Canadian Blood Services
it's in you to give

RESEARCH & DEVELOPMENT
ACTIVITY REPORT 2012-13
EXECUTIVE SUMMARY

Canadian Blood Services (CBS) is committed to advancing Canadian innovation in transfusion and transplantation. In 2012-2013, CBS realized progress towards this objective through (1) relevant and productive discovery research, (2) the training of highly qualified researchers, as well as (3) a series of development projects fully integrated into CBS’ core operations in the pursuit of enhanced quality, efficiency, and cost-effectiveness. Among those delivering this progress were 12 CBS staff scientists and their teams, along with resources of the Network Centre for Applied Development (netCAD). CBS’ ongoing partnership with Canadian Institutes of Health Research (CIHR), our intramural grant program, and small projects fund supported a number of projects of direct relevance to immediate needs of Canada’s blood system. CBS also continued to maintain a focus on the training of highly qualified personnel with the operation of a graduate fellowship program, a postdoctoral fellowship program, and the provision of numerous training positions in the research laboratories of CBS scientists and adjunct scientists.

Over the course of the year, CBS continued its emphasis on dissemination of research output. In this regard, CBS researchers published 69 peer-reviewed journal articles and another 14 have been submitted. We contributed to 17 review articles and nine book chapters, as well as 44 other peer-reviewed articles such as letters to editors and commentaries, as well as published abstracts. Our researchers also assisted CBS operations by providing 26 internal reports in which their research and subject matter expertise was thought to inform product and process improvement. In addition, new knowledge mobilization tools were introduced to further maximize the impact of our research. Further effort was also made to move CBS’ basic science discoveries to the bedside, through the development of promising intellectual property.

INTRODUCTION

Through creating and mobilizing knowledge, CBS seeks to enhance CBS’ products and services, through applied development work in collaboration with the main business lines of the organization. We also seek to innovate, invent, and discover information and products that will improve transfusion and transplantation in Canada. In this regard, CBS supports a range of discovery research, practical product-directed research, and clinical studies. This work also provides an appropriate platform for the training of highly qualified personnel so that Canada will have a research and medical workforce to draw upon in transfusion and transplantation medicine in the future.

CBS’ knowledge creation activities are divided into three intersecting areas: research, development and the quality monitoring program. These activities are supported by a knowledge mobilization function. The research area is responsible for discovery transfusion research and the operation of CBS’ training programs for scientists. In general, these programs are supported through competitive, peer-reviewed project application processes. The development function is responsible for primary scientific support to the CBS operations, and for assisting with the development of research innovations when appropriate.
The research undertaken in the epidemiology and surveillance areas by CBS staff is also considered to be linked to development work. The quality monitoring program is home to the research that CBS undertakes to improve product standards as well as to the troubleshooting program which assists the core business on demand. All 12 CBS staff scientists have a primary affiliation in either the research or the development function, but almost all scientists perform a mixture of research and development work. CBS’ knowledge mobilization activities have focused on knowledge dissemination, education, leading practices development, and commercialization.

I. KNOWLEDGE CREATION

Research Program

In 2012-13, Canadian Blood Services continued to fulfill a leadership role in scientific research related to blood transfusion and in training talented researchers, with the aim of meeting Canada’s current and future needs in the highly knowledge-based sector of blood and blood products.

The program continued to provide both operational and personnel awards in order to advance relevant research. Operating funds were disbursed via three programs: the Intramural R&D competition; the Small Projects Fund (SPF); and through leveraged partnership programs with the Canadian Institutes of Health Research (CIHR). As in previous years, CBS Scientists, Adjunct Scientists, and Medical Staff were eligible to compete for intramural operating funds, while Small Projects Fund resources targeted innovation closer to the front-line of CBS’ operations and were available to be led by any non-R&D CBS staff member. The CBS/CIHR competitions that ran in 2012-13 were open to all Canadian public sector researchers. In all of the competitions, CBS maintained its strict commitment to the principles of peer review. The Intramural competition relied upon an external review panel of Canadian and international blood experts. All SPF applications were reviewed by CBS’ Vice-President (VP), of Medical, Scientific & Research Affairs (MSRA) and the Associate Director (AD) of Research. Partnered CBS/CIHR programs used the peer review system of CIHR, after anonymized summaries were assessed for relevance on a pass/fail basis by the VP and AD.

Intramural R&D Program

In order to continue to foster collaboration, each research team applying for this grant was required to include a minimum of three investigators drawn from the ranks of CBS staff scientists, adjunct scientists, and medical staff. Six Intramural R&D team applications were received and three were funded. The funded projects relate to: 1) the role of a specific class of white blood cells, the T regulatory cell, in the mechanism of action of intravenous immunoglobulin (IVIG); 2) moving “stealth” modification of red blood cells (RBC), a process rendering them less likely to cause rejection by the transfused patient, from bench to bedside; and 3) understanding which factors in transfusable plasma are most important in reducing bleeding in the transfused patient. The new projects started in 2012-13 joined four projects in progress related to:
• Countering the RBC storage lesion with liposomes, natural additives used in the food industry;
• Preclinical investigations of candidate drugs for IVIG replacement;
• Basic inquiries into the nature of platelet destruction in autoimmune diseases; and
• Clinical studies aiming to determine the appropriate dose and timing of red cell transfusion, for patients receiving hematopoietic stem cell transplants.

The average annual monetary value of the Intramural grant program proposals funded in 2012-13 was $156,398 per annum.

**Small Projects Fund (SPF)**

Any SPF projects funded prior to 2012-13 had been successfully concluded in by the close of 2011-12. A single SPF project started in 2012-13, which involved a structured epidemiological study of platelet transfusion in a group of Canadian children with cancer. The project will provide data to support the generation of practice guidelines, which are currently lacking in this area of transfusion medicine.

**CBS/CIHR Partnership**

CBS ran three operating grant partnership programs with CIHR in 2012-2013.¹ In the fall 2012 competition, the specific requests for applications related to: blood utilization and conservation (BUC); systemic risks to the blood supply (BSR); and transfusion-related acute lung injury (TRALI). Under the partnership agreement, proposals judged by CIHR peer review mechanisms to be of high quality were funded by CBS. Those judged to be of very high quality were funded by CIHR. Unlike CBS intramural operating grants, which are limited to two year awards, CBS/CIHR projects can be funded for a maximum of 3 years.

Two new proposals submitted in the fall 2012 BUC competition were awarded funding with CIHR (or a non-CBS partner) as the paying partner: 1) a clinical study of the effects of the age of blood transfused to children in intensive care units; and 2) a clinical and pharmacoeconomic study of blood product utilization in patients bleeding as a side effect of their treatment with a new class of oral anticoagulant drugs. Five new proposals from the fall 2012 BUC competition were also funded with CBS as the paying partner:

• Developing novel blood vessel sealants to conserve blood during surgery;
• Improving the storage of frozen blood cells using novel additives;

¹ This marked the second year in which partnership competitions ran once per year, in the fall only, as opposed to both fall and spring competitions. This decision meant that CBS commitments to the program, which vary depending on the relevance and quality of applications in a given competition, would be known at the start of the fiscal year in April, allowing better financial tracking and planning.
• Determining the clinical appropriateness of RBC transfusion in the context of hematopoietic (blood cell forming) stem cell transplantation;

• Development of small molecule drugs that block antibody destruction as an IVIG replacement strategy;

• Understanding changes in a potential platelet quality biomarker, micro-RNA profile, during platelet storage.

In the BSR stream, a single new proposal was funded, with CBS as the paying partner. This project was a clinical study assessing the risk of transmission of Epstein-Barr virus, to children receiving stem cell transplants. Finally, in the TRALI stream, in 2012-2013, no submitted proposals were found to pass the required condition of relevance to the call for proposals. Overall, in 2012-2013, the CBS/CIHR program continued to be an effective and efficient partnership, in which program funding was leveraged to promote high quality research aimed at improving transfusion-related health outcomes.

With respect to CBS-administered CBS/CIHR partnership operating grant funds, 19 other projects were either in progress or concluded in 2012-13. In terms of the three streams in the operating grant partnership, sixteen fell under BUC, two under TRALI, and one under BSR. The group as a whole included: a clinical study of potentially pathogenic antibodies in TRALI cases in Canadian patients; a translational study investigating the possibility of using RBC from cord blood as a new blood product for neonatal patients; a risk-related study of demographic and geographic challenges to supplying Canadian hospitals with sufficient blood; and the remainder were non-clinical basic research studies aimed at providing relevant new information applicable to a variety of areas. This final group comprised studies of storage of red blood cells and platelets; stem cell preservation; red cell replacement; immunoglobulin replacement candidates applicable to immune platelet disorders and RBC destruction in the newborn; plasma and plasma replacement product utilization in an animal model of bleeding; blood products versus salt solutions as resuscitation fluids in animal models of critical illness; extraction of products of value from plasma by fractionation; genetic studies of the mechanisms controlling hematopoietic stem cell function and hemoglobin production; and the development of new biomaterials for blood storage and delivery.

The average annual monetary value of the CBS/CIHR partnered operating grants awarded in 2012-13, for which CBS was the paying partner, was $118,047 per annum.

**Researcher Training**

Although the CBS/CIHR partnership remained predominantly focused on operating grant support, it continued to contain a New Investigator Award in Transfusion Science. Unlike the cost sharing arrangement in the three streams of the operating grant partnership, CBS is the sole paying partner in this personnel competition. As in the operating grants, CIHR provides peer review and CBS makes relevance determinations of anonymized application excerpts. No new awards were made in 2012-13, as the candidates who did apply failed the relevance screen. CBS continued to support two New
Investigators, one in the early, and one in the later, stages of their five year awards. Both individuals are clinical investigators.²

Autonomously, CBS also continued to operate Summer Internship (SIP), Graduate Fellowship (GFP), and Post-doctoral Fellowship (PDF) competitions in 2012-13. CBS Scientists who were not sponsoring candidates formed review committees in each case, with the Assistant Director (Research) chairing each review committee.

**Summer Internship (SIP)**

SIP awards may be held in any CBS department, but most awardees work in CBS’ MSRA laboratories or those of Adjunct Scientists. In 2012-13, this was the case for all 11 awardees; a total of 14 applications were received and ranked. This total represents the sum of those applicants who applied with an identified supervisor and those for whom a potential supervisor was identified after applications were submitted; both streams continued to be permitted under the program guidelines.

**Graduate Fellowship (GFP)**

GFP awardees are graduate students studying for their PhD degrees and conducting research in Canadian university laboratories. Awards are for two years, renewable for a second two year term. Preference is given to those sponsored by CBS Scientists. In 2012-13, 5 students were supported by new awards from this program: 3 in non-CBS laboratories; and 2 in CBS laboratories. An additional two students won renewals of their awards, both held in CBS laboratories. All successful awardees demonstrated that their projects related to one of the four priority areas of pathogen reduction; immunoglobulin therapy; modified cellular products, including stem cells; and product quality. The doctoral trainees’ projects specifically related to developing new cryoprotectants for hematopoietic stem cell storage; synthesizing drugs to absorb excess, harmful iron in chronically transfused patients; using ultrasound to deliver IVIG to the brain in an animal model of Alzheimer’s Disease; discovering biomarkers for RBC quality; improving donor blood group typing using microfluidic technology; assessing liposome addition to RBC to extend storage; and studying what factors limit the circulatory lifespan of RBC. The newly supported students joined 11 other PhD candidates previously funded by the program who were in the final half of their supported doctoral research training.

**Post-doctoral Fellowship**

Three new post-doctoral fellows were supported from the CBS Research program in 2012-13 via CBS PDF awards, and a fourth trainee received a one-year renewal. In contrast to the graduate student support program, this program requires postdoctoral fellows to work in CBS R&D laboratories, where they are expected to bring new research skills and directions into these groups. The projects of these senior trainees therefore reflect a closer alignment to the research directions of the host CBS laboratory.

² In 2012-13 CBS also maintained its commitment to a postdoctoral trainee in an external laboratory, who had won a CBS/CIHR Postdoctoral fellowship before that program was closed to new applicants in 2011.
and to either internally or externally funded transfusion science research initiatives. Of the new awards, two related to immunoglobulin mechanism of action and/or replacement and the third to platelet quality. The new trainees joined six who received ongoing CBS support in 2012-13.

**Transfusion Medicine Research Program: Support to Existing Centres Of Transfusion Research Excellence**

As part of its mandate to innovate, invent, and discover information and products that will improve transfusion and transplantation in Canada, CBS R & D makes targeted investments in existing centres of excellence in transfusion and transplantation in its Transfusion Medicine Research Program. In 2012-13, these were the Centre for Blood Research (Vancouver, BC); the McMaster University Transfusion Research Program (Hamilton, ON); and the Ottawa Hospital Research Institute (Ottawa, ON).

**Development Program**

CBS’ development program is a unique network of research laboratories and development centres that support the design and development of new products, processes and instruments for the organization. This Network Centre for Applied Development (netCAD) links basic science and development activities to provide scientific and technical evidence to drive internal change. The primary netCAD development facility, located in Vancouver, is a world-class innovation centre – a “sandbox” – that allows Canadian Blood Services to play with new technology, test new ideas, or translate knowledge from the research bench to the clinic and production environments. To achieve this, netCAD operates as a self-contained blood centre with the same standard operating procedures and equipment for blood collection, testing and distribution used by Canadian Blood Services operations, but with the flexibility to be able to vary any part of the process in a controlled test situation. The netCAD program is unique in that it invites temporary and permanently deferred blood donors to be active participants in the research and development activities at Canadian Blood Services. This keeps blood donors engaged with Canadian Blood Services while they wait out a temporary deferral and builds and maintains relationships with those individuals who are unable to donate at regular clinics. Development centres in Edmonton, Ottawa and Halifax provide critical expertise and resources to support our development efforts. By leveraging these capabilities, the development program is able to support the translation of knowledge to practice - achieving the incremental innovation needed by our internal operations groups, and the breakthrough innovations that will change transfusion medicine and blood banking in the future.

**Supporting Transfusion Medicine Research and Education in Canada**

In 2012-2013, the netCAD clinic in Vancouver provided 2225 blood products and whole blood samples and project support to 36 internal and external research, development and educational initiatives. Working from an active pool of 186 whole blood and 37 apheresis donors who are deferred from regular blood donation, netCAD had a total of 876 appointments booked at 44 whole blood and 51 apheresis clinics. The provision of blood products to more than 29 biomedical research groups across Canada provides them the opportunity to perform world-class research in such areas as immunohematology, blood borne infections, disease pathogenesis, blood cell proteomics, blood preservation, and blood quality characterization, using human blood products that would be very difficult for them to secure without the assistance of Canadian Blood Services. By making blood products available to educational
institutions, the netCAD development program is supporting the next generation of laboratory professionals in their transfusion science and blood bank training.

**Supporting Innovation at Canadian Blood Services**

In 2012-2013, the development program provided scientific and technical leadership on a number of initiatives aimed at improving the safety and quality of our blood products, supporting our business lines and partners and enhancing efficiencies in blood product manufacturing in Canada.

**ACP-215 Cell Processor**

The R&D department has been involved in the assessment of the Haemonetics ACP-215 closed system cell processor as an alternative technology for the preparation of specialized RBC products since 2009. The double wash process developed by R&D in 2011-2012 underwent validation in Q1-Q2 and the data to support the extended storage washing time and the double wash process was submitted to Health Canada for review in February 2013. CBS received approval from Health Canada in May 2013 and will be implementing this new technology in CBS manufacturing sites in Q2 of 2013-2014.

**Evaluation of the Trima for Apheresis Collection of Double RBC units**

Technology is available to collect two apheresis RBC units from a single donor. As part of our evaluation of this technology, the R&D department conducted a pilot study using the Terumo Trima Accel device whereby we measured the quality of the RBC units produced at 5 days and 42 days post-collection. The data collected by the R&D team was used to determine the product specifications and sample size for subsequent validation activities in 2012-2013. Performing a detailed technical evaluation of the apheresis RBC collection processes and the resulting product quality characteristics allowed for the CBS operations groups to determine whether this was a technology that would be beneficial in our supply chain.

**Microbiology Testing Validation of Cord Blood**

Canadian Blood Services has received funding and the mandate to create and manage a national cord blood bank. The purpose of this project was to validate the use of the automated blood culture system (BacT/ALERT 3D Microbial Detection System) to evaluate the microbiological sterility of the banked cord blood units. The development group has lead the evaluation and transfer of this method into the National Cord Blood Bank and will continue to support efforts to ensure that best practices are used in the microbiological testing of cord blood.

**Impact of Room Temperature on Red Blood Cells (RBCs)**

Standards require that RBC products are only held outside of a storage temperature of 1-6 °C for less than 30 min. This measure is taken to preserve component quality and safety. Since 2010, the development group has been collecting important data to support an extension of the time at which products can be held outside of the refrigerator. Results of the development group’s studies were presented to the Canadian Standards Association in November 2012 and received support for an extension of the 30-minute rule of RBCs to 60 minutes. However, the power of the safety (ie, microbiological) studies needed to be improved and therefore additional repetitions of the microbial
work are required. A work plan for the additional study was presented to the 30-minute rule CSA Subcommittee in January 2013 and was unanimously approved. The study will be carried out during fiscal year 2013-2014.

**Follow up Investigations of Positive Bacterial Cultures**

NetCAD receives bacterial cultures and/or blood products for identification and confirmatory purposes. Data obtained from these investigations is used to confirm initial positive results and make decisions about following up with blood donors and recipients. These results are also used to issue reports related to adverse transfusion reactions. In 2012-2013, confirmatory testing of 14 positive results obtained during routine platelet screening and quality control sterility testing of blood components was performed. In addition, 16 blood products associated with contaminated platelet pools obtained either during routine platelet screening or quality control sterility testing were assessed for sterility. The microbiology laboratory at netCAD continues to provide Canadian Blood Services with a unique site for internal investigations carried out by highly skilled personnel.

**Proficiency Testing Program for the BacT/ALERT System**

NetCAD has developed an in-house Sterility Testing Program for CBS. Twice a year, blinded panels of four small platelet bags containing one or two bacteria are prepared at netCAD and are distributed to Production and Quality Control Sites (15 in total) across the country. Results of the testing are analyzed reported to each participant site. Two proficiency testing panels were prepared and distributed in fiscal year 2011-2012.

**Evaluation of Bacterial Detection in Buffy Coat Platelet Concentrates**

Bacterial contamination of platelet concentrates continues to pose the major post-transfusion infectious risk. Early screening cannot capture 100% of contaminated units, therefore, the introduction of a point-of-issue method is one of the alternatives to further decrease transfusion reactions. The development group has evaluated the BacTx® System (Immunectica Inc.) for its efficacy to capture bacterial contamination in buffy coat platelet pools and for its sensitivity to detect bacterial clinical isolates. Results from the study demonstrated that the BacTx® Assay detected all bacterial species at concentrations ≥10^3 CFU/ml. The data was comparable to results obtained in previous studies using leukocyte-reduced apheresis and whole blood random donor platelet units and commercially-available bacterial strains. Therefore, the BacTx® System is a universal point-of-issue method that could be used to further increase the safety of transfusible platelet concentrates. CBS has been invited to present results of this study to the International Society of Blood Transfusion’s Working Party on Transfusion Transmitted Infectious Diseases (June, 2013).

**Evaluation of Co-infusion of Dextrose-containing Solutions with PRBCs**

The R&D department was asked to develop a protocol and collect data that may be used to assist in changing clinical practice for neonatal transfusion. Working with a neonatologist at the Sick Kids hospital, an *in-vitro* study to determine if co-infusion of dextrose solutions with packed red blood cells (PRBCs) in neonatal transfusions impacts the quality of the PRBCs was executed in 2013. This data will be used by our hospital partners to develop an in-vivo study to assess the safety of dextrose-solution co-infusion of RBC products.
**DEHP-Free study**

Plasticizers are added to plastics, such as polyvinyl chloride (PVC), to improve flexibility and durability. Bis (2-ethylhexyl) phthalate (DEHP) is a commonly-used plasticizer in medical devices and is found in blood bags and tubing. DEHP stabilizes red blood cell (RBC) membranes thereby reducing hemolysis levels in stored RBC; however, there is interest in finding alternative plasticizers as DEHP’s potential toxicity is a concern, especially for vulnerable populations such as infants. The development group performed a series of studies evaluating the impact that potential alternative plasticizers have on quality of stored red blood cells. Our work has identified a potential alternative that may be suitable for blood bags used to store red blood cells for use in pediatric transfusions.

**Cryopreservation of Gerbich-negative RBCs**

During routine antenatal testing in November of 2012, a patient was found to have an antibody against the Gerbich blood group system. Due to the low frequency of the Gerbich antigens, the likelihood of finding allogeneic donor units that match this patient was very low; therefore, it would be beneficial to cryopreserve units collected from this patient. Since Gerbich negative phenotypes exhibit changes in the RBC membrane that could affect its structural stability, the consequences of cryopreserving red blood cells (RBCs) from the Gerbich blood system are unknown. The development group developed a method to obtain information on the impact of cryopreservation without using destructive testing methods on rare blood type units. This method allows the RBC units to remain in frozen inventory for transfusion while data is collected to estimate what the quality of the unit will be upon future thawing for transfusion.

**Irradiation Investigation**

RBC units were recalled due to a non-conformance. Rather than being discarded, these units were utilized by the R&D group to investigate the impact of irradiation on RBC quality. RBC units were irradiated at varying ages post-collection and tested throughout post-irradiation storage to evaluate the impact of pre-irradiation age and the length of post-irradiation storage on RBC quality. These data will be used to re-assess policies and procedures for RBC irradiation and guide international discussions on the appropriate criteria for the irradiation of blood products.

**Elimination of Mixing in First Stage Buffy Coat Production**

A 2011-2012 study evaluated a change in our whole blood production method that would save time, lower the risk of repetitive strain injury for our production staff and improve efficiency of our manufacturing process resulting in cost savings for Canadian Blood Services. Our study demonstrated that there was no impact on the quality of RBCs, platelets and plasma product produced using this optimized production method. Over the past year, the development team supported the regulatory submission and review process which was approved by Health Canada in 2012-2013 based on the data obtained from our work. Implementation of this change in production is scheduled for the first half of 2013-2014.
Atlantic Facilities Redevelopment Project

CBS manufacturing facilities in the Atlantic provinces were consolidated at Dartmouth, Nova Scotia, in the spring of 2013. As part of the monitoring of this initiative, inventory data has been collected from consumer sites and is being used by the Development group to conduct a pre/post-test of product availability to ensure that customer service is maintained. The results of this work will be available in 2013-2014.

Age of Red Blood Cells Study

Recently a body of literature has emerged that suggests poorer clinical outcomes with older red cells. Accordingly, there is an interest in limiting the shelf life of red cells to perhaps 21, 14 or even 10 days. However, decreasing the shelf life of red cells is not costless; blood systems are already tightly constrained by increasing demand for product and a limited supply. In this project we evaluated the impact of shorter shelf life for red blood cells on inventory, availability and outdates within an end-to-end supply chain. A simulation methodology was employed to test the impact of shorter red cell shelf life within a geographically distributed network that includes multiple supply points and demand points. The simulation showed that a reduction of shelf life to 21 days could be accomplished with little impact on product availability or outdates rates. Once shelf life drops below 21 days, the impact was observed to be much more significant. The model suggests that flexibility in collections and a robust transport network will be critical if the rated shelf life of red blood cells is decreased below 21 days.

Evaluating Labour Requirements for a Paperless Clinic

When individuals donate blood, extensive records are kept about the donor and the process through a paper-based record of donation (RD). A paperless clinic has been suggested. The objective of this project was to model process flow through clinics to establish cycle times, labour requirements, and staffing for standard clinics using standard engineering methods. Standard industrial engineering methods were used to: map donor flow; estimate station-by-station workloads; and determine the number of workstations required under standard clinic configurations to achieve target throughput. Once completed, the clinic templates were converted into staffing requirements to estimate the total number of personnel required to operate standard clinic models. These were then compared to current staffing levels to estimate overall labour savings when a paperless clinic is adopted. These results were used to support the business case for a paperless clinic.

Re-Evaluating Inventory Levels at Canadian Blood Services

Canadian Blood Services collects, tests, and distributes approximately 850,000 units of red blood cells annually. These units are, or will be, distributed through ten sites, including nine production and distribution facilities and one distribution-only hub. Canadian Blood Services has an established set of inventory targets and thresholds for all of its products, measured in median days demand on hand (DOH). Threshold levels have been established through long experience and, while likely conservative, are simple to follow and well accepted within the organization. However, whether the established thresholds are ideal has not been established. The objective of this project is to revisit inventory policies for distribution sites within the CBS network with the idea of quantifying the risk profile associated with particular inventory levels. A two-phase project is underway. In the first phase, individual distribution hubs will be modelled; in the second phase of the project we will integrate the individual site models
into a network model. Phase I of the project was initiated in 2012-2013 with the development of a generic framework capable of representing a CBS distribution site and its associated consumer hospitals has been constructed and validated. Model instances have been completed for two sites (Calgary and Brampton), which shows that consumer ordering behaviour is the primary driver of outdates, while supplier policies have a greater influence over shortages. At the conclusion of Phase I, an analysis will be completed to determine if a common recommendation for CBS inventory can be adopted or whether it is advantageous to tailor inventory and ordering policies to accommodate specific demand profiles or geographic dispersion of consumer sites. In addition the model will be used to make recommendations for supplier inventory in relationship to consumer holdings.

Quality Monitoring Program (QMP)

The Quality Monitoring Program includes the development of improved quality assurance measurements for blood component manufacturing and a troubleshooting function for day-to-day production issues. In so doing, QMP provides a valuable link between CBS operations and the scientific expertise within CBS. QMP works closely with the NetCAD Development team in support of a variety of initiatives. The following examples are indicative of the type of involvement and support provided by QMP in 2012-13.

Product Shipping

Shipping products from manufacturers to customers in a manner that maintains product safety and quality integrity is an area of intense focus within the cold chain arena. As new technologies are introduced, the ability to provide greater assurance of temperature maintenance across a wide range of environmental conditions for longer periods of time becomes more feasible. This is expected to be an area of ongoing continuous improvement and the quality monitoring program provides expertise for two particular areas related to product shipping. First, QMP contributes to the review of opportunities for improvement generated via non-conforming shipments. This evaluation is critical to understanding the shipping process as an enabler to process improvement. Second, QMP links CBS operations with expertise related to cold chain technologies and other scientific competencies.

QMP Product Testing

The data generated from the testing function of the program has proven invaluable. The quality monitoring program is responsible for the evaluation of CBS manufactured products. The initial application of this information has been to acquire baseline product knowledge and characterize our products in a statistically rigorous manner. This information allows CBS to understand the potential impacts that modifications to the manufacturing process may have on final product quality. It also provides a data set that can be used to assess site-to-site variability in manufacturing practices, both internally as well as among international blood product manufacturers. This product quality set is also used to define product specifications that aid in the validation of new processing steps and procedures.
Contribution to Scientific Body of Knowledge

Outputs from QMP product testing, troubleshooting efforts and continuous improvement initiatives are published in scientifically relevant, peer-reviewed journals where appropriate. This work contributes to the international body of knowledge regarding blood products and enhances Canada’s credibility in this scientific area.

Circular of Information (COI)

The Circular of Information is a regulatory extension of the blood component label. These documents are the equivalent of a product monograph for CBS manufactured products and are the responsibility of the quality monitoring program. QMP data, routine quality control information, product manufacturing expertise, and medical input are all collated to define the product characteristics, indications, contraindications and storage requirements as outlined in the Circular. This expertise is also being leveraged to aid in the development of new circular of information documents for CBS’ new and emerging products. The most recent work focused on the creation of a new Circular of Information for cord blood.

II. KNOWLEDGE MOBILIZATION

Knowledge mobilization has always been an integral part of the activities of the R&D group. However, recognizing the need to enhance the impact of all R&D activities, CBS established over the last year a knowledge mobilization structure with the ultimate goal of advancing patient care and influencing policy and practice. This new strategy will leverage knowledge and facilitate the creation of a network of partners in the domains of transfusion and transplantation. Over the last year the knowledge mobilization activities have been focused on integrating existing activities into efficient and durable programs, as well as on the establishment of new programs. The focus has been on three areas: dissemination of knowledge, education and leading practices, and commercialization.

Dissemination of Knowledge

Our researchers continue to share their expertise by publishing their research findings. Over the last year, they have published 69 peer-reviewed journal articles in prestigious journals such as Blood, Transfusion, and Vox Sanguinis and another 14 have been submitted. We have also contributed to 17 review articles and nine book chapters, as well as 44 other peer-reviewed articles such as letters to editors and commentaries, and published abstracts. Our researchers also assisted CBS operations by providing 26 internal reports in which their research and subject matter expertise was thought to inform product and process improvement. A full list of publications is appended to this report, while copies of the actual articles can be obtained at research.education@blood.ca.

CBS staff made a total of 69 presentations at scientific and educational events at a wide variety of national and international venues. These events included national and international research
conferences, and hospitals, universities and blood centres in Canada, the United States, South America and Asia. The list included both Health Canada and the American National Institutes of Health (NIH) and included rounds at the Hospital for Sick Children in Toronto and grand rounds at Harvard Medical School in Boston.

A new knowledge brokering tool was established to maximize the impact of our research by providing clear research summaries, called ResearchUnits, which are “collected” and “distributed” (based on the analogy to units of blood). Written by Canadian Blood Services researchers in collaboration with the knowledge mobilization team, these ResearchUnit summaries will help to further disseminate research findings, and to explain why they matter, to the larger community in order to enhance knowledge mobilization and facilitate informed decision-making. Three ResearchUnits have been published to date and are accessible via www.transfusionmedicine.ca.

In addition, a national CBS Conference Report program was established during the year to disseminate research findings and facilitate knowledge exchange between research and operations. Last year, the Conference Report program disseminated 168 CBS research abstracts to CBS staff via online resources as well as national Lunch & Learn and Poster Week events. Attendance at our Lunch & Learn events reached a combined 348 CBS participants with representatives from nine provinces. These programs will be further developed over the coming year.

**Education and Leading Practices**

Our knowledge mobilization efforts have also aimed to develop and offer learning opportunities and educational resources. In 2012, our CBS scientists organized an International Symposium focusing on the topic of “Current State of Knowledge for IVIG Use and Mechanism.” Over 160 participants came to Toronto to attend this event which featured International and national speakers. Over the last year, the Symposium was integrated within the activities of the new knowledge mobilization structure. With this integration, the educational component has been optimized by seeking CME accreditation in collaboration with the University of Toronto, Faculty of Medicine, Continuing Education and Professional Development office. This year’s event is scheduled for September 21, 2013 and will focus on the “Utilization of Blood Products: A focus on platelets”, and was organized by a planning committee which brought together the expertise of our CBS medical and scientific staff.

Another knowledge mobilization focus has been the development of clinical guidelines and leading practices. In the last year, the International Collaboration for Guideline Development, Implementation and Evaluation for Transfusion Therapies (ICTMG), a CBS-led effort, completed two systematic reviews which are now informing an evidence-based transfusion medicine guideline regarding platelet transfusion. An international effort is also proceeding in the area of leading practices for risk-based decision making. CBS is leading this effort to create a risk-based decision making framework for blood safety.

In order to continue to advance the knowledge mobilization function, an internal Education Committee was established with scientific, medical, and operational members. One key focus was the updating of
the www.transfusionmedicine.ca website, our primary vehicle for the dissemination of CBS education tools. Another key focus was on updating the Clinical Guide to Transfusion, an online book including 18 chapters written by over 25 transfusion medicine specialists. The Guide is a practical summary of our current knowledge of blood components and transfusion medicine practices for use by health care professionals.

**Intellectual Property and Commercialization**

To meet the ongoing needs of the blood system, our researchers continue to develop a stream of innovations — new tools, technologies, product lines, and services — with significant and demonstrable improvements and changes across the following three areas: patient safety, clinical efficacy, and novel products. Building upon our successful research and development foundation, innovations that are both highly relevant to the mission of Canadian Blood Services and potentially valuable to other blood providers have been selected for intellectual property protection (i.e., patenting). The selected innovations range from near to far term investments in the future of transfusion medicine but are all based on the production of a “product” for use by both CBS and other blood operators.

Our IP portfolio is subdivided into 4 categories comprising: 1) Cellular Therapies and Biologicals; 2) Antibodies, IVIg, and Immune Regulators; 3) Instrumentation and Related Methods; and 4) Clotting, Infectious Agents & Other. A continuously updated Executive Summary of our patent portfolio is available upon request. Highlighted innovations within each of these categories are provided below. In 2012-13, CBS was granted 6 patents from various patent offices (US, Canada, European Patent Office) and 28 validations of granted European patents.

A promising example of our work in the area of cellular therapies and biologicals continues to be the production of “stealth” or immune-camouflaged red blood cells. This innovation is a masking technology which provides a tool for the prevention and treatment of alloimmunization in chronically transfused patients. Continued progress has been made in determining the predictive efficacy of these cells in patients with antibodies to blood group antigens. Key to the clinical use of these cells, CBS has recently filed patents for the manufacturing device necessary to produce clinically compliant stealth red blood cells. Also of interest in this category of the portfolio is the patented process for prevention of bacterial biofilm formation in blood products with a technology known as PEGylation. With respect to antibodies, IVIg and immune regulators, we continue to pursue ground-breaking research on inexpensive alternatives to IVIg (the biggest line item expense in CBS blood product inventories). Successful development of these alternatives would result in very significant (tens of millions of dollars) savings. In the realm of clotting, we continue to pursue improved thrombotic and thrombolytic agents, which are therapeutic agents capable of either enhancing or inhibiting the thrombotic potential of patients. And in our portfolio with respect to infectious agents are enhanced tools for the molecular detection of viral (e.g., Hepatitis C Virus) and bacterial (e.g., Staphylococcus epidermidis) agents in blood products.

In the category of instrumentation and related methods, CBS intellectual property to measure platelet quality is being commercialized in an ongoing partnership with LightIntegra Technologies. The
ThromboLUX is the outgrowth of CBS-owned technology that was initially funded as a basic research grant to a CBS Scientist. LightIntegra’s ThromboLUX instrument is close to approval from both Health Canada and the US Food and Drug Administration (FDA), with the intention of marketing the device in 2013-2014. Implementation of this technology may significantly improve the treatment of thousands of Canadian patients by ensuring they receive quality platelets, thereby preventing secondary complications.

CONCLUSION

This report reflects the progress that Canadian Blood Services has achieved in the last year with respect to both creating and mobilizing relevant knowledge. The outputs and results described in this report are part of CBS’ multifaceted strategy to attain positive immediate, intermediate, and long-term outcomes in transfusion and transplantation in Canada.

For further Information, please contact:

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Ottawa, ON K1G 4J5
Email: dana.devine@blood.ca
APPENDIX I - PUBLICATIONS (2012-2013)

Legend for publications numbers:
- Peer-reviewed Journal Articles [1-69]
- Other Peer-reviewed Articles (e.g., Review articles [70-86], Book Chapters [87-95], published abstracts and others [96-139]
- Technical Reports [140-165]
- Other Non-peer Reviewed Articles [166-168]

Legend for authors: Bold= CBS staff, underlined= non-CBS staff funded researchers.


54. Kim M, Binnington B, Sakac D, Lingwood CA, **Branch DR**. CD4+ T-cells are unable to express the HIV natural resistance factor globotriosylceramide. *AIDS* 2013.


74. Menitove JE, **Leach-Bennett J**, Sher G. Lessons learned from Trypanosoma cruzi test implementation. *Transfusion* 2012, **52**:1849-1851.


77. **Webert KE**. Acquired hemophilia A. *Semin Thromb Hemost* 2012, **38**:735-741.


101. Kanias T, Yazer M, Hildesheim M, Read A, Holovati J, **Acker J, Gladwin MT.** Female Red Cell Donor Units Have Reduced Hemolysis During Routine Storage Related to Red Blood Cell Cytoplasmic Membrane Stability. *Transfusion* 2012,**52**:24A.

102. Tchir JD, Almizraq RJ, Holovati J, **Acker J.** Rejuvenation of ATP During Storage Does Not Reverse Effects of Hypothermic Storage. *Transfusion* 2012,**52**:72A.

103. Hansen A, Turner TR, Tchir JD, Lefresne W, **Jenkins C, J. A.** Transport Conditions of Whole Blood Prior To Leukoreduction and Processing Impacts Quality of RBC Products. *Transfusion* 2012,**52**:75A-76A.


105. **Goldman M, Uzicanin S, Scalia V, O’Brien SF.** Iron Stores in Female Donors Failing Initial Fingerstick Hemoglobin_SNP-93. *Transfusion* 2012,**52**:89A.


107. Hansen A, Turner T, Tchir J, **Jenkins C, Acker J.** Segments from RBC Units Should Not Be Used for Non-destructive Quality Control Testing_SP79. *Transfusion* 2012,**52**:84A.


112. **Branch DR.** Solving the dilemma of prevention of red cell alloimmunization. *Immunotherapy* 2012,4:903-905.

113. Taha M, Greco-Stewart V, Greco C, Brown E, **Ramirez-Arcos S.** Biofilm-Positive Staphylococcus epidermidis is Resistant to Donor Skin Disinfection_S79-030M. *Transfusion* 2012,52:44A.


115. Schubert P, Culibrk B, Goodrich R, **Devin DV.** Changes in the Protein Profiling Triggered by Riboflavin/UV Treatment Using Quantitative Proteomics: Increase in Cytoskeletal Protein Expression_S17-010C. *Transfusion* 2012,52:19A.


117. Li C, Chen P, Lang S, Yougbare I, **Ni H.** Co-stimulation with Lipopolysaccharide or Poly I : C Markedly Enhances the Immune Response Against Platelet Antigens in Murine Models of Fetal and Neonatal Immune Thrombocytopenia_S11-010B. *Transfusion* 2012,52:17A.

118. Schubert P, Culibrk B, **Devin DV.** Dynamics of Signal Transduction Triggered in Platelets by Riboflavin/UV Treatment: Relocalization of GTPases Enhances Platelet Function_S15-010C. *Transfusion* 2012,52:19A.


125. **O’Brien SF**, Scalia V, **Fearon M.** Monitoring Hepatitis B in Blood Donors with HBsAg, Anti-HBc and HBV NAT Testing_S5-010A. *Transfusion* 2012,52:15A.

126. Yu H, Smith N, Zimring J, Crow AR, Suppa SJ, Stowell SR, **Lazarus AH.** Monoclonal antibodies can inhibit alloimmunization to an immunogenic antigen linked to Duffy in mice_S26-020B. *Transfusion* 2012,52:17A.

127. Tessier L, Lapierre D, **Goldman M.** Online Survey of Views on the Deferral Policy for Men who have Sex with Men (MSM)_A7-030C. *Transfusion* 2012,52:233A.


130. Hansen A, Turner T, Tchir J, Lefresne W, **Jenkins C, Acker J.** Transport Conditions of Whole Blood Prior To Leukoreduction and Processing Impacts Quality of RBC Products. *Transfusion* 2012, **52**:75A.


136. Zhurova MIC, **Acker JP**. Use of hemoglobin autofluorescence for determination of red blood cell osmotic parameters. *Biopreservation and Biobanking* 2013, **11**:73.

137. **Branch DR.** Unraveling the IVIG mystique. *Transfusion* 2013, **53**:242-244.

138. Hayward CP, **Webert KE.** Expert approaches to common bleeding and thrombotic problems, part II. *Semin Thromb Hemost* 2013, **39**:113-116.


146. **Ramirez-Arcos S.** The Effects of Room Temperature Exposure on Red Blood Cell Units Phase II. *Internal Report submitted to Dr. Eiad Kahwash, CBS Medical Director Halifax* 2012.


151. **Bigham M.** CBS Blood Donor Eligibility of Transgender/Transexual Donors. *Internal Report presented to DSCWG (Discussion paper)* 2012.


160. **Sheffield W.** Literature review: Updated state of knowledge regarding cryoprecipitate 2009-2012. *Internal Report to David Howe, CBS Product and Hospital Services working group* 2012.


163. **Sheffield W.** Freezing speed of plasma: Review of the biomedical literature and critical analysis. *Internal Report submitted to Wanda LaFresne, CBS Product and Hospital Services* 2013.


167. **Blake J.** How does consolidation of blood production and distribution services impact hospitals? *CBS ResearchUnit published online at transfusionmedicine.ca* 2013.

168. **O’Brien SF.** What is the risk of a transfusion transmitted infection? *CBS ResearchUnit published online at transfusionmedicine.ca* 2013.
## APPENDIX II - FINANCIAL SUMMARY

### R & D FUNDING SUMMARY

**Expenditures - April 1, 2012 to March 31, 2013**

<table>
<thead>
<tr>
<th>Schedule 1 - Overview</th>
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</thead>
<tbody>
<tr>
<td>Other R&amp;D Projects - Operating (Schedule 2)</td>
<td>1,503,202</td>
</tr>
<tr>
<td>R&amp;D Grant Projects - Operating (Schedule 3)</td>
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</tr>
<tr>
<td>CBS Co-Funded Projects - Operating (Schedule 4)</td>
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<tr>
<td>Federally Funded Grants (Schedule 6)</td>
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<td><strong>Total</strong></td>
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<table>
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<tr>
<th>Schedule 2 – Other R &amp; D Projects - Operating</th>
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<tr>
<td>R&amp;D Federal Funds</td>
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<td>Research &amp; Education</td>
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<td>Applied Development Lab</td>
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<td>Legal R&amp;D</td>
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<td>Facilities BC Lab</td>
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<td>Capital Purchases</td>
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<td><strong>Total Other R&amp;D Projects</strong></td>
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<table>
<thead>
<tr>
<th>Schedule 3 – R &amp; D Grant Projects</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Intramural Grant Projects</td>
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<tr>
<td>Small Projects Funds</td>
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<td>Graduate Fellowships</td>
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<tr>
<td>Post Doctoral Fellowships</td>
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<td>Miscellaneous Projects</td>
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<td>Top-ups</td>
<td>151,657</td>
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<td><strong>Total R &amp; D Grant Projects</strong></td>
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<tr>
<th>Schedule 4 - CBS Co-Funded Projects</th>
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<tbody>
<tr>
<td>CIHR Personnel Awards</td>
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<tr>
<td>CIHR Grants</td>
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<tr>
<td><strong>Total CBS Co-funded Projects</strong></td>
<td><strong>$614,322</strong></td>
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### Schedule 6 – Federally Funded Grants

#### 2007-2008 Grant Year

<table>
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<tr>
<th>Organization</th>
<th>Project Description</th>
<th>Investigator</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lady Davis Institute</td>
<td>Chelation, mobilization and metabolism of storage iron</td>
<td>Dr. Ponka</td>
<td>33,170</td>
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<tr>
<td>University of British Columbia</td>
<td>Biomembrane adhesion mechanism</td>
<td>Dr. Brooks</td>
<td>161,588</td>
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<td>University of Laval</td>
<td>Fanconi anemia proteins as regulators of genes involved in hematopoietic stem cell function</td>
<td>Dr. Carreau</td>
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<td>Ottawa Health Research Institute</td>
<td>Strategies for the management of early suspected septic shock</td>
<td>Dr. McIntyre</td>
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<td><strong>Total -2007-2008 Grant Year</strong></td>
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#### 2010-2011 Grant Year - CIHR

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<th>Organization</th>
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<th>Investigator</th>
<th>Amount</th>
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<tr>
<td>McMaster University</td>
<td>Fluid resuscitation in early sepsis: microcirculatory effects on inflammation and coagulation</td>
<td>Dr. Fox-Robichaud</td>
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<td>University of British Columbia</td>
<td>Development of a novel method for the surface engineering of red blood cells</td>
<td>Dr. Kizhakkedaathu</td>
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<td>McMaster University</td>
<td>Canada's blood futures: geography, demographic change, and the supply and demand of blood in Canada</td>
<td>Dr. Paez</td>
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<td>University of British Columbia</td>
<td>Hydrophilic polymer brushes as biocompatible coatings</td>
<td>Dr. Brooks</td>
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<td>Institute de Recherches Cliniques de Montreal</td>
<td>Characterization of regulatory interactions/complex in hemoglobin switching</td>
<td>Dr. Trudel</td>
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#### 2011-2012 Grant Year - CIHR

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<td>University of British Columbia</td>
<td>Nova cell surface engineering</td>
<td>Dr. Chapanian</td>
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<td>St. Michael's Hospital</td>
<td>New Investigator Award</td>
<td>Dr. Shehata</td>
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<td>University of Ottawa</td>
<td>CBS/James Kreppner Fellowship Award</td>
<td>Jennifer Chandler</td>
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<td>St. Michael's Hospital</td>
<td>TRALI Grant</td>
<td>Dr. Semple</td>
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<td><strong>Total - 2011-2012 Grant Year - CIHR</strong></td>
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<td><strong>$ 310,310</strong></td>
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<tr>
<td>Transfusion Medicine Research Programs</td>
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<tr>
<td>-----------------------------------------------------------------</td>
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<tr>
<td>Ottawa Health Research Institute - Infrastructure support for</td>
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<td>transfusion research</td>
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<td>University of British Columbia - Infrastructure support for</td>
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<td>McMaster University - Infrastructure support for</td>
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