Centre for Innovation Annual Progress Report

2017-2018

June 7, 2018





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Opening letter

7 June 2018

Dear reader,

We are delighted to present the Canadian Blood Services Centre for Innovation progress report for 2017-2018. This past year our team realized many achievements in support of the patients that we serve as part of Canadian Blood Services' mission.

As new leaders of this team, we are grateful to our predecessors, Dr. Dana Devine and Judie Leach Bennett, for their insightful leadership and for bringing to life Justice Krever's vision for a research program and innovation infrastructure that ensures the Canadian blood system is well-informed and supported by evidence. As a result of the work of the Centre for Innovation, Canadian Blood Services, along with the broader healthcare system, is better positioned to address emerging medical and scientific trends, risks, opportunities, and technologies, and to lead change for the benefit of Canadian donors and patients.

This report details achievements that have been made over the past year by our network of scientists, medical experts, research partners, and collaborators. A few key outcomes are highlighted below:

- In August 2017, we provided scientific knowledge and evidence to support Canadian Blood Services' transition from a five-day to a seven-day shelf life for platelets. The Centre optimized the procedure for detecting bacterial contamination of platelet products, and their cocomponents (red blood cells and plasma), to improve safety and reduce discards. The Centre completed simulations to study system-wide changes resulting from extending platelet shelf life to inform donor recruitment and hospital inventory management.
- In October 2017, we provided scientific and medical knowledge to inform the National Advisory Committee (NAC) Blood and Blood Products statement on cytomegalovirus (CMV)-safe products, and supported Canadian Blood Services' transition to providing primarily CMV-safe products.
- We developed a simulation model to support the optimization of Canadian Blood Services' Rare Blood Program, which was relaunched in May 2018.
- We provided product and process development expertise to support Canadian Blood Services' 2018 implementation of new equipment, and to optimize new manufacturing processes to produce red blood cells, plasma, and platelet products.
- Over the past year, we published paradigm-altering studies in the areas of intravenous immunoglobulins (IVIg and RhIg), and the immune disorders they treat. Our researchers uncovered a previously unknown mechanism of miscarriage in fetal and neonatal alloimmune thrombocytopenia, which suggests a new therapeutic target. We have shed light on the mechanisms by which red blood cell antibodies can suppress the immune system that may inform better treatments for immune disorders, such as hemolytic disease of the fetus and newborn. Our research teams have also identified several potential IVIg replacement drugs that may reduce the burden on IVIg supply and improve patient outcomes.



- We created valuable information for health care providers to help them choose between two common treatments for immune thrombocytopenia, ensuring appropriate treatment for patients, and potentially reducing the need for IVIg.
- In partnership with Héma-Québec, we initiated funding for 11 research projects investigating blood and plasma donors' eligibility criteria and screening process with the goal to evolve the current eligibility criteria for men who have sex with men (MSM). We also published a review of MSM deferral policies worldwide and the current state of science in this area.

Program outputs for the year include:

- Our research network published 332 peer-reviewed publications and delivered over 300 poster and oral presentations at local, national, and international conferences.
- We shared 30 technical reports within Canadian Blood Services and with partners to support decision-making.
- Over 70 major knowledge mobilization and educational events were organized or supported.
- Our team formalized 43 agreements with partners.

This year we received a successful program evaluation from Health Canada. The evaluation, which engaged our stakeholders and analyzed our performance over five years, noted the continued need for, and relevance of, our program. It acknowledged our progress toward identified outcomes, and praised its cost efficient and effective operation. Following this successful evaluation, the team submitted a proposal to Health Canada and secured continued funding for a new five-year cycle. This funding will complement the funding received from provincial and territorial ministries of health, and partners.

We remain deeply grateful for the ongoing support we receive from our funders, and our partners and colleagues across the transfusion and transplantation medicine communities. As we conclude the previous funding cycle and look ahead to the next five years, it is with renewed vigor to continue innovating and educating to support Canadian Blood Services in its vigilant stewardship of the safety, quality, and efficiency of the products and services it delivers for the benefit of Canadians.

Sincerely,



Dr. Isra Levy Vice President, Medical Affairs and Innovation Canadian Blood Services



Dr. Chantale Pambrun Director, Centre for Innovation Canadian Blood Services



Executive summary

The 2017-2018 Canadian Blood Services Centre for Innovation annual progress report provides an update on the activities and achievements of the Centre for Innovation over the past fiscal year (April 2017 – March 2018). In this report, we provide an overview of the Centre for Innovation, which facilitates the creation, translation and application of new knowledge to support a safe, effective, and responsive system of blood and related biological products for Canada.

Complementing the achievements highlighted in the opening letter, we present several stories that illustrate the impact of the Centre's programs. In these stories, you will learn about: advances in the areas of donor and recipient health and safety; the large body of work conducted by the Centre to support last year's extension of platelet product storage time while ensuring continued safety; developments in understanding red blood cell biology to improve transfusion products; discovery research into immune and inflammatory diseases for which blood products are treatment options; and work to improve Canadian Blood Services' products and processes; research progress in the area of organ and tissue donation and transplantation; and the Centre's collaborative training and education programs engaging researchers and health care professionals and increasing knowledge in transfusion.

Through these stories, the interdisciplinary and collaborative nature of the Centre is evident. You will find contributions from the Centre's scientists, development staff, medical directors and consultants, project managers, as well as funding recipients, collaborators, and partners. Through the Centre for Innovation, the knowledge and expertise of this network, located across Canada, serves the Canadian blood system and ensures its continued safety, quality, and sufficiency.

The report concludes with appendices which comprehensively list the Centre's outputs for 2017-2018, including research projects funded through our programs, and the diverse publications resulting from these projects.



Overview of the Centre for Innovation

Integrated within Canadian Blood Services, the Centre for Innovation is a unique and essential bridge that facilitates the creation of new knowledge and its translation into practical outcomes for the blood service and stakeholders working to maintain a safe, effective, and responsive system for blood and blood products for Canadian patients. The Centre focuses on making a measurable impact across four program areas: Research; Product and Process Development; Knowledge Mobilization and Education; and Policy Research and Leading Practices (Figure 1).

Over the last five years, the Centre has delivered value to the system as exemplified by the program performance metrics highlighted below (Table 1), and by the key achievements of the last year described throughout this report.



Fig. 1: The Centre for Innovation's four program	۱
areas.	

		April 2013 – March 2018
	Knowledge products (see Appendix II)	1713
Outputs	Knowledge exchange mechanisms (e.g. symposiums, presentations)	1890
	Awards and grants (see Appendix I)	92-160 per year
	Partnerships/collaborative working arrangements	183
Immediate Outcome	Key stakeholders in the transfusion and transplantation community are knowledgeable about the evidence/knowledge generated by Centre for Innovation projects	Event attendees report knowledge gain (>85%)
		100% of Canadian Blood Services staff researchers with an H-index that meets the Canadian Science Standard of 10.6
		89 highly qualified people completing training
Intermediate Outcome	Key stakeholders in the transfusion and	59 new or updated policies, procedures, practices, products, and standards
	transplantation community apply knowledge created by Centre for Innovation projects	Stakeholders report perception of knowledge created to be of high quality (98%) and useful (96%)

Table 1: Centre for Innovation performance measurement framework results, April 2013 – March 2018



Research and development

The Centre for Innovation leads the primary coordinated research and development effort in Canada that addresses blood safety — it supports, connects and complements research efforts that are conducted at an organizational level at local Canadian academic and hospital centres.

Canadian Blood Services' mission is the guiding principle by which the Centre sets its research and development priority areas. In consultation with internal and external stakeholders, the Centre's resources are allocated into areas where they can be used to drive innovation and improve the blood system.

Canadian Blood Services operates Canada's blood supply in a manner that gains the trust, commitment and confidence of all Canadians by providing a safe, secure, cost-effective, affordable and accessible supply of quality blood, blood products and their alternatives.

Canadian Blood Services' mission (Read more)

Supporting discovery research

One unique element of the Centre's research strategy is the suite of competitive funding programs that are designed to facilitate discovery research in strategic priorities that include:

- Promoting appropriate blood product utilization;
- Ensuring an adequate blood product supply;
- Minimizing the adverse effects of blood product transfusion;
- Optimizing blood product quality;
- Replacing or improving blood products through new therapies or technologies.

Currently, <u>six unique programs</u> support research projects over a period of one to three years based on a rigorous peer-review process that promotes excellence, and ensures relevance. In 2017-2018, 54 research projects received funding through these programs, including 23 new projects (Appendix I). Of note are the new financial commitments awarded to support clinical research through the McMaster Centre for Transfusion Research and the University of Toronto Quality in Utilization, Education and Safety in Transfusion research programs.

Complementing the competitive funding programs, the Centre supports eight research staff scientists. These staff scientists have a range of expertise and knowledge in support of key strategic areas, hold university faculty appointments at institutions across Canada, and conduct their own research projects.

Together, these programs support a multidisciplinary network of more than 70 researchers based in British Columbia, Alberta, Ontario, Quebec, and Nova Scotia. The impact is seen in their significant contribution to the nearly 400 publications published in 2017-2018 (Appendix II) as well as the achievements described in this report.

"Much of our research is 'translational'. We are engaged in work that drives either practice change, or policy development that results in practice change, or that improves how the blood system operates. We do this always with patients in mind."

Dana Devine, Chief Scientist, Canadian Blood Services, in RED blog (<u>Read more</u>)



Responding to emerging research needs

Leveraging its expertise in administration of competitive grants and programs, the Centre responded to emerging needs for the generation of adequate evidence-based research for alternative screening approaches for blood and plasma donors. Following the Health Minister's directive to evolve the deferral policy for men who have sex with men (MSM), the Centre with Héma-Québec launched the MSM Research Grant Program and, with funding from Health Canada, initiated 11 research projects in fall 2017. A second competition was launched in January 2018 with additional projects expected to begin in fall 2018.

Supporting product and process development

As well as supporting discovery research, the Centre leads product and process development in support of Canadian Blood Services supply chain. Priorities include:

- Deepening the understanding of our products and the processes used to manufacture them;
- Developing new or next generation products and the processes used to manufacture them;
- Improving current generation products and the processes used to manufacture them.

The Centre's Product and Process Development group includes a development team of 21 scientific, engineering, laboratory, and project management professionals, as well as dedicated development facilities in Vancouver and Ottawa. The development facilities include a smaller version of the regulated environment of supply chain where new products and processes can be tested and optimized before introduction by the organization. In addition, this group has strong partnerships with industry, with whom they work to develop and/or optimize processes and products. The Centre also runs programs for the provision of biological products (blood, blood products, cord blood) and data to researchers at Canadian Blood Services and across Canada.

A hub-and-spoke model – building a better brain trust

Our discovery research and development research network, built around a distributed, hub-and-spoke model, connects highly accomplished Canadian researchers in the fields of transfusion and transplantation medicine and science. and integrates experts from complementary disciplines (Figure 2). The distributed research network allows Canadian Blood Services to tap into a wealth of research areas, expertise, opportunities and individual scientists who are affiliated in various ways with Canadian Blood Services. This approach creates a rich fabric of research areas that facilitate impactful, targeted research along the entire life-to-life continuum from donors to patients (Figure 3).



Fig. 2: The Centre for Innovation's hub-andspoke research network model.



Education and knowledge mobilization

The Centre has a Knowledge Mobilization and Education Program that coordinates Centrewide knowledge translation activities. Facilitated by dedicated knowledge broker staff, as well as support from the Canadian Blood Services communications group, this program has developed a knowledge mobilization toolbox to increase dissemination and awareness of the knowledge developed by the Centre.

The Centre also develops educational and learning opportunities for researchers and health care professionals to further disseminate knowledge to impact research and clinical practice. Supported by strong partnerships with engaged health care leaders and organizations, the Centre provides educational funding programs, resources, and organizes and supports educational events across Canada. The impact of the educational and training events is monitored through participants' surveys to evaluate knowledge gained and application of knowledge to practice.

Policy research and leading practices

One of the Centre's primary activities regarding policy research and leading practices is the continued support of the International Collaboration for Transfusion Medicine Guidelines (ICTMG), which was established in 2011. The ICTMG follows well-accepted methodologies to establish evidence-based transfusion medicine guidelines to optimize transfusion care, increase the credibility of guideline development for transfusion medicine, and enable more timely and cost-effective creation of transfusion medicine guidelines.

Guidelines are disseminated through publication and other methods, including podcasts and treatment algorithms. One systematic review, "Antenatal management in fetal and fetal/neonatal alloimmune thrombocytopenia", was published in 2017. This collaborative effort brings together experts from eight countries with administrative support from the Centre.

The selected stories that follow highlight the Centre's key achievements and publications over the past year. They demonstrate the Centre's commitment to research along the entire life-tolife continuum, demonstrate progress across the Centre's four focus areas, and exemplify the value and impact of our programs. The names of the Canadian Blood Services staff, including Centre for Innovation investigators, medical experts and epidemiologists, and the names of organizations and investigators receiving funding from the Centre, are bolded throughout the report.



Fig. 3: The Centre for Innovation conducts research along the entire "life-to-life" continuum.



Balancing safety and sufficiency of the blood supply

Blood donors provide the gift of life. A dedicated group of repeat donors account for close to 90 per cent of the donations received by Canadian Blood Services. Our donor recruitment and selection must balance sufficiency of supply with donor and recipient health and safety. Donor health questions, inter-donation interval and hemoglobin testing help to protect the health of donors. Donor deferrals, questionnaires, testing of collected blood, and timely surveillance help protect recipients against adverse reactions and transfusion transmissible diseases.

Donor demographics and health

An aging population, and consequently an older average donor base, presents challenges to both supply and demand. To understand the composition of the donor base and ensure future adequacy of the blood supply, an international Biomedical Excellence for Safer Transfusion (BEST) collaborative study compared donor and general population demographics over time, between 2001 and 2011.¹

Led by Mindy Goldman and Sheila O'Brien, this study surveyed 17 blood centres in 12 countries. In all countries that participated, the general population is aging. Donor demographics in some jurisdictions suggested a reliance upon younger donors, who contribute disproportionately to the donor base. In North America, this reliance was most striking in the United States, and less so in Canada, where data showed the median age of donors is 43 years, while the median age of the general population is 46 years. Donor demographics have implications for donor health; teenage donors have lower iron stores than adults, so reliance on younger donors could disproportionately impact donor iron stores. Further research is needed to understand strategies to encourage donation across all age groups.

The previous study also showed that the oldest cohort of donors is contributing an increasing proportion of the overall blood supply. Canadian Blood Services removed the upper age limit for regular repeat donors in 2004 and recently removed the upper age limit for first time donors, a change also made by several other blood operators in recent years. **Goldman** and **O'Brien** reviewed data on older donors, and concluded that donation is safe in older individuals who continue to donate past their 71st birthday.² In Canada, approximately 1.5 per cent of whole blood donations are made by donors aged 71 or older. There are a greater number of healthy older individuals than ever before, and the evidence suggests that they can make a significant contribution to the blood supply.

While maintaining the safety of the blood supply, Canadian Blood Services aims to make blood donation as minimally restrictive as possible. Deferral policies are based on evidence and must take into consideration scientific and technology advances, as well as ethical and moral concerns. In early 2017, an international meeting hosted by Canadian Blood Services, Héma-Québec, and Health Canada reviewed deferral policies for men who have sex with men (MSM) worldwide, and the current state of science. The main goal of the meeting was to kick-start thinking about research priorities in this area that could be addressed under a new MSM Research Grant Program.

Goldman, O'Brien, and **Dana Devine**, together with Andrew Shih, summarized the past, present, and future of MSM criteria, with an emphasis on research priorities elaborated at the Toronto meeting intended to guide the research community.³ The priorities identify multiple ways to address the interface between



blood safety and social justice, which will guide researchers, including those funded under the MSM Research Grant Program launched last year.



Read the ResearchUnit: <u>Developing</u> more inclusive deferral policies for blood and plasma donors.

Safety of the blood supply

Transfusion transmissible diseases

High quality and timely surveillance is key to the safety of the blood supply. This includes monitoring of transmissible disease markers that the blood is tested for, investigating reports of possible transfusion transmission, and horizon-scanning for pathogens that might present a risk now or in the future.⁴ In the most recent Annual Surveillance Report (2016), **O'Brien** described very low transmissible disease rates detected. Residual risk estimates of a potentially infectious donation remain very low at 1 in 21.4 million donations for HIV, 1 in 12.6 million donations for HBV.

Emerging threats, including babesiosis and Chikungunya virus continue to be monitored. The mosquito-borne Zika virus remains a risk for travellers to affected areas. The risk and travel deferrals subsequently put in place for blood donors were well described in last year's annual report. This year, the impact and risk of Zika virus on cord blood donations and adult stem cell donations to the OneMatch Stem Cell and Marrow Registry was assessed.⁵ Conducted by David Allan, and involving Margaret Fearon and Heidi Elmoazzen, this study demonstrated that impact of screening the (via donor questionnaire) for Zika virus exposure risk was minor, for both cord blood donations and unrelated adult stem cell donations. Only rarely did transplant centres cancel donor workups due to potential Zika virus exposure. The cord blood bank identified and discarded 25 (out of 875) cord blood units from women who had at least one risk factor for Zika. Continued surveillance and vigilance for emerging threats is necessary to maintain the safety of the blood supply.

Pathogen inactivation technologies

Technologies such as pathogen inactivation could further improve the safety profile of blood products by providing broad-spectrum, nonspecific inactivation of pathogens. Currently two technologies are commercially available (INTERCEPT Blood System[™] by Cerus and Mirasol[®] Pathogen Reduction Technology by TerumoBCT) and one is in clinical trials (THERAFLEX UV by Macopharma). INTERCEPT was recently licensed by Health Canada (April 2018), providing new opportunities for blood operators in Canada. Balancing the potential safety benefits of pathogen inactivated platelet and plasma products, against potential impacts on the quality and clinical effectiveness of these products remains an active area of research, with many unanswered guestions that warrant further investigation.^{6,7}

Sandra Ramirez-Arcos investigated the efficiency of riboflavin and ultraviolet light (riboflavin/UV) pathogen inactivation against high levels of biofilm-derived S. epidermidis in platelet products.⁸ In line with previous reports, this study showed that pathogen inactivation reduced but did not completely eliminate S. epidermidis when present in high concentrations, and that the effectiveness of the inactivation pathogen appeared to be dependent on the bacterial strain. However, it is worth noting that the bacterial concentrations used in the study were high enough that they would be unlikely to be found in a unit being pathogen inactivated, unless pathogen inactivation treatment was delayed, and the unit was contaminated with a fast-growing bacterium.



A separate study led by **Devine** looking at the timing of riboflavin/UV pathogen inactivation and its impact on platelet quality found that delaying pathogen inactivation until later in the platelet storage period lessened the negative impact on platelet quality.⁹ This approach may allow blood operators to modify testing and pathogen inactivation regimes to maximise the benefit of pathogen inactivation while minimizing impact to product quality, but efficacy against high levels of bacteria would need to be considered.

Understanding TRALI

Transfusion-related acute lung injury (TRALI) is a serious adverse reaction. It is the leading cause of transfusion-related fatalities but its pathogenesis is poorly understood and no specific therapy is available. John Semple conducted a critical analysis of recent preclinical insights into TRALI pathogenesis.¹⁰ Focusing on potential therapeutic approaches to combat this devastating complication of transfusion, his review identified some approaches that warrant further exploration in the laboratory and the clinic. The most promising of these approaches target the transfusion recipient, and include interleukin-10 therapy, down-modulating C-reactive protein levels, targeting reactive oxygen species, or blocking the interleukin-8 receptors.

Understanding and optimizing blood product utilization

While a sufficient and appropriate donor base is critical, appropriate utilization lies at the other end of the life-to-life continuum but is equally central to maintain a sufficient supply, reduce health care costs and protect the health of transfusion and transplantation recipients. Canadian Blood Services' medical officer,

Michelle Zeller of the McMaster Centre for Transfusion Research, was the lead author on two international studies to understand utilization of blood products.^{11, 12} One study looked at red blood cell utilization practices at hospitals around the world, with a focus on use of O-negative blood.¹¹ The supply of O-negative red blood cells is especially important because these "universal donor" products can be safely transfused to patients of any ABO and Rh blood type, making Type O red blood cells critical for emergency transfusions when the recipient's blood type is unknown, or if there is an insufficient supply of ABO-matched blood products available for a patient in need. This, and several other studies, showed that overall red blood cell use is decreasing, but the proportion of O-negative products used is increasing, particularly for non-Type O recipients.^{13, 14} A large percentage of O-negative blood products are used for patients who are not O-negative.

While Type O is the universal donor for red blood cells, Type AB is the universal donor for plasma, and shortages can occur if there is increased demand for this product. In a study exploring AB plasma utilization in hospitals around the world, transfusion policies, and practices, patterns were found to be variable across sites, but overall, AB plasma units are frequently transfused to non-AB recipients.¹² Indeed only 27 per cent of AB plasma units were transfused to AB patients. Both studies provide data for benchmarking and determining best practices to optimize Type O-negative red blood cell and AB plasma utilization. Hospitals with higher use of these precious resources might be able to alter their policies to decrease non-essential use.



Read the RED blog post: International researchers collaborate to understand trends in blood product use.



Blood donation and blood transfusion are very safe in Canada. Transmissible blood-borne infections are very rare in Canadian Blood Services donations, and surveillance, testing, horizon-scanning and other measures help keep patients safe. Careful utilization of blood products to ensure they are used optimally and efficiently helps ensure sustainability. Attention to both the extremes of the life-to-life spectrum is required for the continued safety and sufficiency of the blood supply.

Applying an old tool to a new process

Philip Berardi, Gwen Clarke and Goldman led a study investigating nucleic acid extraction from buccal tissue to predict red blood cell phenotype in donors.¹⁵ Leveraging over 10 years of expertise using buccal swabs for DNA extraction and genotyping participants in the OneMatch Stem Cell and Marrow Registry, this non-invasive, costeffective, and stable alternative to venipuncture was explored. The results, though preliminary, are promising, and support the use of buccal swabs for predicting red blood cell phenotypes with high accuracy. The Rare Blood Program launching in 2018 at Canadian Blood Services will use buccal swabs to genotype prospective rare donors identified through family studies. The buccal swab process allows for screening of donors that do not have access to a collection site.



Supporting system change: The platelet story

Platelets are small cell fragments circulating in our blood that help stop bleeding. To maintain this biological function, blood operators store platelet products at room temperature with gentle agitation in gas permeable bags. Unfortunately, these conditions are favourable to bacterial growth making bacterial contamination of platelets the leading infectious risk from blood transfusion. The limited shelf life of platelet products is also a challenge in managing their inventory.

Safely extending the shelf life of platelets

Platelet contamination and adverse reactions

In 2017, Canadian Blood Services extended its platelet products shelf life from five to seven days.¹⁶ This change was informed by research conducted at the Centre.

At Canadian Blood Services, safeguards against contamination of platelet products include disinfecting the donor's skin before venipuncture, discarding the first portion of the blood draw, performing sterility testing on all platelet products, and visual inspection of the platelet products. Summarizing six years of experience of sterility testing at Canadian Blood Services (2010 - 2016), Ramirez-Arcos and Goldman reported similar true positive rates in platelet products pooled and apheresis (approximately 1/10,000).¹⁷ True positive results represent products for which the same bacterium is isolated during the initial and confirmatory sterility test. Products with positive sterility testing are immediately removed from inventory or recalled from hospitals if already distributed. During the same period, six transfusion adverse reactions associated with bacterial contamination of platelet products were reported by hospitals, giving a rate of reaction of 1 per 100,000, similar to rates reported in other jurisdictions. These findings suggest that, while platelet products are safe, a residual risk remains that merits further intervention.

Ramirez-Arcos and her team led the development of a new procedure designed to increase the sensitivity of bacterial detection in platelet products. Essentially, the new procedure involves delaying sampling for bacterial testing from 24 hours to 36 hours after collection to allow more time for bacteria to grow if present in a collection, and increasing the sampling volume to allow for bacterial testing in both aerobic and anaerobic conditions to improve our ability to detect different bacterial strains.¹⁸ In addition, the new process includes a six-hour post-sampling guarantine of platelet products during which they are not issued to hospitals, to allow detection of fast growing or high levels of bacteria, and remove these products before release.^{19, 20} Testing to confirm the results of initial positive bacterial screens, previously conducted by a third party, was brought in-house in March 2018. This is an important change. It permits an algorithm to allow release of co-components (four red blood cell units and three plasma units for every pooled platelet product) from the same donor if the initial result was false positive. If the results are true positive, and the platelet unit has been transfused, it allows the results of the microbial testing to be relayed to the recipient's physician. The physician can use this information to make informed decisions about the recipient's monitoring, treatment, and follow-up.



Devine and her team investigated whether an extended storage period would impact platelet quality.²¹ They assessed platelet concentration, volume, metabolism, and markers of platelet activation and responsiveness in platelet units stored for five or seven days. All changes observed were small and consistent with the known effects of storage. They concluded that platelet products stored for seven days continued to fulfil quality control requirements, and thus extended storage should have no impact on their clinical effectiveness.



Read the article: <u>Platelet product</u> <u>quality remains high after seven</u> days of storage.

Predicting outcomes of system-wide change

Using a network simulation model, John Blake examined the potential impacts of the seven-day shelf life and the extended bacterial testing on the platelet inventory, and found that, compared to a five-day shelf life, extending to seven days should lead to an approximately 35 per cent reduction in product discards due to outdate, without increasing shortages.²² The simulation also suggested that the lowest rates of outdating were seen when the hospital inventory was set at 1.1 days on hand and Canadian Blood Services inventory was set at 2 days on hand. Location was also a key factor, with the simulation indicating that wastage decreased more rapidly at hospitals than at Canadian Blood Services' sites, and smaller Canadian Blood Services sites had higher outdating rates that benefited less from extending the shelf life than larger sites. The detailed information from the simulations can help Canadian Blood Services manage donor recruitment to maintain a consistent platelet supply while accounting for the increased bacterial testing time. Data from this study can also guide hospital inventory policies.^{23, 24}

Monitoring the impact of the change

Since introduction of the new sterility testing method, extended shelf life, and hospital adjustments to inventory levels and redistribution practices, data from hospitals and Canadian Blood Services indicates a system-wide reduction in the number of platelet units discarded due to outdate of 39.6 per cent, similar to the reduction anticipated by Blake's simulation. The implementation of 7-day platelets impacted both production and collection scheduling, and optimization work continues. Importantly, there have been no shortages related to the change, and the rate of confirmed positives for bacterial testing has increased — suggesting that the new testing algorithm is more sensitive and captures more contaminated platelets at screening. The translation of evidence from multiple sources supported this important change, which has led to an improvement in health care delivery, safety, and efficiency (reducing waste).



Read the **ResearchUnit**: <u>A model for</u> <u>change</u>: predicting the impact of <u>system-wide improvements</u>.

Investigating biofilm formation

Ramirez-Arcos also made progress understanding the platelet safety implications of bacterial biofilms (bacterial aggregates, often found adhered to surfaces). Biofilms can be a virulence factor, and biofilm-producing bacteria can be more resilient to disinfection or detection efforts. For example, S. epidermidis, part of normal human skin flora and the predominant contaminant of platelet products, can form biofilms in human skin. These may not be destroyed by skin disinfection, could avoid detection by bacterial screening systems, and may not respond to pathogen inactivation. The team has shown that S. epidermidis adopts a



biofilm-forming phenotype in platelet products, regardless of its genetic background or origin. Positive selection of *S. epidermidis* biofilm-producers during blood donation and platelet product manufacturing was not observed.²⁵ The team has also investigated the ability of lytic bacteriophages to augment antibiotic activity against *S. aureus* biofilms in a proof-of-principle study that could guide future investigations into clinically effective ways to target infections.²⁶

Collaborating with **William Sheffield**, **Ramirez-Arcos** has shown that bacterial attachment inside platelet bags is enhanced by plasma residues independent of the type of bags.²⁷⁻²⁹ Adhesion of bacteria to storage bags has a negative impact on platelet safety, even with very low bacteria levels, as it decreases detection during routine screening. As platelets are pooled and stored in plasma, finding ways to reduce plasma residues attaching to the inside of storage bags could enhance the safety of platelet products by reducing bacterial attachment.

At the **Centre for Blood Research**, a team from the laboratory of **Don Brooks** and **Jayachandran Kizhakkedathu** has developed new surfaces to prevent bacteria/biofilms from adhering to platelet bags.³⁰ Based on dopamine chemistry, these surfaces are antifouling and bactericidal and aim to improve the biocompatibility of PVC bags used to store platelet products.

Platelets in the clinic

Research led by **Donald Arnold** at **McMaster Centre for Transfusion Research**, and including **Kathryn Webert**, looked at the effectiveness of platelets transfusions in critically ill patients with low platelet counts.³² Although commonly used in this patient population, whether platelet transfusions are associated with a reduction in the risk of major bleeding is unknown. This study

Establishing a repository of bacterial strains

Ramirez-Arcos is involved in an international effort led by the World Health Organization (WHO) Expert Committee on Biological Standardisation to establish a repository of standardized bacterial strains, a valuable resource necessary to validate bacterial detection systems and pathogen reduction technologies.³¹

showed no difference in the rates of major bleeding for patients who did and did not receive platelet transfusions and suggests clinical trials are needed to better investigate the benefit versus harm of platelet transfusions for this highrisk population.

Webert and **Alan Tinmouth** were involved in an initiative by the BEST collaborative to assess a common bleeding assessment tool (BAT) to document bleeding during platelet transfusion trials in hematological malignancy. This initiative saw a high concordance across multiple sites for the consensus BAT which may ensure consistent measurement of this clinically important outcome.³³

These recent research and development efforts to optimize platelet safety and enhance clinical outcomes exemplify the integrated, multidisciplinary approach that the Centre for Innovation is known for. This is an approach that provides a solid, context-driven evidence base and facilitates system-wide improvements. From optimal collection and product inventory, to pathogen testing, product manufacturing, new technology assessment, clinical practice and clinical outcome assessment, these efforts encompass the full life-to-life spectrum, and demonstrate the value and impact of Canadian Blood Service's unique research model.



Red blood cells: Still vital after all these years

Red blood cells are the most common blood product Canadian Blood Services distributes, approximately 700,000 units per year. Stored for up to 42 days in the refrigerator, red blood cells are transfused to treat anemia and blood loss to improve oxygen delivery to tissues.

Investigating patient outcomes

How old is too old?

As noted at the Food and Drug Administration's public workshop on new red blood cell product regulatory science,³⁴ after 20 years with little change in how red blood cells were evaluated for transfusion, we have seen many fundamental questions raised in recent years, including when red blood cells should be transfused, how many should be transfused, and whether the storage age of red blood cells impacts patient outcomes. These questions probe how we can best use red blood cells for transfusion, and when the balance tips between benefit and harm for recipients.

Some answers are emerging, following a barrage of investigations aimed at providing a solid evidence-base. Randomized control trials have settled the question of whether "old" red blood cells are detrimental. These findings were further confirmed by a recent secondary analysis of the landmark INforming Fresh versus Old Red Cell Management (INFORM) trial, which was led by colleagues from the McMaster Centre for Transfusion Research, and included Canadian Blood Services medical director, Webert. This study concluded that "older" blood (stored for longer than 35 days) does not impact patient outcomes, measured by in-hospital mortality, and that current storage limits for these products are reasonable.35

While the question of "old" red cells seemed to be settled, those studies prompted many more fundamental questions that have become

Informing health care professionals about advances in red cell research

The 15th annual Canadian Blood Services International Symposium took place in September 2017. Host to 129 delegates, this CME-accredited event featured an international line up of speakers who presented on vital aspects of red blood cells, from blood banking, laboratory medicine and clinical perspectives.

emerging areas of research. The impact of donor characteristics, such as age or sex, and red cell processing methods on patient outcomes continue to be studied by **McMaster Centre for Transfusion Research** and **The University of Ottawa Centre for Transfusion Research**, and are enabled by provision of Canadian Blood Services manufacturing and donor demographic data. **Shuoyan Ning**, Canadian Blood Services Transfusion Medicine residency fellow, along with **Nancy Heddle** from **McMaster Centre for Transfusion Research** and **Jason Acker** from the Centre for Innovation, summarized nicely the pre-clinical and clinical studies evaluating these associations.³⁶

Clinical evidence to reduce transfusion

Avoiding red cell transfusions altogether can avoid the adverse reactions associated with transfusion while protecting a scarce resource and reducing costs. Clinical studies are ongoing to provide the evidence to ensure transfusion



avoidance is safe for patients. Nadine Shehata participated and Dean Fergusson in a noninferiority multinational randomized controlled trial, the TRICS III, to assess the transfusion requirements in cardiac surgery.^{37, 38} The study found a restrictive red cell transfusion strategy to be non-inferior to a liberal strategy for certain clinical conditions.³⁹ In obstetric patients, red cell transfusions carry the risk of alloimmunization. Shehata, Tinmouth and Fergusson completed a retrospective study using administrative data to identify trends and risk factors of red cell transfusion in this patient population which can be used to improved patient blood management and transfusion practice for patients at highest risk of needing a transfusion.40

Selecting the optimum blood donor

Donor iron health

Ensuring donor health is of paramount importance to blood operators, not only to ensure public health but also to maintain the security of the blood supply. In 2016, Canadian Blood Services, with evidence provided through research, implemented new donor deferral policies to safeguard our donors from iron deficiency. Iron deficiency is common in whole blood donors, particularly female donors, frequent donors, and donors failing their hemoglobin screening test. Fatigue is the most commonly reported symptom of iron deficiency, but overall there is evidence that it impairs quality of life.

Safeguards introduced to help prevent iron deficiency in blood donors included increasing the waiting time between whole blood donations for females from 56 days to 84 days, and increasing the minimum hemoglobin for males from 125 g/L to 130 g/L. These measures reduced the low hemoglobin deferral rate overall, as deferrals in females decreased substantially from 13.9 per cent to 9.5 per cent of donation attempts, while the increases in

deferrals in males was smaller, from 1.4 per cent to 2.3 per cent.

The Centre developed knowledge mobilization tools to inform donors and physicians about the impact of blood donation on iron storage and measures that can be taken to prevent iron deficiency. Canadian Blood Services' Donor Relations group leveraged these tools to inform the donor community via email. This information and resources appear to be desired by the community as two blog posts (developed in 2016) ranked among the most read of all blog posts during in 2017-18 (3,400 and 2,020 views, respectively) and the ResearchUnit on this topic was the most viewed article (1,100 views). Furthermore, the publication on Canadian Blood Services' Professional Education website targeted specifically at health care professionals received over 1,200 views.

"When individuals have iron deficiency (or iron deficiency anemia), they may experience decreased exercise tolerance, increased shortness of breath with activity," explains Dr. Pambrun, "possibly can also have a decrease in concentration or changes in mood."

Excerpt from a knowledge dissemination tool kit developed to inform the donor community and health care professionals about donor iron health.

Donor variation

Hemolysis, the rupture of red blood cell membranes, is an important quality marker when manufacturing red cell products for transfusion. There is a considerable donor-todonor variation in hemolysis levels. Understanding the molecular mechanisms behind this inter-donor variation may shed light on how to improve donor screening and ultimately enhance transfusion products.



Devine's laboratory identified a group of 10 healthy volunteer donors who repeatedly exhibit high hemolysis levels when tested at product outdate and compared these donors to age- and sex-matched controls.⁴¹ The research team identified notable differences at the red blood cell membrane and a reduction in proteins involved in oxidative response pathways in the donors with high hemolysis. Studies are ongoing to understand these markers and determine their potential use to develop a donor screening tool.

Blood type, characterized by the antigens expressed on red blood cells, is unique to each donor. Each red cell product needs to be carefully matched to the patient. For patients with rare blood types, finding a match can be difficult. For these patients, Canadian Blood Services, like many other blood operators, operates a rare blood program that includes a process to screen donors for rare phenotypes, a registry for rare blood donors, and a small inventory of frozen rare blood units. Over the last year, the organization has leaned on the expertise of our research and medical group to redefine this small yet crucial service provided to Blake developed computational patients. models to determine how rare blood must be before a frozen inventory is necessary, what donor screening rate is necessary to support a rare blood program and performed a simulation study to evaluate the impact of limits for frozen blood on patient access.⁴²

Irradiating red blood cell products

Irradiation of red blood cell products is used to prevent transfusion-associated graft-vs-host disease (TA-GvHD) in vulnerable populations. Irradiation works by inflicting irreparable DNA damage to T-lymphocytes present in the products in order to prevent their replication. However, irradiation accelerates the progressive red blood cell storage lesion, and therefore storage time after irradiation is limited.



Jason Acker received the 2017 Canadian Society for Transfusion Medicine Ortho Award <u>Read more</u>

A research collaboration between Canadian Blood Services scientists Sheffield and Devine examined gamma irradiation and subsequent storage in the additive solution SAG-M.⁴³ Irradiation late in storage correlated with unacceptably high levels of hemolysis, promoted red blood cell microvesiculation, stress-sensitive phospholipid scrambling, and increased vulnerability to eryptosis. However, no harmful changes in irradiated red blood cell quality were seen earlier than 21 days after irradiation, supporting current regulations for red blood cell irradiation timing and storage limits.

Similarly, **Acker** was involved in a BEST collaborative study looking at the influence of timing of gamma irradiation and blood donor sex on red blood cell in vitro quality. This study provided support for the current Council of Europe guidelines on the time limitations for the irradiation of red blood cells, and showed an impact on manufacturing method and donor sex on hemolysis and potassium levels.⁴⁴

Neonates represent a vulnerable population who need transfusion of irradiated red blood cells products. **Chantale Pambrun** and **Devine** optimized a process to prepare aliquots of gamma-irradiated red blood cell units for neonatal transfusions.⁴⁵ They determined that supernatant reduction by centrifugation effectively reduces potential harmful substances (potassium, mannitol and red blood cell microvesicles) in aliquots stored up to 21 days, producing safer transfusion.



New ways to assess red cell quality

There are many laboratory measures to assess red blood cell quality, particularly in the context of the cell storage lesion. The membrane is one of the most critical cellular components affected by storage, and Acker's group examined membrane water permeability - an essential cell membrane function - as an indicator of red cell quality.⁴⁶ Measuring osmotic blood permeability, the group demonstrated that water parameters are a predictor of membrane damage and loss of membrane integrity in stored red blood cells. In a separate study, they showed that membrane water permeability differed depending on the manufacturing method used to produce the red blood cells.⁴⁷ In this study they also examined donor factors such as sex and age, but found no effect on membrane water permeability.

Devine, with Michael Blades and Robin Turner from the University of British Columbia, explored

a non-conventional (in blood banking) analytical technique, Raman spectroscopy, to assess hemoglobin oxygenation in red blood cell concentrates.⁴⁸ Their results indicated comparability to traditional morphological assessment, a subjective microscopy-based technique which is often used to assess red blood cell quality, and suggest that Raman spectroscopy has promise as a rapid and objective measure of red blood cell quality.

Hongshen Ma from the University of British Columbia, in a collaboration with **Mark Scott**, used a microfluidic devise to analyze red blood cell deformability.⁴⁹ They applied this device to assess hemin-induced oxidative stress in red blood cells resulting from *Plasmodium falciparum* – malaria infection – and determined that it has potential to be used to perform clinical assessment of disease progression in severe malaria.



The intersection of transfusion medicine, inflammation, and immunity

An immunomodulator is an agent that modifies the immune response or the functioning of the immune system. Immunomodulation plays a role in many of the disorders that rely on blood products, and in the mechanisms of action of many therapies derived from blood, including the plasma-derived antibody-based therapies, intravenous immunoglobulin (IVIg) and RhD immune globulin (RhIg).

IVIg was originally developed as an antibody replacement therapy for patients deficient in IgG, but its use has expanded greatly due to recognition of its immunomodulatory effects in autoimmune disorders.⁵⁰ RhIg, a polyclonal IgG against RhD on red blood cells, is isolated from alloimmunized donors, and is considered a type of IVIg.⁵¹

These are effective and important therapies in a wide range of immune disorders. However, IVIg and RhIg are expensive drugs in limited supply, that carry a theoretical biosafety risk. Developing replacements for these products is desirable, and a focus of research at the Centre for Innovation.

Understanding how therapies work

Several studies by **Alan Lazarus** and his team used mouse models to understand how RhIg therapy works to prevent hemolytic disease of the fetus and newborn (HDFN).^{52, 53} This lifethreatening disease is the result of an immune response due to an incompatibility between a mother and her baby's blood in pregnancy. Treatment with RhIg suppresses the mother's immune response by a not-yet-fully understood mechanism known as antibody-mediated immune suppression (AMIS).

It was thought that interactions between RhIg and receptors on immune cells, followed by red blood cell clearance, were required for AMIS to be effective, but **Lazarus**'s work demonstrated that this is not the case. In a separate case study, **Lazarus** and colleagues demonstrated that RhIg antibodies can induce changes in the level of detectable RhD antigen on red blood cells in a clinical setting.⁵⁴ This suggests that upon RhIg treatment, detectable RhD antigen on red blood cells is lost. This may influence red blood cell clearance. These studies can help shape future research to develop non-plasma-derived alternatives to RhIg to prevent HDFN.

Donald Branch was involved in a study which looked at a recombinant Fc hexamer as an alternative to high-dose IVIg.⁵⁵ This drug also shows promise as a potent anti-inflammatory in a model of arthritis, likely mediated by blockade of Fc receptors and its inhibition of complement activation. Fc hexamers have the potential to replace all IVIg indications except for IgG replacement therapy in IgG-deficient patients; this work was done in collaboration with CSL Behring, the pharmaceutical company developing these agents.



Read the ResearchUnit: <u>How does</u> anti-D prevent hemolytic disease of the fetus and newborn? Lessons from a mouse model



Laura Sly developed protocols for use with mouse models to assess the impact of biologics such as IVIg on the inflammatory state of macrophages, providing information on the role of macrophage activation in the efficacy of these drugs and providing insights into mechanisms of action.⁵⁶

Understanding the mechanisms of immune disorders

Published in Nature Communications, work from **Heyu Ni**'s laboratory shed light on the mechanism of fetal loss in Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT), a lifethreatening bleeding disorder which affects approximately 1 in 1,000 live births, though its incidence may be underestimated due to miscarriage.⁵⁷ FNAIT occurs when an immune response is mounted by the mother against antigens on the baby's platelets during pregnancy, leading to low platelet counts which can result in severe bleeding, brain hemorrhage, growth restriction, or death of the fetus or newborn.

"By understanding what causes reduced growth and miscarriages in fetal and neonatal alloimmune thrombocytopenia (FNAIT) cases, we are one step closer to being able to identify FNAIT cases early and reduce the rates of the devastating outcomes of this disease."

Heyu Ni, Scientist, Canadian Blood Service, in RED blog post, August 2017. (<u>Read more</u>)

In contrast to many previous studies that have focused on the bleeding symptoms of FNAIT, **Ni**'s study, using mouse models, examined maternal antibodies in the uterus and discovered that they activate immune cells called natural killer or NK cells. These NK cells destroy trophoblasts leading to dysfunction of the placenta, fetal growth restriction and miscarriage, providing a nonbleeding reason for fetal loss in this disorder. This previously unknown mechanism also suggests a new therapeutic target — NK cells which could be exploited to help prevent fetal loss in this devastating disorder. IVIg treatment, which due to its immunomodulatory activities may prevent activated NK cells from attacking trophoblasts, may improve FNAIT, although developing other therapeutic options that are more efficient or lower cost would be beneficial.

Ni's work has also helped elucidate mechanisms underlying immune thrombocytopenia (ITP).⁵⁸ Some ITP patients do not respond to standard immunosuppressive treatments such as IVIg. **Ni** and colleagues uncovered a novel mechanism that may explain why. They showed that antibodies against the ligand-binding domain of a platelet antigen called GPIbalpha, which ITP patients refractory to IVIg often have, exert a mechanical force on GPIb-IX via platelet crosslinking, inducing Fc-independent, and thus IVIGresistant, platelet clearance. Understanding this mechanism may help develop effective therapies for these patients.

Branch, in a study conducted with several Canadian Blood Services medical directors and adjunct scientists, used genetic testing of patients to determine who is more at risk of developing IVIg-related red cell hemolysis, a potentially serious adverse reaction that occurs in some patients following treatment with high dose IVIg.^{59, 60} They showed that patients with blood group AB are more susceptible to the adverse reaction, and would benefit from close monitoring for signs of hemolysis following treatment. The team has also used the monocyte monolayer assay, a technique pioneered by Branch, to show that IVIg-related hemolysis appears to occur via delayed-onset phagocytosis of red blood cells by the patient's monocytes.





Read the **Research**Unit: <u>Patient blood</u> <u>group impacts susceptibility to IVIg-</u> <u>associated hemolysis</u>.

The concept of immunomodulation can also be used to develop other therapies. Scott has been pioneering immunocamouflage as a means to fool the immune system. This approach has potential applicability in a variety of transfusion and transplantation scenarios, as well as in immune disorders. Scott has investigated immunocamouflaged (stealth) red blood cells, generated by the covalent grafting of biologically safe polymers to red blood cell membrane proteins. This masks non-A/B blood group antigens and could be used to improve blood inventory and transfusion safety.⁶² Scott is researching a related method to trick the immune system to make tissue transplantation safer and more accessible. In this approach, polymer-based bioengineering of T-cells is used to prevent allorecognition, and could help prevent transplant rejection without the harmful side effects observed with anti-rejection drugs, increasing transplantation safety.63,64

Systematic review to inform clinical guidelines

Shehata, Lieberman and Arnold were involved in a systematic review of antenatal management in fetal and neonatal alloimmune thrombocytopenia (FNAIT). Their review of four randomized controlled trials and 22 nonrandomized studies suggests that first-line antenatal management in FNAIT is weekly IVIg administration. This non-invasive management approach was found to be effective, without the relatively high rate of adverse outcomes seen in invasive strategies, such as serial fetal blood sample and intrauterine platelet transfusions.⁶¹



Driving innovation for Canadian Blood Services' operations

Under the leadership of **Ken McTaggart**, the Centre for Innovation's development laboratories and dedicated facilities address the needs of Canadian Blood Services' supply chain by providing the evidence needed to introduce change.

The group works closely with industry partners, including Macopharma and TerumoBCT, to test or co-develop new instruments, reagents, equipment and products to facilitate innovation. In the last year, the Product and Process Development group has conducted 65 research projects (Appendix I) and published 30 technical reports (Appendix II) to develop and share evidence with partners and inform decisions. The group has also distributed significant amount of blood products to researchers.

Distributing research products across Canada

3,255 blood products supporting **73** projects

258 cord blood products supporting 11 projects

Supporting changes in manufacturing blood products

Centrifuges and blood extractors

Canadian Blood Services must update the equipment it uses for blood components processing, in particular when this equipment reaches its end-of-life. The in-house testing capabilities that the Centre for Innovation's netCAD facility offer are essential to support the organization in making informed decisions about the optimal processes and the associated impact to product before these changes are implemented in our supply chain.

Led by Janet McManus and Craig Jenkins, and working closely with supply chain staff, the Centre was involved in the Request for Proposals carried out to identify new centrifuges and blood extractors from several vendors. The Centre also conducted a series of studies with the selected pieces of equipment to test the quality of the products manufactured, as well as to develop new processes.⁶⁵ The findings from these studies provided the evidence necessary for Canadian Blood Services to select new equipment while being confident of the quality of the products provided to hospitals for patient care. The data also informed the organization about the number of equipment and the staff required to implement the new process while maintaining adequate productivity.

Incremental change in support of transformational change

When testing the new centrifuges, netCAD staff identified an opportunity to improve the inserts that are used to safeguard the collection bags when being centrifuged. Working with an industry partner and supply chain, the group developed a new insert that is made of silicone providing a more durable and easier to wash insert. With this improvement, it is expected that the useful life of the inserts will go from months to years.⁶⁵



With the support of the development data that were produced over the last two years, in 2017 Canadian Blood Services submitted a licence amendment to the regulator, Health Canada. After receiving approval from our regulator in April 2018, the organization is now in the process of implementing these changes at its Dartmouth facility before deployment to its eight other manufacturing sites. The Centre continues to provide support as this change is being implemented.

Hematology analyzers

The Siemens ADVIA 120 hematology analyzers used for quality control program have reached end-of-life and are being replaced with Sysmex XN-1000 hematology analyzers. These analyzers are used to determine platelet count, which together with unit volume determines the dose of platelets in a unit. Different counting technologies and methods mean there is a recognized discordance in platelet counts obtained among different analyzers. To account for this potential discordance and support the organization-wide change in analyzers, the Product and Process Development group, with expert support from **Devine's** laboratory, established and tested a flow-cytometry based platelet counting 'reference' method.⁶⁷ This method, based on a clinical reference method for counting platelets developed by the BEST Collaborative, helped supply chain manage and understand the inter-instrument shift in quality control measurements as the new analyzers were implemented.

Collection bags

Canadian Blood Services uses two different collection bags (or collection sets) and manufacturing processes to produce blood components from whole blood. The Buffy Coat (B1) method is used to produce all three components, red blood cells, platelets and plasma components. However, this process requires the cooling of the collected whole blood to room temperature and its processing within 24 hours of collection.

In contrast, the Whole Blood (B2) method allows cooling of the whole blood to 4°C which extends the processing to up to 72 hours after collection but prevents the production of platelets due to their fragility in cold temperature. The Product and Process Development group is supporting supply chain in exploring the feasibility of using the B1 collection set in a "cold" (between 1 and 10°C) processing method to produce red blood cells and plasma.

This change could help better manage B1 manufacturing timelines, and could potentially replace or reduce reliance on the B2 collection set. The research study, conducted at netCAD, showed that red cell and plasma components manufactured using the B1 collection set and a "cold" processing method passed quality control acceptance criteria and were non-inferior to currently produced B1 components.⁶⁸ This suggests cold-processed B1 collection sets could be a suitable replacement for the B2 collection set.

Incremental change in support of transformational change

When reviewing the processing steps for preparing platelet products from pooled donors, netCAD staff identified an opportunity to remove a two-hour "resting" period after components extraction. With this improvement, the process is more streamlined without impacting platelet product quality.⁶⁶



Non-destructive testing

In accordance with Health Canada regulations, Canadian Blood Services conducts ongoing quality control testing on a small fraction of its blood products. However, the current procedure requires that entire blood products be removed from the inventory, precluding their entry into the inventory and transfusion to patients. Over the last few years, the Centre for Innovation has lead an initiative to determine the feasibility of using small aliquots, drawn from units at production, to use in the quality control testing. Led by McTaggart and Peter Schubert, this approach, called non-destructive testing, could improve product availability and reduce production costs while maintaining quality control testing.

Leveraging the expertise multiple from the researchers, Product and Process Development team has focused its efforts on the following three areas: optimizing the design of the small aliquots containers to ensure appropriate representation of product quality parameters compared with the "mother unit", assessing the impact of small aliquot removal on the dose of the final blood product, and developing new sterility testing algorithms.

In the last year, **Blake** used a product simulator to determine the impact of aliquot removal on red blood cell unit volumes and hemoglobin dosage.⁶⁹ Performance was evaluated based on current Canadian Standards Association quality control criteria for hemoglobin levels in red blood cell units. The preliminary findings indicate that, after the removal of aliquots for nondestructive testing, most red blood cell units should meet criteria. However, this simulation study will need to be repeated once the new equipment and processes described above are fully implemented. Simulation studies are essential in predicting the impact a process change may have on the quality and efficacy of blood products.

Supporting implementation of new blood products

CMV-safe products

The National Advisory Committee on Blood and Blood Products (NAC) made a public statement in February 2017 recommending that leukoreduced cellular blood products be considered equivalent to Cytomegalovirus (CMV) IgG-seronegative blood products for all patient populations except for intrauterine transfusion. Later that year, Canadian Blood Services stopped testing the majority of donor blood for anti-CMV antibodies and implemented a new process to maintain only a small inventory of CMV seronegative blood components for the sole purpose of intrauterine transfusion. This recommendation was based on the review of available literature which included numerous research publications supported by Canadian Blood Services dating back to 2000 thus demonstrating the long-term impact of the Centre's research on the blood system.

To inform health care professionals about this change and ensure appropriate blood products utilization for optimum patient care, the Centre participated in several knowledge mobilization efforts. Chapters 13^{70, 71} and 15^{72, 73} of the Clinical Guide to Transfusion, edited by **Clarke** and **Sophie Chargé**, were updated and posted in both French and English on Canadian Blood Services Professional Education website, and attracted 10,000 views during the period September 2017 to March 2018.

In addition, an educational presentation and two accompanying videos were produced by Canadian Blood Services with **Jeannie Callum** from the University Health Network to provide an overview of the evidence and use of CMV-



seronegative and CMV-safe (leukoreduced) blood and blood products. These resources were published on the Professional Education website, and received 637 views.^{74, 75}

To increase awareness of these tools amongst the transfusion medicine community, links were provided in a Canadian Blood Services Customer Letter sent to the approximately 720 hospitals served by our organization and presentations were made by Canadian Blood Services Hospital Liaison Specialists. Knowledge mobilization tools are essential to inform health care professionals impacted by the change and to support them in their continued provision of the best care possible for transfusion recipients across Canada (except Quebec).

Supporting changes in manufacturing hematopoietic stem cell products

According to best practices in the field of hematopoietic stem cell transplantation, Canadian Blood Services stores its cord blood units frozen at -196°C until they are required by physicians for transplantations. Standard protocols for storage or shipping of frozen cord blood units are not available although a transient warming of the units above critical subzero temperatures could impact cell viability and product efficacy. Nicolas Pineault and Acker, with expertise in cell biology and cryobiology, conducted research studies to optimize and standardize cord blood units handling and thawing procedures. These evidence-based procedures contributed to the success of Canadian Blood Services Cord Blood Bank in achieving FACT accreditation, a global standard for top quality patient care in cellular therapies.⁷⁶ The protocols are also expected to optimize Canadian Blood Services cord blood product quality and reduce variability between processing centres at Canadian Blood Services and hospitals.

Ramirez-Arcos and supply chain staff developed a protocol for neutralizing antibiotics that may be present in a collected cord blood unit.⁷⁷ This protocol can be applied to any culture-based bacterial screening method and ensures the accuracy of sterility tests performed to detect bacterially contaminated units that may pose a risk to patients. Considering that approximately one third of cord blood units donated in Canada are obtained from cesarean section deliveries, during which the mothers are undergoing prophylactic antibiotic treatment, the impact of this protocol is of importance.

"Every project we are involved in, no matter how big or small, has the goal of generating data that helps inform decisions. I am thrilled each time we can provide an answer and the organization can use our evidence to move forward."

Sandra Ramirez-Arcos, Development Scientist, Canadian Blood Service, in RED blog post, February 2018. (<u>Read more</u>)

Allan studies Canadian policy on the responsible use of umbilical cord blood for proven indications in regenerative therapy. To balance heightened public expectations and ensure appropriateness of emerging cell-based treatment choices, Allan notes the importance of regular evidence-based assessment of novel umbilical cord blood-derived therapies.⁷⁸ In a systematic review of the literature and metaanalysis of studies using umbilical cord blood in clinical studies of cell-based transplantation, Allan identified neurologic diseases as the most commonly reported novel indication of therapy. Of the 57 studies identified that looked at novel uses for umbilical cord blood, only 16 included a control group. A clearer understanding of the



clinical benefit of umbilical cord blood for specific indications is anticipated once more controlled studies are reported. Blood establishments, transplantation centers, and regulatory bodies need to prepare for greater clinical demand.

As part of Canadian Blood Services horizon scanning for novel uses of cord blood donations, **Pineault, Acker, Scott** and **Sheffield** conducted a review of the literature.⁷⁹ This indicated that finding new medical uses for existing cord blood products and developing new biological products from cord blood donations could increase the value of the Cord blood Bank for Canadians. Creating new or improved therapeutic products from cord blood donations is an area in which there are extensive preclinical and clinical research efforts, some of which are generating excitement in the scientific community. While none of the innovations are approved clinical protocols, the review revealed, similar to the conclusions of **Allan's** systematic review, that they will likely lead to increased demand for cord blood units.



Read the RED blog post: <u>A Q&A with Dr. David Allan</u>.



Organ and tissue donation and transplantation

The Centre for Innovation, in consultation with Canadian Blood Services' Organ and Tissue Donation and Transplantation (OTDT) group, supports research in the area of organ and tissue donation and transplantation. Both the James Kreppner Award Program and the Kenneth J. Fyke Award identify research priorities related to the issues of organ and tissue donation and are open to all Canadian researchers, while our Small Project Funding Program is open to internal staff, including those affiliated with the OTDT group. The Centre also partnered with CIHR to support the Canadian National Transplant Research Program (CNTRP).

This year, the Canadian Critical Care Trials Group and the CNTRP published the Canada-DONATE study protocol a prospective national observational study of the medical management of deceased organ donors.⁸⁰ This ongoing prospective observational study, led by **Maureen Meade** and Frederick D'Aragon aims to build a national platform for future clinical trials in donor management. Currently, research on the management of deceased organ donors is limited in Canada by the regionalization of donation services within provinces, as well as the separation of donation from transplantation services.

By engaging collaborators at donation hospitals and organ donation organizations, and gathering information about current practices, the study hopes to evaluate interventions and assess the feasibility of future clinical trials. Jennifer Chandler and Vanessa Gruben are supported by the James Kreppner Award. Studying legal and ethical challenges around organ donation, and understanding public and stakeholder attitudes towards organ donation are central themes of their work. Together they have conducted preliminary work to understand organ donation in the context of new medical assistance in dying legislation, which was introduced in 2016 in Canada.^{81, 82}

They are addressing the challenging issue of whether those accessing medical assistance in dying would be eligible to donate organs and tissues, and the associated ethical and legal questions this poses – a topic that has not been studied or addressed in detail thus far.



Building transfusion and transplantation capacity through training and education

The Centre for Innovation facilitates the development of professionals in transfusion and transplantation science and medicine by providing formal training and education opportunities and by promoting knowledge dissemination. One of the focus of the Centre is to collaborate and partner to accelerate local activities and amplify their reach to the broader Canadian community.

A national training program

The Centre administers programs to provide financial supports for training professionals at various stages in their careers. Over the last year, the Centre's Graduate and Postdoctoral Fellowship Programs provided salary support to 16 junior researchers conducting projects aligned with our research priorities and in academic laboratories across Canada. In addition, the Centre's 11 scientists and development scientists supervised more than 20 graduate trainees and postdoctoral fellows with funding from research grants or external sources.

In 2017, the Centre also entered into a new partnership with the Canadian Institutes for Health Research (CIHR) to fund a CIHR Health System Impact fellow. **Jennie Haw** began her fellowship in September to conduct qualitative research to gain new perspectives on cord blood donor experiences and motivations, and the public banking process. The academic expertise she brings to our organization through this Fellowship will help the cord blood bank gather the data it requires to inform future policy development to best serve the needs of patients and donors.



Read the RED blog post: <u>Unique</u> <u>fellowship brings academic</u> <u>expertise to an organizational</u> <u>challenge</u>.



Mariam Taha studies bacteriophages — viruses that infect and consume bacteria. Taha is part of a project at Ottawa Hospital Research Institute looking at how to use bacteriophages in conjunction with antibiotics to treat biofilm infections in prosthetic joints.

Taha credits her work with Centre for Innovation scientist Ramirez-Arcos — made possible through the Canadian Blood Services Graduate Fellowship Program — for giving her the necessary experience and training to partake in this innovative medical work.

RED blog (<u>read more</u>)

In partnership with **Robert Skeate**, Canadian Blood Services associate medical director, the Centre continues to provide support to the training of transfusion medicine specialists via the Transfusion Medicine Areas of Focused Competency (AFC) diploma program. In 2017-2018, **Ziad Sohl** and **Jacqueline Trudeau** completed their diplomas. **Sohl** joined the London Health Sciences Centre and St. Joseph's Health Care London facility as a transfusion specialist and **Trudeau** is at the Vancouver General Hospital. Through their affiliation with



Canadian Blood Services, these research and clinical specialists gain a unique exposure to the Canadian blood system that prepares them to contribute to new advances in this field and engages them in a national network.

The Centre continues to provide administrative support to facilitate the national expansion of Transfusion Camp. This unique program is targeted at postgraduate medical trainees from various specialties that use blood products. It consists of five one-day events that include lectures and team based learning sessions. In 2015, the Centre partnered with the Toronto based team to deliver this unique training on a national scale. In 2017-2018, Western University ioined the seven Canadian universities (University of Toronto, University of British Columbia, University of Saskatchewan, University, Queen's McMaster University, University of Ottawa and Dalhousie University) and Oxford University in delivering this program to their medical trainees. In addition, more medical programs joined bringing the number of trainees registered to 302 (134 more than in 2016-17) from a total of 18 specialties. The impact of this training program on knowledge acquisition, postgraduate trainee attitudes, and self-reported behavior vis-à-vis transfusion practice is currently being evaluated.

Webinars and symposiums for health care professionals and researchers

Since 2007, Canadian Blood Services, under the leadership of medical director **Peter Lesley**, and the Ontario Regional Blood Coordinating Network (ORBCON) co-chair an annual transfusion medicine symposium in partnership with a community hospital. The involvement of the community hospital is key in identifying topics of relevance to the transfusion issues faced by their health care professionals. The community hospital also serves as the host site for the symposium, from where the speakers present to the local audience and from where the lectures are webcasted to more participants.

In April 2017, the education program focused on managing patients with gastrointestinal (GI) bleeding. Speakers shared tools to assess the severity of the GI bleed, provided best practices for treating bleeding in patients with advanced liver disease, compared the available options for anticoagulant reversal in the GI bleed setting, and discussed strategies for red blood cell utilization. In recent years, with videoconferencing and webcasting technology provided by the Ontario Telemedicine Network, the reach of this symposium has been extended to include more hospitals across Ontario and Canada. In fact, this year, 136 healthcare facilities participated, including nine Canadian Blood Services sites, two pharmaceutical companies and one postsecondary institution, engaging more than a thousand professionals.

"This is a great learning experience, with wonderful speakers. I was able to come away with a better overall picture as to the care and decisions towards a patient."

Feedback from a 2017 attendee of the Annual Transfusion Medicine symposium, RED blog (read more)

Through its collaboration with the **Centre for Blood Research**, the Centre supports the annual Norman Bethune and Earl W. Davie symposia. These events feature expert presentations from Canadian and international leaders as well as from patients, and are broadcast to facilitate remote attendance. With attendance in the hundreds, these events inspire researchers to further innovative research and provide opportunities for students and early career researchers to network.





Read the RED blog post: <u>Earl W.</u> <u>Davie Symposium - Eleven years and</u> <u>counting</u>.



Dr. Earl W. Davie, Dr. Ross T. MacGillivray and Dr. Edmond H. Fischer at the 2017 Symposium in Vancouver, (Photo courtesy of the Centre for Blood Research.)

Educational resources made available online

In collaboration with the Canadian transfusion medicine community, the Centre develops educational resources for health care professionals that are made available free of charge via the new Canadian Blood Services Professional Education website (profedu.blood.ca). In 2017-2018, the website recorded 163,000 sessions engaging 130,000 users with over 300,000 page views. Users are primarily from Canada (45 per cent of users) but also from the United States as well as francophone countries which seek French content. The most sought-after resources are the 18 chapters of the Clinical Guide to Transfusion, with over 60,000 page views and an average of 3.5 minutes spent on each page, as well as an article on TRALI with 50,000 page views.

Through its BloodTechNet competitive program, the Centre continues to fund projects aimed at delivering educational tools and resources that support the development of skills, knowledge, and expertise of health professionals in the transfusion, cellular therapy, and transplantation communities in Canada. In 2017-2018, **Andrew Shih** (a former Transfusion Medicine AFC diploma recipient) received funding to develop an online curriculum dedicated to the management of bleeding and thrombosis with transfusion medicine as a central concept. **Shih's** project developed Blood&Clots resources that are now housed on CanadiEM, an online portal for emergency medicine specialists.

Also in 2017-2018, **Clinton Campbell** led a multidisciplinary team to bring the Choosing Wisely Canada transfusion recommendations to life in video form. The <u>five short videos</u> are housed on Canadian Blood Services professional education website as well as on the Canadian Society for Transfusion Medicine website. To date, they have attracted more than 1500 views.



Video developed through the BloodTechNet program.

These resources are further disseminated via the Centre's Research and Education monthly enewsletter, which currently has 849 subscribers, the <u>RED blog</u>, and partners' newsletters including Canadian Blood Service's Circulation and BloodNotes.

When appropriate, educational resources are also included in Canadian Blood Services Customer Letters and in presentations delivered by Canadian Blood Services Hospital Liaison Specialists to hospital stakeholders.



Good governance and a collaborative approach increase impact

As illustrated throughout this report, the achievements of the Centre's strategic activities are complemented and enhanced by strategic partnerships and collaborations. Internally, the Centre continues to benefit from sound governance from Canadian Blood Services, with oversight provided by the external Scientific and Research Advisory Committee and by the Safety, Research and Ethics Committee of Canadian Blood Services' Board of Directors. Program administration is strongly supported by Canadian Blood Services' enabling functions: Talent Management, Finance, Legal, Information Technology, and others. Significant value and rigour are achieved by the contributions of these support services and the infrastructure surrounding the programs operated by the Centre for Innovation.

External stakeholders and partners include other blood operators and related organizations, academic and research institutes, not-forprofits, industry, and government partners. These bring value and contribute greatly to the impact of the Centre for Innovation. The broad spectrum of partners enhances our national and international standing, establishes the Centre as a leader in the field, and allows us to benefit from the expertise and resources of global endeavors in transfusion and transplantation. Strong connections with our partners also facilitate dissemination and uptake of knowledge created by the Centre, maximizing our impact and helping attain our outcome of a safe, effective, and responsive system for blood and blood products in Canada.

Through the contributions of the Centre for Innovation, the Canadian blood system is wellpositioned to address emerging scientific and clinical knowledge, risks, opportunities and technologies. This annual progress report highlights many of the important accomplishments of the Centre for Innovation and, together with the outputs and outcomes reported as part of its performance measurement framework (Table 1, Appendices I and II), demonstrates the value of the Centre's activities in improving patient outcomes and system performance while ensuring maximal cost-efficiency.



Centre for Innovation research network: Canadian Blood Services' scientists, medical directors, trainees, team members, and external researchers participated in the Centre for Innovation annual research day.



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Appendix I: Funded projects

Summary of funded research projects by program

Projects receiving funding in fiscal year 2017-2018	Total: 152
Research Program	54
Canadian Blood Services/CIHR partnership operating grants	20
Canadian Blood Services/CIHR partnership new investigator awards	1
Intramural research grants	9
MSM Research Grants	11
James Kreppner awards	2
Kenneth J. Fyke awards	2
Blood efficiency accelerator awards	2
Small projects funding	6
CIHR partnership: transplantation research	1
Development Program	65
Deepening the understanding of our products and the processes used to manufacture them	21
Developing next generation and/or new products and the processes used to manufacture them	11
Improving current generation products and the processes used to manufacture them	18
Improving and/or enabling the product and process development group	11
Improving and/or enabling Canadian Blood Services	4
National Training Program	21
Transfusion medicine fellowships	4
Postdoctoral fellowships	5
CIHR health system fellowship	1
Graduate fellowships	11
Education Program	7
Education research grant	1
Program support collaboration	1
BloodTechNet awards	5
Transfusion Medicine Program Support Award	5



Titles of projects funded by Research program

* Note: Projects that are italicized are those for which funding was initiated in fiscal year 2017–2018

Canadian Blood Services/CIHR Partnership National Operating Grant Program

Purpose: Transfusion science

*Expanding treatment options for inflammatory bowel disease: a novel mechanism of antibody-based

Fetal and neonatal alloimmune thrombocytopenia: novel mechanisms and therapeutic approaches

Novel mechanisms of platelet aggregation: roles of non-classical beta-3 integrin ligands and fibronectin in thrombosis and hemostasis

Purpose: Blood supply risk

Examining the relationship between repeated blood donations in female donors on maternal/neonatal outcomes: a cohort study

Exploratory analyses to determine if method of donor blood processing affects outcome in transfused recipients

Transfusion-related Epstein-Barr Virus (EBV) infection among allogeneic stem cell transplant pediatric recipients: a multicenter prospective cohort study (TREASuRE Study)

Purpose: Blood utilization and conservation

Aneurysmal SubArachnoid HemorrhAge - Red blood cell transfusion And outcome (SAHaRA): a pilot randomized controlled trial

Characterization of the hematopoietic reconstitution enhancing activity of osteoblasts derived from human mesenchymal stromal cells

Defining disease mechanisms in Immune Thrombocytopenia (ITP) and their association with clinical outcomes

Design and implementation of circulatory oxygen therapeutics derived from human hemoglobin by improved systematic chemical coupling and cross-linking

Microfluidic devices to measure the deformability of stored red blood cells

Myocardial Ischemia and Transfusion. The MINT rollover trial

Pathogenesis and treatment of immune thrombocytopenia: Are there fundamental differences between anti-GPIba- and anti-GPIIbIIIa-mediated thrombocytopenia?

Polyhemoglobin catalase superoxide dismutase carbonic anhydrase: a novel soluble biotherapeutic with no cardiac toxicity for hemorrhagic shock and other uses

Polymer-based manufacturing tolerogenic miRNA-based therapeutics

Release, delivery and cell programming effects of platelet microparticles and microRNAs

Understanding transcriptional and epigenetic control by Gfi1b towards the development of a therapy for sickle cell disease

Purpose: Transfusion-related acute lung injury

Identification of host cellular immune mechanisms responsible for the initiation and/or modulation of transfusion related acute lung injury (TRALI)

Mechanisms of antibody-independent transfusion-related acute lung injury (TRALI)

Transfusion-related acute lung injury and delayed TRALI: a prospective study in critically ill children

Canadian Blood Services/CIHR Partnership New Investigator Program

Code sepsis: defining and translating optimal resuscitation and care for children with septic shock



Intramural Research Grant Program

Influence of eryptosis and storage on transfused red cell recovery in sepsis

Monovalent Fc receptor blockade using novel fusion proteins: the road towards an IVIg replacement Optimization of monoclonal anti-erythrocyte antibodies for improved immunoprophylaxis in a murine model

A multifaceted intervention to optimize red blood cell transfusion practice in two provinces

Elucidation of the mechanism of IVIg-associated hemolysis

Human monoclonal CD44 antibodies as potential IVIg replacements

Monoclonal antibodies with anti-D-like activity in the amelioration of murine immune thrombocytopenia

Plasma versus plasma protein concentrate transfusion for coagulopathic control

Role of blood component manufacturing on microvesicle-induced transfusion-related immune modulation

MSM Research Grant Program

A longitudinal analysis of behavioural and biological risk among men who have sex with men in metro Vancouver ACB and MSM - it's not an oxymoron: a research project that explores the importance of ACB people in MSM blood donation research

Assessing alternative Canadian Blood Services blood donor deferral screening policies for men who have sex with men

Assessing unintentional creation of bias against MSM as a function of exposure to blood donor screening questionnaire and assessing sexual behaviour risk factors of those successfully passing blood donor screening

Attitudes, behaviours, and acceptability related to current and future blood donation policy: A qualitative study of gay, bisexual, and other men who have sex with men in Vancouver, Toronto, and Montreal

Estimating the probability of HIV risk in MSM donor policies through biobehavioural and mathematical modelling studies

Évaluation de l'acceptabilité et de la faisabilité d'un programme de dons de plasma destiné au fractionnement, pour les hommes ayant des relations sexuelles avec d'autres hommes de la communauté gaie montréalaise

Mathematical modeling - comparing HIV risk between MSM donation strategies

Operational impact of individual risk assessment options

Safety, Acceptance, Fairness & Equality (SAFE project): acceptable risk and donor selection Sex Now 2018: A national survey on blood donation and undiagnosed blood borne infections

James Kreppner Award Program

The role of stakeholder trust in organ and tissue donation and transplantation policy change: public and professional attitudes to ante-mortem interventions in organ donation

Organ donation in Canada: engaging with stakeholders and proposing solutions to current legal and ethical challenges

Kenneth J. Fyke Award Program

Developing a Canadian policy on the responsible use of umbilical cord blood for proven indications in regenerative therapy

Prospective observational study of organ deceased donor management in three ICUs – a pilot study (the DONATE pilot study)

Blood Efficiency Accelerator Award Program

A program to minimize preventable and inappropriate blood product transfusions in liver surgery Feasibility in Canada for a non-invasive prenatal testing using single-exon fetal RHD determination



Small Projects Funding Program

Data sharing with CBMTG registry

National evaluation of platelet transport bags to reduce wastage

Neonatal outcomes after transfusion of ABO non-identical blood (Neo-ABO)

Pre-transfusion furosemide for TACO

ROTEM-guided transfusion protocols – impact on the manufacturer

Use of red blood cell antigen genotyping to assess RhD diversity in sickle cell disease patients

CIHR Partnership: Transplantation Research

The Canadian National Transplant Research Program: increasing donating and improving transplantation

Titles of projects conducted by Product and Process Development program

Deepening the understanding of our products and the processes used to manufacture them

ACP215 cryopreserved international unit exchange

An international investigation into O red blood cell unit administration in hospitals: the Group O Utilization Patterns (GROUP) study

Bacterial growth in red blood cells prepared in different additive solutions

Characterizing blood bag defects/failures

Comparison of donor and general population demographics over time: a BEST collaborative group study

Cord blood and registry composition analysis

Cord blood transient warming events

Critical review whitepaper on in vitro and in vivo platelet product quality characteristics

Evaluation of irradiation conditions for red cell concentrates

Frozen red blood cell products international standardization

Platelet leukoreduction filter from various manufacturers: performance comparison

Post thaw hematopoietic stem cell product quality attributes cord blood unit to segment correlation

Preliminary assessment of residual IgG and IgM in cryoprecipitate products

The effects of room temperature exposure on plasma

Understanding of impact of freezing profile/freezing time on plasma quality project

Understanding of, and feasibility of predicting changes in, product quality attributes during red cell storage in various anticoagulant and additive solution combinations

Understanding the impact of pre-processing delay on the potency of cord blood units

Understanding the impact of time to test on product quality attributes for frozen plasma products

Vox Sanguinis international forum on platelet cryopreservation

Where are the platelets? Understanding causes for platelet production yield and quality attribute variation to identify opportunities to better optimize the process

WHO international repository for platelet transfusion-relevant bacteria reference strains



Developing new or next generation products and the processes used to manufacture them

Cord blood derived products whitepaper

Gamma versus x-ray irradiation whitepaper

Mirasol whole blood pathogen inactivation technology assessment study – product quality perspective

Modeling platelet unit doses after introduction of 7-day platelets and non-destructive quality control testing

Neo-pack and pedi-pack divided red cell units for neonate and pediatric transfusion feasibility

Pathogen inactivation technology whitepaper

Platelet pooling bag request for proposal

SSP+ platelet additive solution assessment – product quality perspective

SSP+ platelet additive solution assessment - safety perspective

Understanding "orange" plasma

Understanding whole blood and red cell concentrate blocked filters

Improving current generation products and the processes used to manufacture them

B2 study – evaluation of the 16 hour hold at 24°C

BacT curve analysis to differentiate false positive BacT bottles

Biosafe Sepax2 large volume cord blood unit processing protocol evaluation

Bringing follow-up of initial testing – positive BacT/ALERT cultures in-house

Contact freezer software evaluation

Counting platelets: Correlation between hematology analyzers and BEST flow cytometer reference method study

Developing a model to optimize the rare red blood cell program

Evaluation of alternative donor skin disinfection methods

Feasibility study into increasing the collection of hematopoietic progenitors from cord blood using alternative collection methodologies

Introduction of anaerobic bacteria to the BacT proficiency testing program

New apheresis collection set

Non-destructive quality control testing for platelet products

Non-destructive quality control testing for red blood cell products

Non-destructive quality control testing for red cell products supplementary studies

Optimization of the flow cytometry staining protocol for post-thaw cord blood samples

Product volume reduction - adult hematopoietic cell stem cell manufacturing

Production equipment request for proposal feasibility and confirmation studies

Sterility stem cells BACTEC validation

Improving and/or enabling the product and process development group

Acquisition and installation of ACP-215 blood processing technology at netCAD

Build the netCAD (Network Centre for Applied Development) donor base

eProgesa for netCAD assessment and options

Evaluation of Vitek 2 Compact for bacteria identification

Investigation into netCAD2 – a blood4research 'east' applied development facility

Product and process development overhead streamlining

Product and process development project portfolio database

Product and process development test method validation: standardization and qualification of test assays in

Centre for Innovation labs supporting product and process group projects

Project management lessons learned

Regulatory asset management entry initiative



Understanding plasma short course for product and process development and supply chain process management staff

Improving and/or enabling Canadian Blood Services

Extended shelf life platelets - post implementation optimization modeling

Holiday platelet planner

Modeling and simulation education and training

Canadian Blood Services clinic simulator

Titles of projects funded by National Training Program

Note: Projects that are italicized are those for which funding was initiated in fiscal year 2017–2018.

Postdoctoral Fellowship Program

The mechanism of action of monoclonal antibody blends in the potential replacement of anti-D in HDFN

Development of a small molecule-based stem and progenitor expansion protocol to accelerate engraftment after cord blood transplantation

DNA aptamers for detection of red blood cells destined for rapid post-transfusion clearance

Transfusion options in coagulopathy: efficacy in controlling bleeding

Understanding the factors that influence bacterial proliferation and biofilm formation in platelet concentrates

CIHR Health System Fellowship Program

Process evaluation of the Canadian Blood Services' cord blood bank: managerial and donor perspectives

Graduate Fellowship Program

Investigating the mechanism of anti-CD44 antibody amelioration of IVIg-treatable disease

Novel cell-surface engineering methods to increase immune-tolerance of allogenic cell transplantation

Studying and alleviating the effects of platelet microparticles induced by pathogen reduction of platelet

Synthesis of carbohydrate derivatives for the improvement of red blood cell storage

Impact of storage on the function of cord blood hematopoietic stem and progenitor cells

Improving pathogen inactivation: the dengue virus-induced platelet proteome

MRI-guided focused ultrasound facilitated IVIg immunotherapy as a therapeutic approach for Alzheimer's disease

Platelet desialylation: novel mechanism of platelet clearance and immune tolerance

Recombinant Fc multimers to replace IVIg

Small molecule ice recrystallization inhibitors as cryo-additives for red blood cell cryopreservation

Study of the mechanisms implicated in platelet microparticle internalization by blood cells

Titles of projects funded by Education Program

Note: Projects that are italicized are those for which funding was initiated in fiscal year 2017–2018.

Program Support Collaboration

Centre for Blood Research program support collaboration agreement

Education Research Grant Program

An evaluation of learner perspectives and outcomes following completion of the transfusion medicine area of focused competence

BloodTechNet Award Program

An innovative digital strategy for dissemination of Choosing Wisely Canada guidelines in transfusion medicine

PID (Primary Immune Deficiency) toolkit app



Podcast for FNAIT and ICTMG red cell specifications for hemoglobinopathies guidelines

Social media for knowledge translation and education 3 (SoMe-KTE3): Transfusion, thrombosis, and hemostasis

The Stem Cell Club: educating medical and nursing students to develop professional skills

Titles of projects funded Transfusion Medicine Program Support Award Program

Note: Projects that are italicized are those for which funding was initiated in fiscal year 2017–2018.

Program Support Award for Canadian Transfusion Medicine and Science Research

Centre for Blood Research

McMaster Transfusion Research Program

University of Ottawa Centre for Transfusion Research

Transfusion Medicine Research Program Support Award

McMaster Centre for Transfusion Research

University of Toronto QUEST research program



Appendix II: Publications

Summary of peer-reviewed and non-peer-reviewed publications from fiscal year 2017-2018

# of peer-reviewed and non-peer-reviewed publications in fiscal year 2017-18	416
Peer-Reviewed Publications	332
Journal Articles	113
Review Articles	23
Clinical Guidelines	1
Comments/Letters/Editorials	21
Books/Book Sections	7
Published Abstracts	164
Canadian Blood Services Circular of Information	3
Non-Peer-Reviewed Publications	84
Canadian Blood Services Website Publications	41
Technical Reports	30
Other	13

Summary of h-index factor analysis



Notes: i) H-Index factors measured using GoogleScholar on April 3 2018. ii) Mean H- index calculated using H-Index factors from the 15 core investigators. Core investigators include (Jason Acker, John Blake, Donald Branch, Dana Devine, Margaret Fearon, Mindy Goldman, Alan Lazarus, Heyu Ni, Sheila O'Brien, Nicolas Pineault, Ed Pryzdial, Sandra Ramirez-Arcos, Mark Scott, William



Sheffield, and Kathryn Webert). iii) H-Index is a single bibliometric indicator that is a measure of both the productivity and impact of published work. H-Index is an indicator of research users being aware of and valuing published research evidence. Average H-index for Canadian university professors in the biological sciences is 10.6.

Publications' Details

Author Legend:

Bold – Centre for Innovation investigators and senior staff; Canadian Blood Services medical directors; Directors of transfusion medicine research programs receiving funding via the Transfusion Medicine Research Program Support Award.

<u>Underlined – Non-Canadian Blood Services investigators leading projects funded in part by Canadian Blood</u> <u>Services.</u>

Journal Articles

- Adams Z, Morris G, Campbell T, Mostert K, Dibdin N, Fearon M, Elmoazzen H, Mercer D, Young K, Allan D. Risk of exposure to Zika virus and impact on cord blood banking and adult unrelated donors in hematopoietic cell transplantation: the Canadian Blood Services experience. *Biol Blood Marrow Transplant* 2018; 24: 861-5.
- 2. Alabdullatif M, Boujezza I, Mekni M, Taha M, Kumaran D, Yi QL, Landoulsi A, **Ramirez-Arcos S**. Enhancing blood donor skin disinfection using natural oils. *Transfusion* 2017; 57: 2920-7.
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- 14. **Blake JT**, **McTaggart K**, Killeen D. Modeling the optimal ethnic composition of an adult stem cell registry. *Eur J Oper Res* 2018; 264: 884-93.
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Appendix III: Health Canada financial contribution

Summary of Expenditures – April 1 2017 to March 31 2018

Note: The Health Canada financial contribution is complemented by funding from the Provincial and Territorial ministries of health and partners.

Schedule 1: Overview		
Operating funds (Schedule 2)		\$ 2,334,092
Funding programs (Schedule 3)		\$ 2,792,577
MSM research program (Schedule 4)		\$ 1,250,000
	Total	\$ 6,376,668

Schedule 2: Operating funds

	Total	\$ 2,334,092
Capital purchases		\$ 9 , 896
Intellectual property protection and other legal activities		\$ 212,818
Centre for Innovation research laboratories operations		\$ 2,111,377

Schedule 3: Funding programs		
Canadian Blood Services/CIHR partnership operating grant program		\$ 829,917
Canadian Blood Services/CIHR new investigator program		\$ 60,000
Canadian Blood Services intramural research grant program		\$ 940,686
Kenneth J. Fyke award program		\$ 100,000
James Kreppner award program		\$ 50,000
Blood efficiency accelerator award program		\$ 40,000
Transfusion Medicine Research Program Support Award		\$ 702,806
CIHR partnership: Transplantation research		\$ 50,000
Additional funding for research projects		\$ 19,167
	Total	\$ 2,792,577



Schedule 4: MSM research program

	Total	\$ 1,250,000
MSM research program administration (Schedule 3)		\$ 21,163
MSM research grant program (Schedule 2)		\$ 1,228,837

Notes:

- Funding programs include capital expenditures under \$10,000
- Appendix III is considered draft until the completion of our external audit and the approval of the financial statements by the Canadian Blood Services Board of Directors