrology, 1984
- Member, The Transplantation Society, 2000
- Fellow, American College of Physicians, 2005

Dr. Rush's Research Interests:
Clinical renal transplantation
Transplant pathology: Acute and chronic rejection
Protocol Biopsies: Subclinical cellular and vascular rejection
Non-invasive biomarkers in kidney transplantation: Proteomics and Metabolomics

During the course of his career, Dr. Rush has been an advisor and mentor for postdoctoral residents/fellows and young investigators, and a role model for excellence in patient care. He has also been the recipient of many honors and awards for undergraduate and postgraduate teaching. Several of his many career awards include:

- **2003**: Illustrious Visiting Professor, National University of Tucumán, Argentina
- **2003**: Nadine Jenkins Distinguished Service Award, The Kidney Foundation of Canada, MB Branch
- **2008:** The Canadian Society of Transplantation Lifetime Achievement Award: for individuals who contribute to advancements in the field on a national and international level.
- **2013:** Founder's Award, The Kidney Foundation of Canada, MB Branch
- **2015**: The Kidney Foundation of Canada Medal for Research Excellence: the award highlights the enduring impact and contributions Dr. Rush has made to kidney disease research and the field of transplantation.

The research Dr. Rush has been working on throughout his career is "leading-edge research and has greatly improved outcomes for renal transplant patients giving people the ability to live life to the fullest."[71]

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[9] Ibid

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[11] Accessed from University of Manitoba, Sept 15, 2015, retrieved from: http://pasweb.cc.umanitoba.ca/extapp/ors/pubapp/exp_search.php?ra307_sname=wiebe&ra307_fname=chris&ra307_semph=rsch&ra307_pi=813658120148156

[12] Cross-matching determines the compatibility between a donor and recipient, in organ transplantation. Compatibility is determined through matching of different blood group systems, and/or by directly testing for the presence of antibodies against a sample of donor tissues or blood.

[13] Interview with Dr. Peter Nickerson (August 27, 2015)

[14] Zahoorullah, S. (ED). (2015). A textbook of biotechnology. SM Online Publishers.

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[18] SciVal is a bibliometric software from Elsevier that utilizes publications and citations data to assess the research performance of investigators, groups, institutions, provinces and even at the country level.

[19] Interview with Dr. Peter Nickerson (Aug 27, 2015)

[20] Interview with Dr. Peter Nickerson (Sept 1, 2015)

[21] Interview with Dr. Peter Nickerson (Aug 27, 2015)

[22] Accessed from University of Toronto, Sept 15, 2105, retrieved from: http://www.lmp.utoronto.ca/research/faculty-research-database/tinckam-kathryn

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[24] Accessed from University of Manitoba, Sept 15, 2015, retrieved from: http://pasweb.cc.umanitoba.ca/extapp/ors/pubapp/exp_search.php?ra307_sname=karpinski&ra307_fname=martin&ra307_semph=rsch&ra307_pi=729419853968156

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[26] Dr. Christopher Wiebe's profile, retrieved from: http://www.krescent.ca/page.aspx?pid=2507

[27] Accessed from University of Manitoba, Sept 15, 2015, retrieved from: http://pasweb.cc.umanitoba.ca/extapp/ors/pubapp/exp_search.php?ra307_sname=wiebe&ra307_fname=chris&ra307_semph=rsch&ra307_pi=813658120148156

[28] Interview with Dr. Peter Nickerson (Sept 1, 2015)

[29] See the Methodology in Wiebe et al. (2012). "Evolution and Clinical Pathologic Correlations of De Novo Donor – Specific HLA Antibody Post Kidney Transplant." *American Journal of Transplantation,* 12, 1157-1167. AND Wiebe et al. (2015). "Rates and Determinants of

Progression to Graft Failure in Kidney Allograft Recipients with De Novo Donor- Specific Antibody." *American Journal or Transplantation, xx, 1-10.*

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[35] "Assessment and Management of Immunologic Risk in Transplantation," A Canadian Council for Donation and Transplantation (CCDT) Consensus Forum (2005)

[36] Interview with Dr. Peter Nickerson (Sept 1, 2015) & CBS (2012). Call to Action. Accessed September 8th and retrieved from: https://preview.blood.ca/sites/default/files/otdt-indx-final-c2a.pdf

[37] Karpinski, M. et al. (2001). "Flow cytometric cross-matching in primary renal transplant recipients with a negative anti-human globulin enhanced cytotoxicity crossmatch" J AM Soc Nephrology, 12: 2807-2814.

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[41] Ibid

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[43] CBS "Kidney Paired Donation Program Data Report 2009-2013." Accessed Sept 10, 2015 and retrieved from: http://www.organsandtissues.ca/s/wp-content/uploads/2015/03/Canadian-Blood-Services-KPD-Program-Data-Report-2009-2013.pdf

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