

BUILDING ON CANADA'S STRENGTHS IN REGENERATIVE MEDICINE

Workshop Report



Council of Canadian Academies
Conseil des académies canadiennes

Science Advice in the Public Interest

BUILDING ON CANADA'S STRENGTHS IN REGENERATIVE MEDICINE

Workshop Report

THE COUNCIL OF CANADIAN ACADEMIES

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Notice: The project that is the subject of this report was undertaken with the approval of the Board of Governors of the Council of Canadian Academies (CCA). Board members are drawn from the Royal Society of Canada (RSC), the Canadian Academy of Engineering (CAE), and the Canadian Academy of Health Sciences (CAHS), as well as from the general public. The Steering Committee and workshop participants responsible for the report were selected by the CCA for their special competencies and with regard for appropriate balance.

This workshop report was prepared for the Government of Canada in response to a request from the Minister of Innovation, Science and Economic Development Canada. Any opinions, findings, or conclusions expressed in this publication are those of the authors, the Steering Committee of the Workshop on the Opportunities and Challenges for Regenerative Medicine in Canada and do not necessarily represent the views of their organizations of affiliation or employment, or the sponsoring organization, Innovation, Science and Economic Development Canada.

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The Council of Canadian Academies

Science Advice in the Public Interest

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Participants in the Workshop on the Opportunities and Challenges for Regenerative Medicine in Canada

Under the guidance of its Scientific Advisory Committee, Board of Governors, and Member Academies, the CCA assembled the Workshop Steering Committee to lead the design of the workshop, complete the necessary background research, and develop the workshop report. The Steering Committee directed the CCA in identifying the experts who participated in the workshop. Each expert was selected for his or her expertise, experience, and demonstrated leadership in fields relevant to this project.

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Message from the Chair and Acknowledgements

The increasing demand for health services is challenging healthcare systems in Canada and abroad, as medical professionals strive to provide excellent care to all patients. Regenerative medicine has the potential to transform healthcare and improve patient outcomes, by providing therapies that treat the causes of conditions and diseases, repairing damaged tissues and organs themselves. In the near future, regenerative medicine therapies may cure several chronic diseases that negatively impact the lives of many Canadians. Canada has long been a leader within the regenerative medicine field, and it has an opportunity to remain at the forefront of translating stem cell research discoveries to real-world treatment options.

Recognition of the importance and potential of regenerative medicine led to the workshop summarized in this report. The charge that guided workshop discussions challenged the participants to examine the strengths of regenerative medicine in Canada, and to identify opportunities that will allow Canada to further excel in the field internationally. The workshop brought together Canadian and international experts with knowledge of the multiple dimensions of the regenerative medicine pipeline, including the scientific challenges associated with early stage and translational research, as well as ethical, legal, economic, and social issues. Despite the range of experiences and viewpoints,

workshop participants reached agreement on Canada's top strengths and weaknesses, and were able to identify several short- and long-term opportunities to drive the field forward. Ultimately expert participants were optimistic that the regenerative medicine community in Canada has the necessary components to foster greater success in the future.

I would like to thank the Council of Canadian Academies for bringing together the range of expertise present at the workshop, including views from academia, medicine, funding agencies, industry, and a patient advocate. The workshop discussions certainly benefited from the diversity of viewpoints. My personal thanks also to the other members of the Steering Committee who donated their time and expertise to plan the workshop and ensure this summary report was both accurate and compelling. A special thank you to Tania Bubela (Steering Committee Member) for leading the bibliometric analyses associated with this report. Additionally, I would like to extend my thanks to all workshop participants for sharing their experiences and engaging in active debate over the course of the workshop. Finally, on behalf of the Steering Committee, I would like to express our sincere thanks to the staff members at the Council of Canadian Academies for their excellent job in translating the discussions into this report.



Dr. Janet Rossant, C.C., PhD, FRS, FRSC,

Chair, Steering Committee of the Workshop on the Opportunities and Challenges for Regenerative Medicine in Canada

Message from the CCA President and CEO

The tremendous potential of regenerative medicine to treat previously incurable chronic diseases and genetic disorders emerged with the discovery of stem cells by Canadian researchers Drs. James Till and Ernest McCulloch in the early 1960s. Since then, significant advancements by other Canadian researchers have followed from the bench to the bedside. Canada is recognized the world over for its excellence in this area.

Seeking to better understand the current state of the science of regenerative medicine, Innovation, Science and Economic Development Canada and Health Canada asked the Council of Canadian Academies (CCA) to undertake an expert panel workshop. We assembled a steering committee, chaired by one of the world's foremost stem cell scientists, Dr. Janet Rossant, C.C., FRSC, to prepare for and lead a two-day workshop on October 13 and 14, 2016. Dr. Rossant, along with Dr. Tania Bubela; Dr. Allen Eaves, O.B.C.; and Dr. Michael Rudnicki, O.C., FRSC, brought together 18 experts to review the published literature and related evidence, and dig deep into what we know about this exciting field.

The resulting report, *Building on Canada's Strengths in Regenerative Medicine*, is more than a set of workshop proceedings. It is an insightful, high-quality, independent

study that examines the available evidence and takes stock of the field. It brings together perspectives from academia, medicine, funding agencies, industry, and patient advocacy. These experts shared their knowledge about the regenerative medicine pipeline, including the scientific challenges associated with early-stage and translational research, as well as ethical, legal, economic, and social issues. We hope their final report will contribute to the policy discussion in Canada and identify those areas holding the greatest opportunities for success in this field.

I would like to thank Dr. Rossant, her fellow steering committee members, and the workshop participants for their efforts to bring this project through to completion. Our Board of Governors, Scientific Advisory Committee, and the CCA's three founding Member Academies — the Royal Society of Canada, the Canadian Academy of Engineering, and the Canadian Academy of Health Sciences — provided key guidance and input throughout the entire assessment process.

Finally, I would like to thank the Minister of Science who, on behalf of Innovation, Science and Economic Development Canada, and with support from the Minister of Health, referred this project to the CCA.



Eric M. Meslin, PhD, FCAHS
President and CEO, Council of Canadian Academies

Report Review

This report was reviewed in draft form by the individuals listed below — a group of reviewers selected by the CCA for their diverse perspectives, areas of expertise, and broad representation of academic, industrial, policy, and non-governmental organizations.

The reviewers assessed the objectivity and quality of the report. Their submissions — which will remain confidential — were considered in full by the Steering Committee, and many of their suggestions were incorporated into the report. They were not asked to endorse the conclusions, nor did they see the final draft of the report before its release. Responsibility for the final content of this report rests entirely with the authoring Steering Committee and the CCA.

The CCA wishes to thank the following individuals for their review of this report:

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The report review procedure was monitored on behalf of the CCA's Board of Governors and Scientific Advisory Committee by **Stuart MacLeod, FCAHS**, Professor of Pediatrics (Emeritus), University of British Columbia and Adjunct Professor, Community Health and Epidemiology, Dalhousie University. The role of the report review monitor is to ensure that the Steering Committee give full and fair consideration to the submissions of the report reviewers. The Board of the CCA authorizes public release of a report only after the report review monitor confirms that the CCA's report review requirements have been satisfied. The CCA thanks Dr. MacLeod for his diligent contribution as report review monitor.

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Key findings

1. Canada-based researchers are recognized scientific leaders in regenerative medicine, as illustrated by the high quality and collaborative culture of regenerative medicine research in Canada.

Discovery research in regenerative medicine is a historic and current Canadian strength. Since the discovery of stem cells in the early 1960s by Drs. Till and McCulloch, Canada has produced many researchers who have made significant discoveries in the regenerative medicine field. These discoveries were born of long-standing strengths in stem cell biology, but Canadian research output is also growing in clinical stem cell research, drug discovery research, cell and tissue engineering, and specific medical fields including cardiovascular/circulatory, nervous, and musculoskeletal systems.

Regenerative medicine is multidisciplinary, and is enhanced by the collaborative culture fostered in Canada. This culture can be directly tied to the Networks of Centres of Excellence (NCE) program that has successfully funded national collaborative networks. These include the Stem Cell Network (SCN), the Centre for Commercialization of Regenerative Medicine (CCRM), and the Regenerative Medicine and Cell Therapy Network (CellCAN). The collaborative culture is also linked to important provincially funded networks such as the ThéCell Network (Quebec) and the Ontario Institute for Regenerative Medicine (OIRM). The long history of strong and collaborative research and innovation in the Canadian regenerative medicine field continues to attract international research talent in this area. However, the field would benefit from continued and enhanced coordination between all of the key stakeholders in the regenerative medicine community. These include researchers in multiple disciplines, funders, federal and provincial regulators, healthcare reimbursement agencies, advocacy organizations, and the patients who could benefit from future regenerative medicine therapies. The Workshop on Opportunities and Challenges for Regenerative Medicine in Canada laid the foundation for improved coordination, and discussions among a range of stakeholders have already begun.

2. Research in regenerative medicine in Canada is strong, and ongoing success will require stable and strategic investment in researchers, collaborative networks, and infrastructure.

Ongoing success in the translation of stem cell discoveries into improved health outcomes requires continued stable funding at all stages in the pipeline. There is an opportunity to develop a clear, long-term funding strategy that would provide stability for key national initiatives that support and encourage R&D across the country, such as SCN, CellCAN, CDRD, and CCRM, enabling them to focus on innovation and long-term planning. This strategy should also include the input of other important stakeholder groups in the regenerative medicine community, such as provincial health funders, clinicians and healthcare practitioners, advocate organizations, and health charities. Canada also has an opportunity to support the development of people with the right skills to ensure continued success. The Canadian university system excels at the technical training of highly qualified personnel (HQP), but cross-training will be essential for the future development of human capital with a wide range of skills.

3. There is an opportunity for Canada to accelerate the translation of stem cell research discoveries to bedside and industry.

Because there now exist so many promising therapies in development in Canada and abroad, funding opportunities that target the entire regenerative medicine pipeline are appropriate and warranted. Major investors are now seeing Canada as a place to invest in the regenerative medicine arena, based on Canada's science strengths and collaborative community. However, the translation and commercialization of regenerative medicines are challenging due to the highly personalized nature of regenerative medicine therapies, which makes the process both costly and time-intensive. Furthermore, as in other Canadian innovation sectors, there is a shortage of venture capital and angel investment, creating a "valley of death" when translating research innovation into therapies. Targeted programs and incentives may help support the growing regenerative medicine industry to become a leading health-related biotech cluster in Canada and the world.

4. Continued and greater success in regenerative medicine involve regulatory and reimbursement coordination and engagement with the public.

Greater coordination between regulators (who make decisions about safety and efficacy at the federal level) and reimbursers (who make decisions about what therapies to pay for at the provincial level) could benefit the whole regenerative medicine community and also help ensure all Canadians have equal access to safe and effective therapies. Moreover, coordinating efforts to ensure that the public — and patients who will benefit the most from these therapies — is informed of potential benefits, as well as the challenges that need to be overcome, could boost public buy-in. This type of public engagement would have additional benefits, allowing health charities and patient groups to inform and improve the research process while also supporting participation in clinical trials and the donation of needed biological materials.

5. Regenerative medicine therapies have the potential to transform Canadian healthcare systems, improving patient outcomes and the efficiency of these systems as a whole. Furthermore, developing and manufacturing these therapies in Canada could build a strong regenerative medicine industry, which would provide jobs for highly qualified personnel and support the Canadian economy.

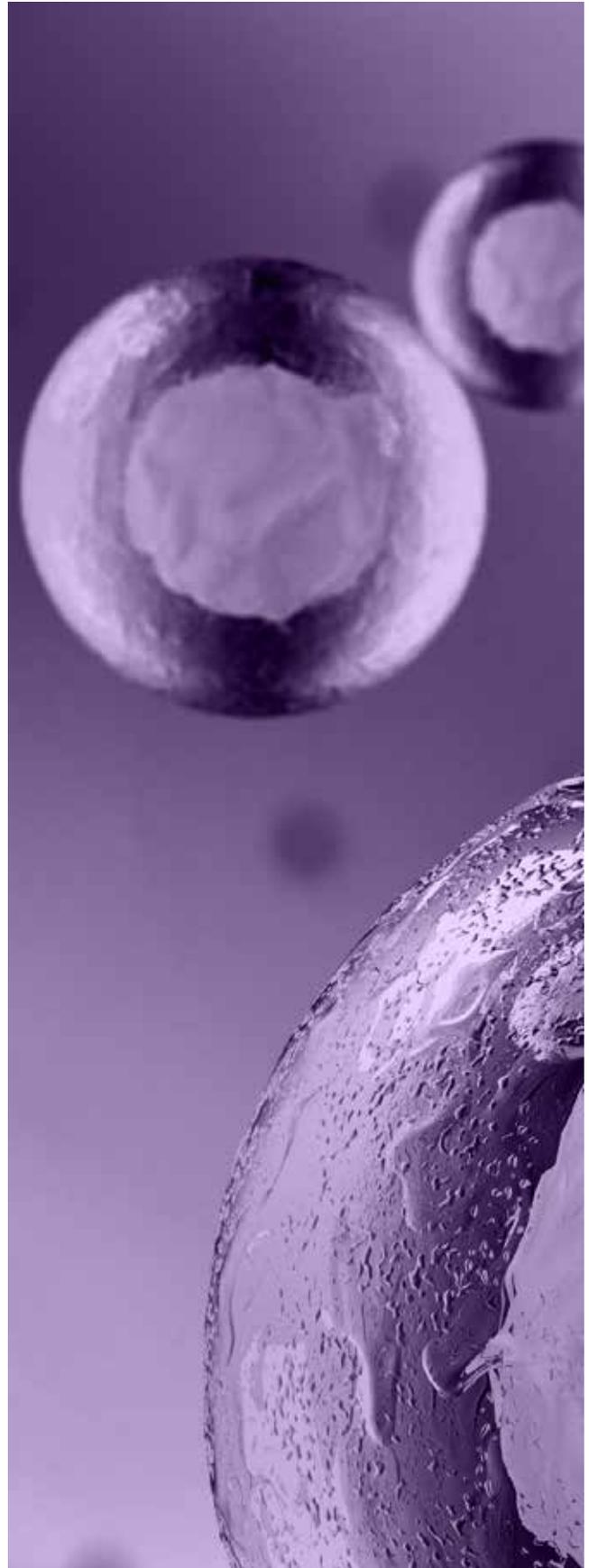
The transformation of healthcare systems through regenerative medicine therapies represents an opportunity to treat and cure disease, improve the sustainability of healthcare, and create new skilled jobs and economic opportunity in Canada. From a health perspective, regenerative medicine therapies may significantly improve patient quality of life, changing the trajectories of diseases and curing chronic and degenerative conditions that currently affect a significant proportion of Canada's population. From an economic perspective, effective regenerative medicine therapies that provide curative options may greatly reduce healthcare and medication costs. Additionally, there are economic benefits to having infrastructure present in Canada that provides materials to support the global regenerative medicine market. The success of Canadian regenerative medicine companies, and the recent US\$225 million investment by Bayer AG and venture capital firm Versant Ventures to develop BlueRock Therapeutics in Toronto, illustrate the economic benefits stemming from a strong Canadian regenerative medicine community.

List of Abbreviations and Acronyms Used in the Report

BMT	Bone and Marrow Transplants
C3i	Centre for Commercialization of Cancer Immunotherapy
CADTH	Canadian Agency for Drugs and Technologies in Health
CBMTG	Canadian Blood and Marrow Transplant Group
CCRM	Centre for Commercialization of Regenerative Medicine
CDRD	Centre for Drug Research and Development
CECR	Centres of Excellence for Commercialization and Research
CellCAN	Regenerative Medicine and Cell Therapy Network
CIHR	Canadian Institutes of Health Research
CIRM	California Institute for Regenerative Medicine
CÚRAM	Centre for Research in Medical Devices
ELSI	Ethical, Legal, and Social Implications
FDA	Food and Drug Administration
FRQS	Fonds de recherche du Québec — Santé
GMP	Good Manufacturing Practice
HQP	Highly Qualified Personnel
iPS	Induced Pluripotent Stem (cells)
IRICoR	Institute for Research in Immunology and Cancer – Commercialization of Research
ISCF	International Stem Cell Forum
ISSCR	International Society for Stem Cell Research
NCE	Networks of Centres of Excellence
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NHS	National Health Service
OIRM	Ontario Institute for Regenerative Medicine
RMEG	Regenerative Medicine Expert Group
SBIR	Small Business Innovation Research
SCN	Stem Cell Network
SFI	Science Foundation Ireland
STTR	Small Business Technology Transfer
ThéCell	Cell and Tissue Therapy Network

Table of Contents

1	Introduction.....	1
1.1	Charge to Workshop Participants	4
1.1.1	Interpreting the Charge.....	5
1.1.2	Workshop Methodology.....	6
1.2	Organization of the Report.....	6
2	Canadian Strengths and Weaknesses in Regenerative Medicine	7
2.1	Strengths in Regenerative Medicine	8
2.2	Weaknesses in Regenerative Medicine.....	14
2.3	Conclusions.....	20
3	Opportunities to Achieve Success in Regenerative Medicine in Canada	21
3.1	Opportunities.....	22
3.1.1	Development and Translation Opportunities: Short-Term (1 to 2 years)	22
3.1.2	Development and Translation Opportunities: Longer-Term (3 to 5 years)	24
3.1.3	Enablement and Adoption Opportunities: Short-Term (1 to 2 years)	26
3.1.4	Enablement and Adoption Opportunities: Longer-Term (3 to 5 years)	27
3.2	Conclusions.....	28
4	Conclusions	29
	References	31
	Appendix A – Bibliometric Analysis	39



1

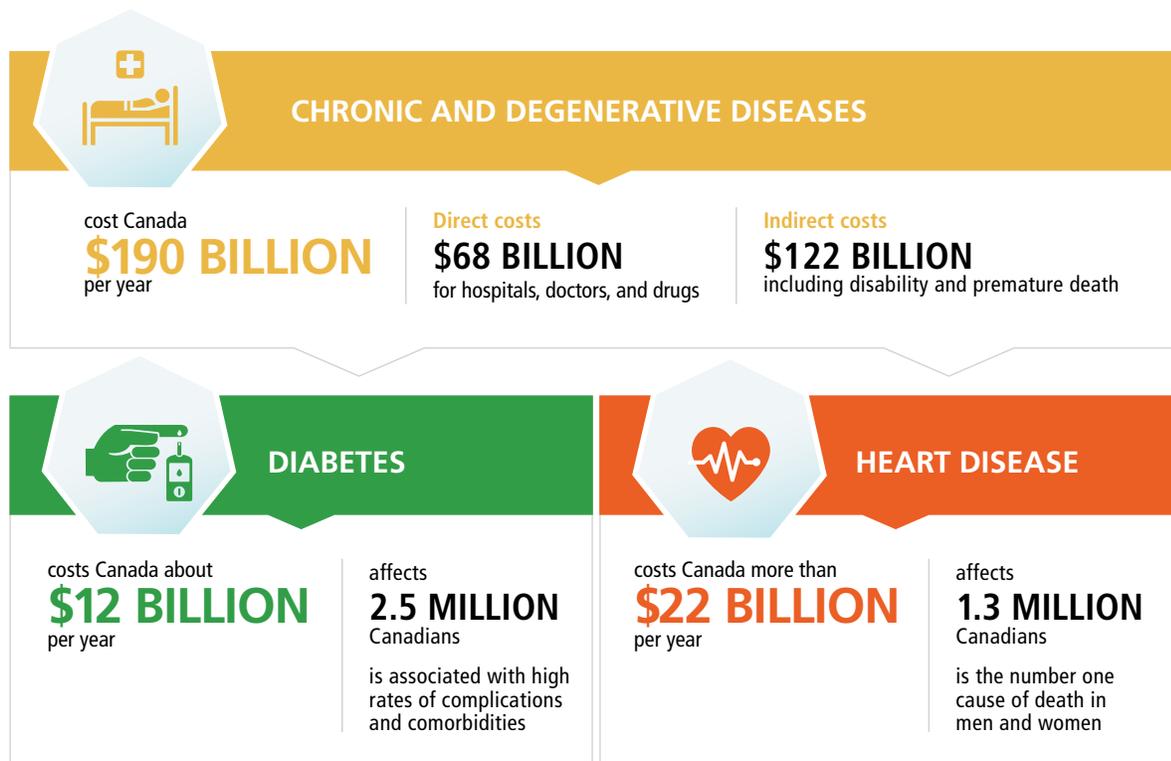
Introduction

- **Charge to Workshop Participants**
- **Organization of the Report**

1 Introduction

Many therapies manage the symptoms of a disease or condition but fail to treat its underlying causes. The appeal of regenerative medicine lies in its curative approach, which involves treating the causes of a range of conditions by targeting the repair of damaged tissues or organs themselves. This could transform healthcare, since chronic diseases are currently responsible for approximately 67% of total Canadian healthcare costs (SCN, 2016f), with \$190 billion annually relating to both direct and indirect costs associated with healthcare (Elmslie, 2012) (Figure 1.1). Regenerative medicine will treat, or even cure, chronic conditions such as Parkinson's disease, multiple sclerosis, diabetes, heart disease, and spinal cord injury, to name only a few (MaRS, 2009; MRC, 2016), and rare diseases such as Stiff Person Syndrome (Sanders *et al.*, 2014); it could also treat genetic disorders like sickle cell anemia or immunodeficiency diseases, possibly even before birth (UCSF, 2013). These conditions all involve cells that are malfunctioning due to slow deterioration, sudden injury, or genetic defects. Using stem cells and their derivatives to restore normal function is at the core of regenerative medicine (MRC, 2016).

Canadian scientists Drs. James Till and Ernest McCulloch first demonstrated the existence of (hematopoietic) stem cells in the 1960s (Becker *et al.*, 1963), paving the way for future generations of Canadian scientists, who carry on their legacy (Figure 1.2). Today Canada is recognized as a global leader in regenerative medicine (KPMG, 2014). Canada currently has more than 400 stem cell scientists working on a range of conditions at 68 centres housed within or affiliated with 25 Canadian universities (NCE, 2014). In 2001, several of those scientists helped form the Stem Cell Network (SCN) (NCE, 2014), hosted by the Ottawa Hospital and the University of Ottawa (NCE, 2016b) and currently receiving funding until 2018 from the Government of Canada (SCN, 2016d). Along with the SCN and several other Network Centres of Excellence (NCE) funded organizations (e.g., Centre for Commercialization of Regenerative Medicine (CCRM), Regenerative Medicine and Cell Therapy Network (CellCAN)) (KPMG, 2014), Canada is also home to provincial networks (e.g., Ontario Institute for Regenerative Medicine (OIRM), ThéCell Network), active health charities, and a national advocacy organization (Canadian Stem Cell Foundation).



Source: CDA, 2011; PHAC, 2009; Elmslie, 2012

Figure 1.1

Economic Burden of Disease

Canadian healthcare systems have large expenditures to treat chronic and degenerative diseases. These include direct costs for hospitals, doctors, and medications, as well as indirect costs such as those associated with disability and premature death. Stem cell therapies have the potential to revolutionize how healthcare systems treat these diseases.

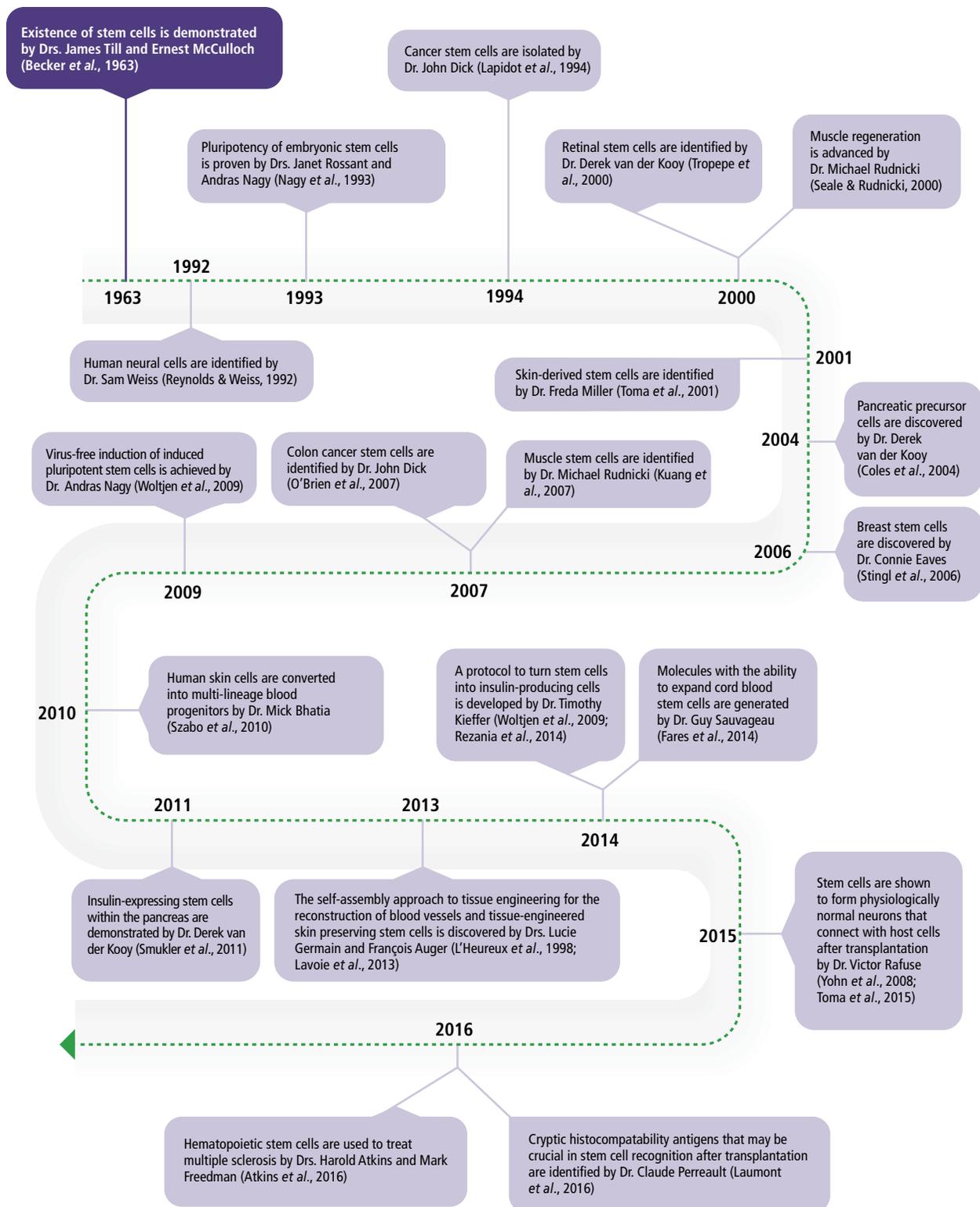


Figure 1.2
Major Canadian Discoveries in Stem Cell Science

In addition to its successful networks, Canada has developed a range of infrastructure to support regenerative medicine research and development (R&D). This includes successful commercial companies that produce inputs needed for research (e.g., STEMCELL Technologies Inc, Tissue Regeneration Therapeutics Inc.), cord blood, stem cell line and tissue banks, and seven large cell therapy manufacturing centres spread across the country (CellCAN, 2016a) (Table 2.2). Researchers in Canada are also active in stem cell governance and policy, both nationally and internationally, working with organizations such as the International Stem Cell Forum (ISCF) and the International Society for Stem Cell Research (ISSCR) (ISCF, 2015b; ISSCR, 2016).

The federal government has demonstrated support for the regenerative medicine community through recent investments. These include \$114 million for a regenerative medicine research initiative, Medicine by Design, at the University of Toronto, awarded in the first round of funding of the Canada First Research Excellence Fund (GC, 2015). The Medicine by Design initiative, its commercial arm CCRM, and the provincial institute OIRM expect to move into an open concept lab space at Toronto's MaRS Discovery District in the near future, providing new opportunities for collaboration (U of T, 2015a, 2015b). Additional funding was announced in early 2016, with the federal government and GE Healthcare each pledging \$20 million to CCRM to establish and operate a new Centre for Advanced Therapeutic Cell Technologies (U of T, 2016). Prime Minister Justin Trudeau noted that this new centre will "use a collaborative approach between research institutions and industry to solve cell therapy manufacturing challenges" (GC, 2016a). The most recent regenerative medicine funding announcement was in November 2016, when SCN, with the support of the Minister of Science, announced funding of \$9 million for regenerative medicine research, which was made available due to a 2016 federal budget commitment of \$12 million over two years to further the work of SCN (SCN, 2016a). Provincial governments are also supporting regenerative medicine initiatives; the Government of Ontario established OIRM in 2014 with \$3 million in provincial funds (OIRM, 2016b), and ThéCell is financed by Fonds de recherche du Québec – Santé (ThéCell, 2016a). International companies are also investing in Canadian regenerative medicine: in December 2016, drug manufacturer Bayer AG and venture capital firm Versant Ventures together announced a US\$225 million investment to develop a stem cell research company in Toronto, BlueRock Therapeutics (Bayer, 2016).

Despite these investments, leading experts in the stem cell field have stated that Canada's funding, in terms of total dollars, has failed to keep pace with that of competitor countries, including the United States (California in particular), the United Kingdom, Japan, South Korea, and Singapore (Quigley, 2016). A closer examination of international funding programs reveals several leading nations in regenerative medicine have recently made significant investments in stem cell research and industry (KPMG, 2014) (Table 1.1). Consequently, there is concern within the regenerative medicine community about Canada's position as a major international player in the field (BioPharma, 2012; Quigley, 2016). This is a critical moment to assess the state of regenerative medicine in Canada and the best ways to further support and encourage R&D in the field.

1.1 CHARGE TO WORKSHOP PARTICIPANTS

Taking stock of the regenerative medicine field involves identifying the key areas that hold the greatest opportunities for Canada, and examining the challenges that must be addressed so researchers can take advantage of these opportunities. To this end, Innovation, Science and Economic Development Canada (ISED), supported by Health Canada, asked the Council of Canadian Academies (CCA) in August 2016 to undertake a workshop assessment on the opportunities and challenges for regenerative medicine in Canada. ISED submitted the following questions:

- *What are Canada's strengths in regenerative medicine (and why are they strengths)? Consider the following categories: basic research, development of cell-based regenerative therapies, drug, device, and technology development, translation of therapies to the clinic, human resources and capital, collaboration/networks, regulatory/ethics environment, funding environment/resource allocation.*
- *Given these strengths, what are the opportunities that exist and barriers that must be overcome for Canada to ensure that it can excel at regenerative medicine in the international arena?*

To address these questions, the CCA assembled a four-person steering committee, chaired by Dr. Janet Rossant, C.C., FRSC, to prepare for and lead a two-day workshop session on October 13 and 14, 2016. The workshop brought together the Steering Committee with another 18 Canadian and international experts from academia, medicine, funding agencies, industry, and a patient advocate. Workshop participants brought knowledge of the multiple dimensions of the regenerative medicine pipeline, including the scientific challenges associated with early-stage and translational research, as well as ethical, legal, economic, and social issues.

Table 1.1
Funding for Stem Cell Research and Industry in Other Leading Nations

Country	Key Funding Developments
United States	<p>There is no federal stem cell strategy in place in the United States, but many states have made significant investments (KPMG, 2014):</p> <ul style="list-style-type: none"> • California has committed US\$3 billion to stem cell research and therapeutic development over 10 years (MaRS, 2009; CIRM, 2016). • New York has committed US\$550 million of public funds over 11 years for stem cell research (Fallik, 2012). • Maryland has committed US\$100 million over five years for stem cell research (Fallik, 2012).
United Kingdom	<ul style="list-style-type: none"> • In 2010, six research councils invested approximately £73 million into the regenerative medicine portfolio (MRC <i>et al.</i>, 2012). • In 2012, a further £70 million was invested in the U.K. Cell and Gene Therapy Catapult Centre over five years (Thompson & Foster, 2013).
Japan	<ul style="list-style-type: none"> • The government has committed US\$1 billion to iPS cell research (Matsuyama & Wainer, 2013). • In 2014, the government passed legislation to provide a framework for accelerated approval of stem cell products and reimbursement (Cyranski, 2013; Sipp, 2015).
South Korea	<ul style="list-style-type: none"> • In 2012, the government spent US\$88 million to support stem cell research. • The government is expected to expand support for clinical research to speed up commercialization (Park, 2012).
China	<ul style="list-style-type: none"> • The government dedicated US\$500 million in federal funding to stem cell research over five years (Yuan <i>et al.</i>, 2012).
Germany	<p>There is no stem cell strategy in place in Germany, but there have been many significant investments:</p> <ul style="list-style-type: none"> • From 2005–2009 the government spent €30 million on cell-based therapy initiatives. • From 2008–2012 the government spent €9 million on stem cell initiatives. • The government has also funded a number of translational centres and research “clusters of excellence” (BIS & DH, 2011).
Israel	<p>There is no dedicated public funding policy in place in Israel (MaRS, 2009), but there have been significant investments:</p> <ul style="list-style-type: none"> • In 2009, US\$3.3–15 million was invested to support regenerative medicine by the national government (MaRS, 2009).

To provide further insight into the regenerative medicine pipeline in Canada, a bibliometric analysis of stem cell research and the sub-disciplines of drug discovery related to or using stem cells, cell and tissue engineering, and regenerative medicine was also performed. The focus of the bibliometric analysis was on the research stage of regenerative medicine; papers related to stem cell policy were not included due to differential citation patterns. Therefore, this analysis does not directly apply to the implementation of regenerative medicine therapeutics.

1.1.1 Interpreting the Charge

Regenerative medicine can be defined simply as that which “replaces or regenerates human cells, tissue or organs, to restore or establish normal function” (Mason & Dunnill, 2008). Stem cells, of which there are multiple types (Box 1.1), are at the core of regenerative medicine (MRC, 2016). More comprehensive definitions of regenerative medicine, such as that of the U.S. National Institutes of Health (NIH), also include tissue engineering, biomaterials, and cellular therapeutics (stem cell-based therapies) under the umbrella of regenerative medicine (MaRS, 2009). Beyond scientific and engineering issues, regenerative medicine is influenced by a range of other relevant factors, including the ethics, regulation, public perception, and economics of stem cell research and related therapies. Some researchers expand the scope of regenerative medicine to include gene editing and gene therapy, but this report does not include these fields.

Box 1.1 Types of Stem Cells

Stem cells can be differentiated into a number of types:

Pluripotent stem cells can differentiate into all cell types present in the body, giving them remarkable flexibility (Mason & Dunnill, 2008; BioPharma, 2012; MRC, 2016). They are derived either from embryos (called embryonic stem cells) or from adult stem cells that have been reprogrammed (or induced) to enter an embryonic stem cell-like state (called induced pluripotent stem or iPS cells) (BioPharma, 2012).

Adult stem cells (also called tissue-specific stem cells) can only mature into cells present in one tissue type (BioPharma, 2012). For example, hematopoietic stem cells can become any type of blood cell, such as a lymphocyte or an erythrocyte.

Early stem cell research raised sensitive ethical issues, especially because embryonic or fetal tissues were the only available sources of pluripotent stem cells. While new technologies that enable the generation of iPS cells from adult cell sources address some ethical concerns, they also create a new set of ethical and legal issues that are still being researched and debated in the field of regenerative medicine.

The Steering Committee and workshop participants highlighted the importance of considering the entire regenerative medicine pipeline in Canada. This pipeline includes both early-stage R&D and translational research, which involves transforming discovery and knowledge acquired from fundamental science to its application in clinical, community, and industry settings (UCSD, 2016). Additionally, participants emphasized that issues and challenges related to commercialization, knowledge mobilization, and infrastructure impact Canada's success in regenerative medicine.

1.1.2 Workshop Methodology

The workshop used the Group Decision Support System (GDSS) (Gray, 1987) platform and a facilitator to guide discussions. Workshop participants arranged themselves at small group tables (4 to 5 people) and worked with these groups during brainstorming sessions. The process used to facilitate the four main discussions (strengths, weaknesses, opportunities related to development and translation, and opportunities related to enablement and adoption) was similar. First, in small table discussions, participants brainstormed and identified a long list of ideas. Each table then narrowed their list to those they felt were particularly important (for example, the top three Canadian strengths). All participants then engaged in a plenary discussion, where the top ideas from each small group were considered, and like ideas were grouped together where appropriate. All opportunities listed in Chapter 3 of this report were generated during this step in the workshop and were not condensed further or ranked. The selection of identified strengths (Section 2.1) and weaknesses (Section 2.2) listed in this report involved an additional facilitation step, whereby each participant selected *only* five strengths (or five weaknesses) from the larger group list, based on the criterion of greatest potential for impact. Thus, the facilitation process examined dozens of

individual strengths (or weaknesses) and narrowed them down into key ideas, forcing participants to identify those strengths (or weaknesses) they felt were the most significant. In short, participants could not vote for all options even if they felt all strengths (or weaknesses) were relevant. It is important to emphasize that the facilitation process was not a consensus exercise but did enable the views of all participants to be considered.

1.2 ORGANIZATION OF THE REPORT

The key messages and themes of this report are informed primarily through the discussions that took place at the workshop meeting. A summary of these discussions as they relate to Canada's strengths and weaknesses in regenerative medicine is given in Chapter 2, supported by relevant information identified through a literature review and bibliometric analysis. Chapter 3 presents the workshop participants' vision of success for regenerative medicine in Canada, and discusses opportunities they identified to achieve this vision, supported through a literature review. Targeted areas of regenerative medicine where Canada has the opportunity to lead globally are not identified, as participants felt that a two-day workshop did not present enough time to adequately carry out this type of analysis. The literature review was primarily informed by a limited number of publicly available reports on regenerative medicine in Canada (see MaRS, 2009; BioPharma, 2012; CIHR, 2013; KPMG, 2014; CCRM, 2016b), as there are data gaps in this field, especially relating to future commercial and economic projections. While references and examples are used to support the participants' views where possible, some ideas are drawn solely from their expertise. Additional results from the bibliometric analysis are provided in the Appendix A. Additionally, a number of health charities were given the opportunity to provide feedback on the report in draft form. The feedback received was considered at the same time as peer review comments.

2

Canadian Strengths and Weaknesses in Regenerative Medicine

- **Strengths in Regenerative Medicine**
- **Weaknesses in Regenerative Medicine**
- **Conclusions**

2 Canadian Strengths and Weaknesses in Regenerative Medicine

During the workshop, participants brainstormed in small groups and identified what they felt were Canada's greatest strengths and most significant weaknesses in regenerative medicine. The results of the workshop deliberations are discussed below, supported by a literature review and bibliometric analysis.

2.1 STRENGTHS IN REGENERATIVE MEDICINE

There was general consensus among workshop participants about Canada's greatest strengths, with the majority of participants identifying a collaborative culture, recognized scientific leadership in regenerative medicine, and provincial healthcare systems as the top three strengths. Five other strengths were also selected as a top strength by more than one participant. All eight strengths are discussed below.

Collaborative culture

The collaborative culture of the regenerative medicine community, across institutions, disciplines, and borders, was identified as a top Canadian strength. Regenerative medicine is a multidisciplinary field that is enhanced by collaboration, and Canada is succeeding at fostering this type of culture. In the opinion of workshop participants, this strength can be directly tied to national networks such as the SCN, CCRM, and CellCAN (funded by the NCE program), as well as provincially funded networks including ThéCell and OIRM. Additional networks and infrastructure that fund and support regenerative medicine in Canada include the Canadian Institutes of Health Research (CIHR), the Centre for Drug Research and Development (CDRD), the National Public Cord Blood Bank, the Canadian National Transplant Research Program, and the Institute for Research in Immunology and Cancer – Commercialization of Research (IRICoR). See Table 2.1 for additional details on the range of Canadian networks and infrastructure. Canadian organizations also collaborate with comparable organizations in other countries; for example, CCRM and Cell and Gene Therapy Catapult (U.K.) have a collaboration agreement to work together to support the development and commercialization of cell therapy (Cell and Gene Therapy Catapult, n.d.-b).

The collaborative and multidisciplinary nature of the regenerative medicine community in Canada has been highlighted in other studies (BioPharma, 2012; CIHR, 2013; KPMG, 2014). The bibliometric analysis on stem cell research undertaken to strengthen this report supports this observation; between 2000 and 2014, researchers in Canada co-authored articles with researchers from

major biomedical research hubs in the United States and with researchers from 88 other countries representing all continents except Antarctica (Figure 2.1). The top 10 countries of origin for co-authors were the United States (California in particular), the United Kingdom, Germany, Japan, France, China, South Korea, Italy, Australia, and the Netherlands. Furthermore, researchers in Canada have large collaboration networks (i.e., total number of co-authors): the median size of these networks is 8, but they range from 0 to 633 research collaborators. In total, 15 researchers in Canada co-authored publications with more than 300 other researchers, the majority of whom were trainees (undergraduate and graduate students and post-doctoral fellows).

Furthermore, in an earlier bibliometric analysis commissioned by the CIHR, Canada placed second when measuring international collaboration rates of leading regenerative medicine nations (56% compared to a world average of 17%) (CIHR, 2013). Another key report explained that the level of collaboration in the Canadian regenerative medicine community has increased in line with the strategic investments in research networks, organizations, and infrastructure that have been made over the past decade (KPMG, 2014).

Recognized scientific leaders and track record

Discovery research is a historic and current Canadian strength. Since the discovery of stem cells in the early 1960s by Drs. Till and McCulloch (Becker *et al.*, 1963), Canada has produced many researchers who have made significant discoveries in the regenerative medicine field (Figure 1.2). These discoveries were born of long-standing strengths in stem cell biology, but Canadian research output is also growing in the sub-disciplines of clinical stem cell research, stem cell drug discovery research, and cell and tissue engineering (Figure 2.2), as well as in specific medical fields such as nervous and musculoskeletal systems, and in stem cell research directly related to cancers (BioPharma, 2012). Impressively, workshop participants emphasized that Canada's significant research achievements were accomplished despite budgetary constraints and highlighted that this long history of strong regenerative medicine research and innovation continues to attract international research talent to Canada. The high quality of Canadian research has been recognized by several reports as a major strength, as exemplified by a large number of citations and high-impact factors of Canadian publications (SM & MNBC, 2004; MaRS, 2009; BioPharma, 2012; CIHR, 2013; KPMG, 2014).

Table 2.1

Collaborative Networks and Infrastructure Supporting Regenerative Medicine in Canada

Network	
Stem Cell Network (SCN)	<p>SCN is a national network, headquartered in Ottawa since its inception in 2001 (BioPharma, 2012) that:</p> <ul style="list-style-type: none"> • Helped to create the regenerative medicine cluster in Canada (CCRM, 2016b) • Supported the founding of other important networks including CCRM, CellCAN, and the Canadian Stem Cell Foundation (KPMG, 2014; GC, 2016b) • Aims to translate “stem cell research into clinical applications, commercial products and public policy” (GC, 2016b) • Provides research and training support across Canada (SCN, 2016a) • Provides early commercialization and clinical trial support (KPMG, 2014) • Is a Founding Member of the International Consortium of Stem Cell Networks (KPMG, 2014) • Is a Canadian Network Centre of Excellence (GC, 2016b)
Centre for Commercialization of Regenerative Medicine (CCRM)	<p>CCRM is a national network, founded in 2010 and headquartered in Toronto (BioPharma, 2012) that:</p> <ul style="list-style-type: none"> • Fosters the development of foundational technologies that advance commercialization of stem cell- and biomaterials-based products and therapies (CCRM, 2016a) • Created 40+ company consortium focused on translating research discoveries into regenerative medicine therapies (CCRM, 2016b) • Is a Centre of Excellence for Commercialization Research (CECR) (BioPharma, 2012)
Regenerative Medicine and Cell Therapy Network (CellCAN)	<p>CellCAN is a national network of cell therapy centres, founded in 2014 and headquartered in Montréal (CCRM, 2016b; CellCAN, 2016a) that:</p> <ul style="list-style-type: none"> • Aims to accelerate the development of stem cell therapy through advanced cell manufacturing (CellCAN, 2016a) • Includes six Good Manufacturing Practice (GMP) compliant facilities (CellCAN, 2016a) and two research units in the areas of ethics, law and regulation, and biotechnology (CellCAN, 2016b) • Is one of Canada’s five Knowledge Mobilization Networks (KPMG, 2014)
Cell and Tissue Therapy Network (ThéCell)	<p>ThéCell is a provincial network, based in Québec City, founded in 2009 (ThéCell, 2016b) that:</p> <ul style="list-style-type: none"> • Supports translational cell and tissue therapy research in Quebec (KPMG, 2014) • Is supported by the Fonds de recherche du Québec –Santé (FRQS) (ThéCell, 2016b)
Ontario Institute for Regenerative Medicine (OIRM)	<p>OIRM is a provincial network, based in Toronto, founded in 2014 through a partnership between Ontario Stem Cell Institute and CCRM (OIRM, 2016b) that:</p> <ul style="list-style-type: none"> • Supports translational research in regenerative medicine and acts as a clinical trial network for Ontario (CCRM, 2016b)
Canadian Institutes of Health Research (CIHR)*	<p>CIHR is a national federal funding agency for health research, with the goal of creating new scientific knowledge, and enabling the translation of this knowledge into improved health through a stronger healthcare system and more efficient health services and products. CIHR:</p> <ul style="list-style-type: none"> • Are made up of 13 institutes (KPMG, 2014)
Centre for Drug Research and Development (CDRD)*	<p>CDRD is a national drug development and commercialization centre, headquartered in Vancouver, founded in 2007 (CDRD, 2016a) that:</p> <ul style="list-style-type: none"> • Aims to produce investment opportunities for the private sector by de-risking publicly funded research discoveries (KPMG, 2014) • Partners with academia, government, industry, and foundations (CDRD, 2016a) • Sources, evaluates, develops, and commercializes technologies associated with small molecules and biologics (KPMG, 2014) • Is a Centre of Excellence for Commercialization Research (CECR) (CDRD, 2016a)
Canadian Blood Services’ Cord Blood Bank*	<p>The Cord Blood Bank is a national division of Canadian Blood Services that:</p> <ul style="list-style-type: none"> • “Collects, manufactures and stores donated cord blood-derived stem cells” • Is used for patient transplants • Provides researchers with cord blood-derived stem cells deemed unacceptable for transplant (KPMG, 2014)
Héma-Québec’s Public Cord Blood Bank*	<p>The first and largest public cord blood bank in Canada, managed by Héma-Québec, strives to make stem cells from umbilical cord blood a public resource and provide high-quality materials for stem cell transplant patients.</p> <ul style="list-style-type: none"> • Cord blood that does not qualify for the bank can be used for research purposes if mothers give consent (Héma-Québec, 2016)
Canadian National Transplant Research Program*	<p>The Canadian National Transplant Research Program is a national research network that was founded in 2013 that:</p> <ul style="list-style-type: none"> • Brings together and coordinates “solid organ transplant, bone marrow transplant and donation, and critical care research communities from across Canada” • Hopes to increase tissue and organ donation (CNTRP, 2016)

continued on next page

Network	
Centre for Commercialization of Cancer Immunotherapy (C3i)*	<p>C3i is a centre focused on the development, translation, and commercialization of cancer immunotherapies, founded in 2016, headquartered in Montréal. C3i:</p> <ul style="list-style-type: none"> • Is composed of three cooperating units, each with a different focus; one unit focuses on providing patients with cutting-edge biomarker and diagnostic tests; one focuses on good manufacturing practice standards and speedy access to clinical trials; and one focuses on regulatory support to bring effectual and cost-effective therapies more quickly to national and global markets • Has key partnerships with pharmaceutical companies have resulted in the first clinical trials in Canada using methods based on cellular therapy, including CAR-T cells • Is a Centre of Excellence for Commercialization Research (NCE, 2016a)
Institute for Research in Immunology and Cancer – Commercialization of Research (IRICoR)*	<p>IRICoR is a drug discovery and commercialization centre, founded in 2008, headquartered in Montréal (IRICoR, 2017) that:</p> <ul style="list-style-type: none"> • Supports the development of new stem cell therapies and new small molecules for stem cell expansion (KPMG, 2014) • Is a Centre of Excellence for Commercialization Research (CECR) (IRICoR, 2017)

* National organizations not specific to regenerative medicine, but which fund and support stem cell research and development and regenerative medicine initiatives

Researchers in Canada published 8,187 stem cell-related research articles between 2000 and 2014, across the translational continuum from discovery research to clinical research (including trials). The number of publications per year from researchers in Canada across sub-disciplines increased steadily between 2000 and 2012, at which point the number of publications remains similar every year (Figure 2.2). This trend holds true for both clinical and non-clinical research. This is similar to global trends over the same period, whereby the number of publications in stem cell research begins to plateau in 2011 (Barfoot *et al.*, 2013). The lack of increase in the number of articles published in Canada from 2013 onwards may reflect either the maturation of the field, or a time lag in the addition of more recent articles to Scopus.

The impact of Canadian articles, as measured by citations, is high; the bibliometric analysis shows that 15 articles with co-authors in Canada have been cited over 1,000 times and the median number of citations is 20. Furthermore, in 2007, coinciding with the renewal of the SCN, 17% of the 83 scientific Canadian Principal Investigators (PIs) were included in the category of highly cited researchers, and these 14 PIs were among the 100 most-cited researchers in the field globally (Bubela *et al.*, 2010). Canadian research has been published in the world's most prestigious research journals, including 281 articles in *Blood*, 118 articles in the *Proceedings of the National Academy of Sciences* (United States), 95 articles in *Cell Stem Cell*, 59 articles in *Nature*, 32 articles in *Cell*, 30 articles in *Nature Medicine*, and 28 articles in *Science*. These results are consistent with an international comparison of stem cell research carried out by Science-Metrix, which found the output of researchers in Canada is equivalent in terms of quantity and higher in terms of quality when compared to the outputs of countries that specifically focus on the field of regenerative medicine (see Appendix A for more details).

Canada's track record of success is now progressing to successful regenerative medicine clinical trials (Box 2.1). Canadian leadership in the field of regenerative medicine can also be seen in the development of globally recognized protocols. For example, the Halifax Protocol, the gold standard for effective brain repair using stem cell implantation to treat degenerative brain diseases like Parkinson's disease, was developed by Dr. Ivar Mendez (SCN, 2012). Dr. Mendez, along with collaborator Dr. Ole Isacson at Harvard University, has continued this research and has shown that transplanted stem cells in the brains of patients with Parkinson's disease remain healthy and functional for at least 14 years (Mendez *et al.*, 2008; Hallett *et al.*, 2014). These positive results are critical steps in the development of stem cell-based dopamine neuronal replacement therapies for Parkinson's disease. Similarly, Dr. James Shapiro and colleagues at the University of Alberta developed the Edmonton Protocol, a method of implanting pancreatic islet cells from cadaver donors into a diabetic recipient, for the treatment of Type 1 diabetes (Shapiro *et al.*, 2000; ADI, 2016).

Provincial healthcare systems

In the opinion of the workshop participants, Canada's provincial healthcare systems and associated disease registries and databases could facilitate multicentre clinical trials with diverse patient populations. This is especially relevant for research relating to orphan diseases, where it can be challenging (or impossible) to recruit enough patients for a clinical trial in a single location. In short, Canada's publicly funded healthcare systems allow for the recruitment of potential patients across the country. Additionally, workshop participants noted that the coordination and organization of multicentre clinical trial research are easier in single-payer systems like those in Canadian provinces and territories.

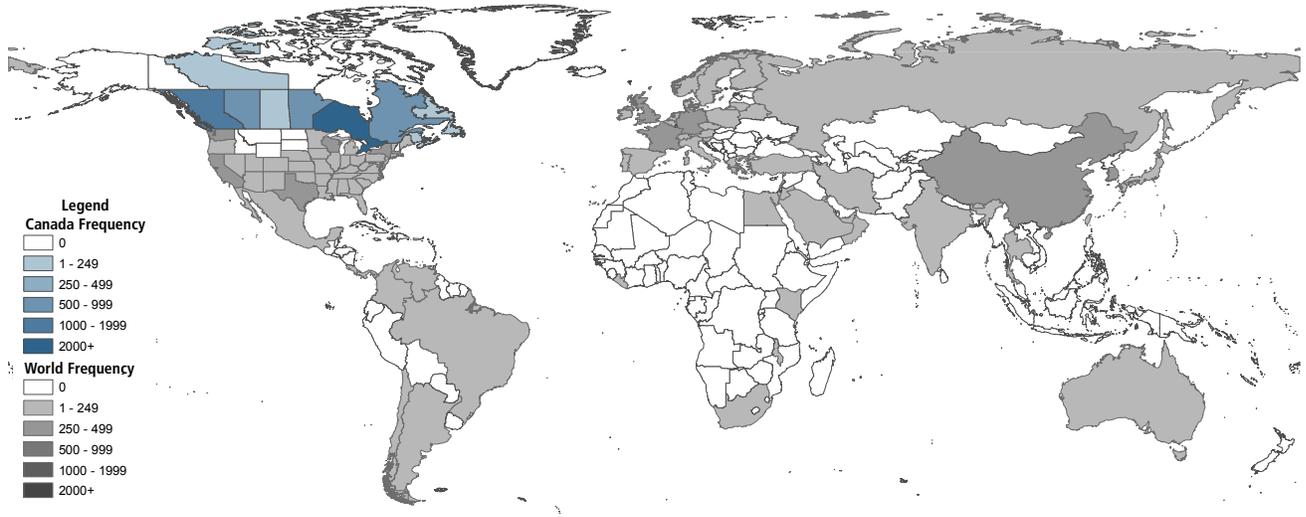


Figure 2.1

Location of Authors of Stem Cell Research-Related Articles with at Least One Canada-Based Author

Location of all authors of stem cell research-related articles published between 2000 and 2014 with at least one author from a Canadian institution. The state/countries that most often collaborate with authors in Canada are California, France, the United Kingdom, and Germany.

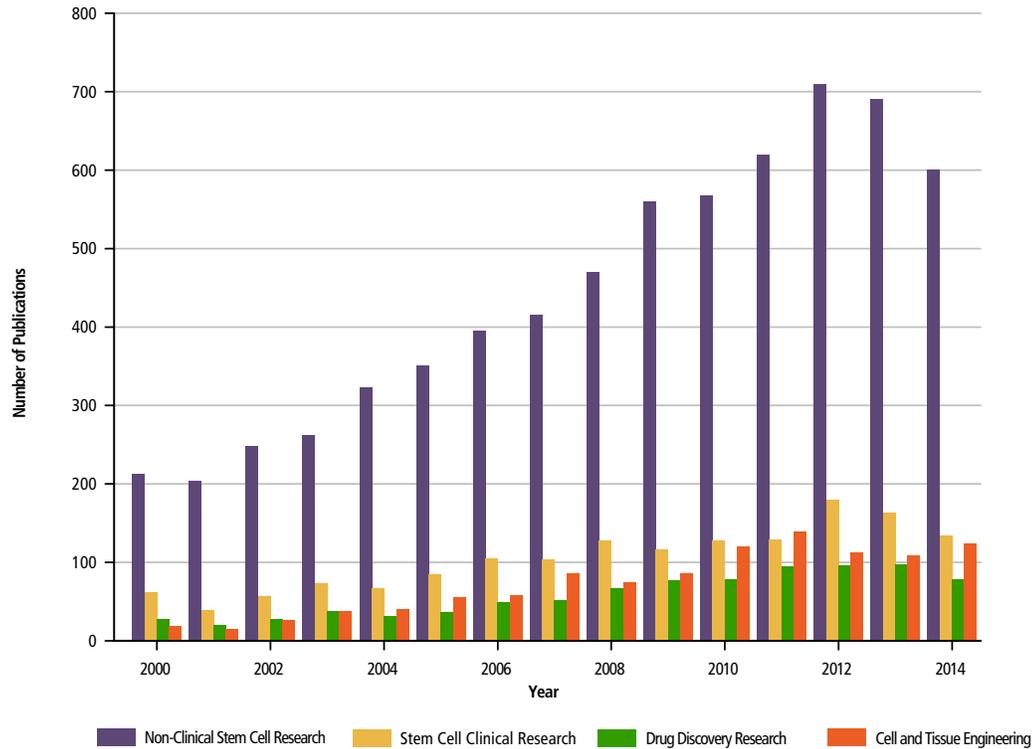


Figure 2.2

Canadian Publications in the Field of Regenerative Medicine, 2000–2014

Number of stem cell research-related articles with at least one author from a Canadian institution published per year between 2000 and 2014. The bars represent the total number of articles published on non-clinical stem cell research (purple), stem cell clinical research (yellow), drug discovery research related to, or using stem cells (green), and research related to cell and tissue engineering (orange).

Box 2.1**Promising Regenerative Medicine Clinical Trials in Canada**

Several promising regenerative medicine therapies are entering the clinical trial stage in Canada. For example, from 2010 to 2016, Drs. Harold Atkins and Mark S. Freedman of the Ottawa Hospital and the University of Ottawa led a phase II clinical trial for early, aggressive multiple sclerosis (Clinicaltrials.gov, 2016c). Their treatment used chemotherapy to wipe out the patient's immune system, followed by autologous hematopoietic stem cell transplantation to regenerate a new immune system. Following the treatment, many trial participants were free of all signs of brain inflammation and demonstrated a lasting recovery (Atkins *et al.*, 2016; OHRI, 2016). Another example is the work of Dr. Freda Miller of the Hospital for Sick Kids and the University of Toronto, which has shown that the commonly used drug metformin is a candidate for nervous system therapy as it may help promote neurogenesis by recruiting neural stem cells and enhancing neural function in the brain (Wang *et al.*, 2012). Dr. Miller is currently the PI of a phase III clinical trial that is investigating the efficacy of metformin in treating brain repair in children with radiation for medulloblastoma, the most common malignant brain tumour (Clinicaltrials.gov, 2016a).

There are also many examples outside of Ontario. For instance, two diabetes clinical trials are being led by Dr. Timothy Kieffer of the University of British Columbia and Dr. James Shapiro of the University of Alberta. The former trial is testing a stem cell therapy for insulin replacement, while the latter is conducting a trial to solve the supply and survival problems that occur with stem cell transplantation for the treatment of Type 1 diabetes (SCN, 2016b). In addition to these trials that are based on the injection of stem cells, two ongoing trials in Quebec use autologous tissues produced by tissue engineering: skin substitutes for the treatment of burn patients (Clinicaltrials.gov, 2016e), and cultured corneal epithelial cells for corneal stem cell deficiencies in the eye (Clinicaltrials.gov, 2016d). These are only a handful of the clinical trials that have been undertaken in Canada in recent years.

Openness in the regulatory environment

Workshop participants stated that Canada is considered an ethical, safe, and diligent place to do research and business, with a responsive regulatory environment. Participants elaborated that the responsive regulatory environment is illustrated by open dialogues on how best to regulate and plan for the scaling up of regenerative medicine therapies among Health Canada, Canadian regenerative medicine

researchers, organizations such as SCN, CellCAN, and OIRM, and international stakeholders. This includes regulators in other countries, with discussion occurring through organizations such as the International Conference on Harmonisation (ICH, 2016). For example, Health Canada participated in a workshop along with representatives from Canadian Agency for Drugs and Technologies in Health (CADTH), the U.K. National Institute for Health and Care Excellence (NICE), and the European Medicines Agency, to discuss ways to bring together market authorization and reimbursement regulations, and methods of assessing the value of regenerative medicine therapeutics (Bubela *et al.*, 2015). Similarly, other discussions with Health Canada and regenerative medicine researchers about the Canadian regulatory framework have occurred (Viswanathan & Bubela, 2015). Health Canada regulators have also demonstrated their commitment to ongoing discussions about regenerative medicine therapies through the creation of a new Cell Therapy Stakeholder Group. Other reports have also identified the Canadian regulatory environment as a strength, elaborating that Canada's welcoming business environment for R&D positions the country as a potential leader in the next wave of regenerative medicine development (KPMG, 2014).

Highly qualified personnel (HQP) and the Canadian university system

Workshop participants identified the technical training of HQP through the Canadian university system as a strength for regenerative medicine, and more broadly as a strength across many disciplines. Participants pointed to the recruitment of Canadian HQP with comprehensive technical knowledge by other countries as evidence of this strength. This asset has been recognized in other reports, with the Canadian Stem Cell Action Plan, for example, stating that Canada's "educated and multicultural workforce" is a strength in regenerative medicine (KPMG, 2014).

International leadership in a) governance and policy and b) in the development of alternative reimbursement models

Researchers in Canada have demonstrated international leadership in governance and policy related to regenerative medicine, as shown through their involvement with the ISCF. CIHR set up ISCF's Ethics Working Party, which is housed in Montréal and led by Canadian researcher Dr. Bartha Knoppers (ISCF, 2015b). The ISCF, where SCN represents Canada as a forum member, also leads the International Stem Cell Initiative, a global collaborative endeavour to create a consensus on criteria and techniques that will govern the development of human embryonic stem cells and induced pluripotent stem cells used for regenerative medicine

(ISCF, 2015a), and the International Stem Cell Banking Initiative, a worldwide network of stem cell banks (ISCF, 2015c). Additionally, Canadian researcher Dr. Jonathan Kimmelman chaired the development of updated guidelines for stem cell research and the development of novel clinical stem cell therapies, released in 2016 by the ISSCR (ISSCR, 2016). Within Canada, SCN has also established a research program that examines important social, legal, and ethical implications of stem cell research (SCN, 2016e). Based on the insight gained from this program, SCN has provided policy recommendations to the government. The CellCAN network also includes two research units examining issues of ethics, law, and regulation (CellCAN, 2016b).

The novelty of regenerative medicine therapies presents a challenge for applicants (developers), regulators, and health reimbursement agencies. In the opinion of workshop participants, researchers in Canada, in collaboration with policy-makers at organizations such as Health Canada and the CADTH, have been global leaders in the development of conceptual alternatives to current reimbursement models. Alternative reimbursement models are, in part, required to account for conditional approvals that may be granted by regulatory agencies. Conditional regulatory approvals recognize that current evaluation methods of safety and efficacy may be inappropriate for regenerative medicine therapies, especially those that target rare diseases. For example, it is not feasible to conduct randomized controlled trials for therapeutics developed to treat rare diseases with small patient populations because the pool of participants is not large enough (Bubela *et al.*, 2015). In these cases, regulatory decisions need to be made with limited evidence on safety and efficacy (Bubela *et al.*, 2015).

In response to these challenges, regulators have been working to develop suitable policy interpretations of existing regulations or, when needed, new efficacy and safety regulations specifically for regenerative medicine therapies (Bubela *et al.*, 2015). The goal of this work is to reduce uncertainties for developers and investors and to integrate these across jurisdictions; one mechanism is to grant a conditional regulatory approval with the removal of conditions contingent on post-market data generation and analysis. In Canada, without reimbursement by a provincial health system payer, post-market data will likely not be generated. Reimbursement agencies must therefore develop new methods to manage this greater evidentiary uncertainty for products that enter the market with less evidence on safety and efficacy. Mechanisms exist to adjust costs when products first come to market reflecting the nature of the evidence.

In addition, public healthcare systems are increasingly concerned about rising costs of therapies. Collaboration between regulatory agencies (who control market authorization) and reimbursement agencies (who pay for therapies) is needed to ensure protection of both patients and budgets (Bubela *et al.*, 2015). Researchers in Canada are also working on models to accurately assess the cost effectiveness of regenerative medicine therapies (Bubela & McCabe, 2013). Therapies that are exorbitantly expensive will never be available to the general public. Investments in research relating to regenerative medicine technologies should therefore take cost into consideration throughout the development process in order to promote affordable therapies that can benefit the public as a whole.

Demonstrated corporate success

Canada provides an example of a home-grown biotechnology success story. The Canadian biotechnology company STEMCELL Technologies Inc. grew out of the Terry Fox Laboratory of the British Columbia Cancer Research Centre, and took on a leadership role in the development and provisioning of materials and technologies to support R&D in regenerative medicine worldwide (KPMG, 2014). Initially, this company was formed to raise funds for research and ensure that cancer researchers had access to the cell culture materials they needed (STEMCELL, 2016). Since its inception in the mid-90s, STEMCELL Technologies has become the largest biotech company in Canada, employing approximately 900 people worldwide (with most working in Canada), providing jobs for almost 300 people with graduate degrees, and making more than 2,000 products (A.C. Eaves, personal communication, 2016). It has enjoyed cumulative revenues of almost a billion dollars and has invested approximately \$130 million into R&D (A.C. Eaves, personal communication, 2016). Additionally, it recently licensed four products for use with T cells in the development of clinical applications to GE Healthcare in the United Kingdom (GE Healthcare, 2016). This success story, along with other emerging regenerative medicine biotechnology companies such as Zymeworks, Tissue Regeneration Therapeutics Inc., ExCellThera, and RepliCel, combined with Canada's emerging cell manufacturing capacity (CellCAN, 2016a), could help secure Canada's leading role in the next stage of regenerative medicine technology translation.

Canada's leading role in the next stage of regenerative medicine translation has already begun, with the recent funding announcement by Bayer AG and Versant Ventures of US\$225 million to create BlueRock Therapeutics, a Toronto-based stem-cell research company (Bayer, 2016). This investment, one of the largest ever for a biotechnology company (Bayer, 2016), is an example of an international

pharmaceutical company and venture capital firm recognizing Canadian regenerative medicine research excellence, and investing in future Canadian companies (Weeks & Silcoff, 2016; Bayer, 2016). While this demonstrates international investment in Canadian regenerative medicine, there is an opportunity to further grow this industry in Canada by encouraging Canadian investment in the field.

Community committed to innovative thinking

Lastly, workshop participants noted that the regenerative medicine community in Canada is constantly pushing innovation and thinking of novel ways to approach healthcare. Participants explained that, with support and resources from various stakeholders, there is a clear opportunity to leverage Canada's strengths in regenerative medicine and, together with this innovative thinking, advance the field and support larger efforts to build on Canada's innovation agenda.

2.2 WEAKNESSES IN REGENERATIVE MEDICINE

There was general consensus among workshop participants about three Canadian weaknesses, with a majority selecting a lack of stable and strategic funding across the regenerative medicine continuum, a thin pharmaceutical and biotechnology ecosystem, and misaligned regulatory and reimbursement frameworks as top weaknesses. An additional seven weaknesses were selected as a top weakness by more than one participant. All ten weaknesses are discussed below.

Lack of stable and strategic funding

Workshop participants noted that there is a lack of stable funding throughout the Canadian regenerative medicine pipeline, from research discovery at the lab bench to treatment at the patient bedside. They observed that recent challenges in the funding environment for discovery science pose a threat to the long-term success of the regenerative medicine pipeline in Canada. Participants also noted that, in their opinion, there are also insufficient funds for the translational research and commercialization stages, notably proof of principle research and phase I/II clinical trials. Additionally, there is a lack of strategic funding for company creation, including a shortage of venture capital and angel investment (Box 2.2). This lack of funding creates a "valley of death" when translating research innovation into therapies. As noted previously, however, the significant investment by Bayer AG and venture capital firm Versant Ventures of US\$225 million to create BlueRock Therapeutics (Bayer, 2016) may signal positive change with respect to international investment.

Box 2.2

Funding Challenges for Canadian Start-Ups

Canada lacks accessible funding for home-grown entrepreneurs and regenerative medicine start-ups. This decreases Canada-based researchers' ability to commercialize discoveries. For example, venture capitals are investing less in Canadian technology versus other regenerative medicine clusters in Australia, California, Israel, Japan, and the United Kingdom. Additionally, Canada lacks a strong presence in pharma venture arms, with only two companies present (Johnson & Johnson, Valeant), compared to between six and eight arms in the other leading regenerative medicine clusters (eight in California, six in the United Kingdom, six in Japan). Lastly, of the regenerative medicine start-ups analyzed for CCRM, Canadian start-ups raised less than 1% of total overall venture capital funding compared to 78% raised by California start-ups and 19% raised by U.K. start-ups.

(CCRM, 2016b)

The translational "valley of death" was illustrated in a bibliometric analysis completed for this report. The proportion of clinical stem cell research relative to basic and applied stem cell research (non-clinical) has remained constant over time (Figure 2.3). As the field matures and the body of basic stem cell knowledge grows, one would expect a greater proportion of clinical research (including trials) compared to early-stage basic research. It should be noted, however, that, while the proportion of each publication type remains fairly constant over time, the raw number of both types of publications is increasing over time (Figure 2.2). This lack of proportional increase in clinical research publications demonstrates that researchers in Canada continue to carry out fewer translational (i.e., clinical) research studies, compared to non-clinical studies. In addition, a bibliometric analysis by CIHR showed that Canada is not keeping up with other leading nations in terms of translational research (CIHR, 2013). The CIHR analysis showed that Canada's global ranking in number and impact of publications greatly increased when basic stem cell research was included (i.e., Canada's ranking was lower when only translational research was included) (CIHR, 2013). While this highlights basic stem cell research as a Canadian strength, it also demonstrates the lack of translational research publications by researchers in Canada. This may reflect Canada's funding and research priorities to date. For example, prior to 2016, SCN was unable to

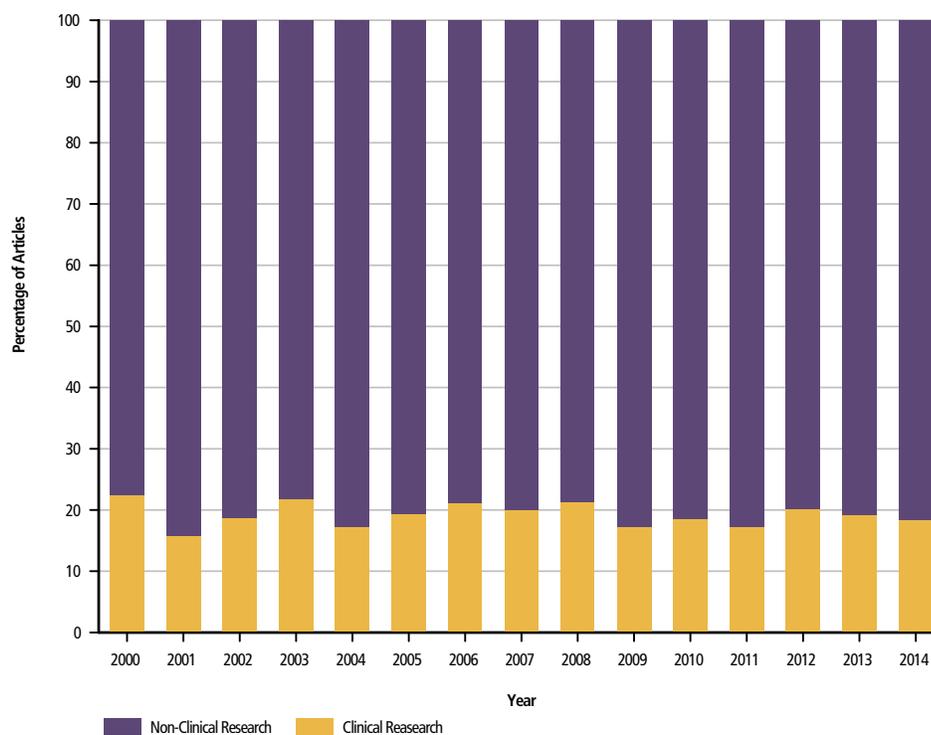


Figure 2.3

Proportion of Clinical and Non-Clinical Stem Cell Research-Related Articles with at Least One Canada-Based Author, by Year

The percentage of stem cell research-related articles published between 2000 and 2014 with at least one Canada-based author, which are non-clinical studies (purple) and clinical studies (yellow). The proportion of each type of study (clinical and non-clinical) has remained relatively constant over time.

provide direct support for clinical trials; with its new funding mandate, however, it can now do so through to 2018 (M.A. Rudnicki, personal communication, 2016).

Two Canadian centres working to address this “valley of death” are CCRM and CDRD, which are NCE Centres of Excellence for Commercialization and Research (CECR), developed to transform promising health-related research into commercially viable investment opportunities for the private sector (KPMG, 2014; CDRD, 2016b). CCRM, CDRD, and SCN have worked together to fund promising regenerative medicine translation, and to provide core infrastructure support. SCN supports goal-directed research up to early-stage clinical trials, and CCRM and CDRD provide commercialization support to realize the full potential of promising research discoveries and to see new therapies reach the clinic (P. Cassar, personal communication, 2016). CCRM focuses on cell-based approaches while CDRD focuses on small molecules. Both organizations bring external industry partners to the academic community. This collaborative funding approach provides an example of three organizations working together to ensure funding of the entire regenerative medicine pipeline. The success of this approach is exemplified by CCRM’s position as the cell-manufacturing partner of the newly announced BlueRock Therapeutics (Bayer, 2016).

Thin pharmaceutical and biotechnology ecosystem

Despite the success stories discussed, workshop participants explained that the Canadian pharmaceutical and biotechnology ecosystem is too thin and has not reached the critical mass necessary to catalyze the industry. As a result, there is only a weak pull for new developments. Participants also observed an additional lack of industry receptors for new opportunities, in the form of both anchor and funded start-up companies, because there are not enough incentives for companies to base themselves and remain in Canada. Moreover, there are few incentives for companies to get involved early in R&D activities. In the opinion of the participants, many companies may be risk averse and/or stop investment after negative clinical trial results despite the need for failure and risk-taking to support innovation and change. The results of a recent analysis carried out by McKinsey and Company for CCRM are consistent with this opinion. In a benchmarking analysis that compared Canada to five other regenerative medicine clusters (Australia, California, Israel, Japan, the United Kingdom), Canada is leading the way in the conversion of academic output into intellectual property (IP), as measured by the number of patents per publication between 2005 and 2015. However, Canada falls behind in commercialization of IP, as measured by the number of patents filed per total

number of companies created, and in the scale-up of IP commercialization, as measured by the number of jobs per created company (CCRM, 2016b).

Challenges relating to the commercialization of regenerative medicine have been highlighted by others who have noted that a novel business model is required for the development of cell-based biologics because of key differences between biologics and traditional drug development (MaRS, 2009). The most significant challenges are increased development time, high production costs, and unclear regulatory guidelines compared to those involving traditional products (CIRM, 2016). Another impediment to commercialization of regenerative medicine therapies is the fact that small start-up biotechnology and cell therapy companies often lack the financial means and clinical and regulatory capabilities needed to establish a sustainable product portfolio and technology pipeline (MaRS, 2009).

Misaligned regulatory and reimbursement frameworks

Workshop participants noted that the frameworks for regulation and reimbursement of novel therapeutics in Canada are not aligned. Fundamentally, gaining federal regulatory approval does not guarantee reimbursement by the publicly funded provincial or territorial healthcare systems, which consider cost-effectiveness in addition to clinical safety and efficacy. Since regenerative medicine products and services may receive conditional regulatory approval that requires post-market data collection on efficacy, adaptive reimbursement models are needed to enable payers to make decisions based on a more uncertain evidence base (Bubela *et al.*, 2015). Furthermore, regulatory and reimbursement frameworks were designed for traditional pharma drugs, and therefore regenerative medicine therapies may require alterations (Bubela *et al.*, 2015). While researchers and policy-makers are actively working together to develop novel and innovative reimbursement strategies for regenerative medicines (a Canadian strength), Canada has yet to implement any of these strategies.

No roadmap to transform healthcare systems

Workshop participants stated that regenerative medicines could enhance return on investment in healthcare systems and ensure these systems become economic drivers. However, healthcare systems in their current form are set up to deliver therapies at the lowest possible cost, rather than provide innovative therapies that support economic growth and better long-term health outcomes. In the opinion of workshop participants, one roadblock that may hinder this transformation is the lack of integration of hospital-based purchasing systems into the innovation framework.

Introducing new technologies that may be more expensive at purchase, even if these technologies are associated with better long-term health outcomes, is not incentivized. Participants emphasized that, currently, buying less expensive technologies and treatments is more valued than more effective or curative options. Additionally, participants were unsure whether Canadian healthcare systems are fully prepared to adopt regenerative medicine therapies, as questions remain about capacity in terms of the personnel and infrastructure needed to support the delivery of these new services. The United Kingdom has been focused on readying the National Health Service (NHS) to adopt regenerative medicine therapies, and a brief synopsis of its action plan is provided in Box 2.3.

Limited cross-training of HQP

In the opinion of workshop participants, Canada trains excellent academic and technically skilled researchers (a Canadian strength), but relevant applied skills are not typically included in this education. Relevant applied skills could include those related to entrepreneurship, legal and ethical affairs, translational research, clinical trial implementation, product development, and large-scale manufacturing. Currently, in the opinion of participants, PhD training can be disconnected from industry requirements, resulting in trainees who lack some of the critical skills to succeed outside of academia. These training shortfalls are not isolated to Canada, and better cross-training would allow this country to be a world leader in turning talented young graduate students into successful researchers with a range of highly sought-after skills. Cross-training is also needed to produce convergence scientists, such as engineers who understand biology and biologists who understand engineering, so that methods and ideas can be shared across the natural sciences, engineering, social sciences, and life sciences fields.

The presence or absence of incentives also encourages HQP to focus their academic research and training away from certain applied fields. For instance, translational quality control and standardization research fields may not be pursued within academia because this type of work is not well recognized by standard academic metrics. Most academic funding is based on authorship position, and the number and impact of publications. Additionally, a limited number of investigators active in a field (e.g., quality control and standardization) leads to an absence of these types of researchers on the review panels of funding agencies, and ultimately less funding is allocated to this type of work. Participants explained that many aspects of translation and standardization research do not typically translate into high metrics.

Box 2.3 **Readiness of the National Health Service to Adopt Regenerative Medicine Therapies**

The Regenerative Medicine Working Group (RMEG) in the United Kingdom was established by the House of Lords in 2013 (RMEG, 2014). One of its mandates was to provide an action plan so that the NHS can be fully prepared to deliver innovative regenerative medicine therapies. In order to embed regenerative medicine as part of the NHS, the RMEG recommended more cell therapy centres of excellence, the central collection of data on cell therapy clinical outcomes to provide quality assurance on different treatments, and the establishment of a ministerial group specifically for regenerative medicine (RMEG, 2014).

The RMEG proposed that the NICE commission a “mock technology appraisal” to assess whether changes to its methods and processes are needed for regenerative medicines (CRD/CHE, 2015). This appraisal found that, in order to limit high upfront reimbursement costs to the NHS and loss associated with wrong decisions by NICE, there is a need for a full evaluation of the level of uncertainty in the cost-effectiveness estimates associated with novel regenerative medicine therapies. Additionally, this evaluation should include the potential value of Managed Entry Agreements, whereby therapies are introduced with price discounts, performance-related schemes, and technology leasing (CRD/CHE, 2015).

To complement the work done by the RMEG to develop an NHS regenerative medicine strategy, the Advanced Therapy Manufacturing Taskforce was set up in 2016 to identify opportunities to secure the advanced therapy manufacturing market in the United Kingdom and to identify any gaps in the manufacturing landscape that need to be filled (MMIP, 2016). There are currently 18 facilities for cell and gene therapy manufacturing in the United Kingdom, and the U.K. Cell and Gene Therapy Catapult Manufacturing Centre is expected to open in 2017. This new facility will complement the existing facilities by manufacturing advanced therapies for late-phase clinical trials and for commercial supplies. The Advanced Therapy Manufacturing Taskforce is meant to ensure that the United Kingdom has sufficient manufacturing infrastructure to produce therapies, once approved, and in large enough quantities to supply the NHS (MMIP, 2016).

Lack of operational funds for cell manufacturing

Workshop participants observed that there is a lack of operational funding to support cell and tissue manufacturing centres in Canada. The Canada Foundation for Innovation provided funding to support the building of this infrastructure (CFI, 2016), but ongoing and enhanced funding to make these centres fully operational (and support continued operation), and to enable them to scale up their operations, is lacking. Currently, CellCAN represents six major Canadian cell manipulation and manufacturing facilities (CellCAN, 2016a) (Table 2.2). Each facility aims to maximize its own research specialities, but they share capacity in terms of development, production, and clinical deployment, and act as both a biotechnology core and an ethical, legal, and regulatory core, with CellCAN acting as the central coordinator. In total CellCAN has 33 clean rooms, with planned expansions to 47 by 2018 (CellCAN, 2016a). Clean rooms are integral to each GMP facility, as this is where the manufacturing of cells occurs; they are literally sterile rooms that are classified by their air purity and, in some cases, other parameters such as temperature, humidity, and pressure (Giancola *et al.*, 2012).

An additional manufacturing facility, which is external but in partnership with the CellCAN network, will also soon be in operation (NCE, 2016c). This advanced cell manufacturing facility was announced in early 2016 and received funding from the federal government and GE Healthcare. It will be established and operated by CCRM (KPMG, 2014; GC, 2016b).

Engagement of philanthropic and patient communities

Workshop participants noted that the Canadian regenerative medicine community could more comprehensively engage philanthropic, medical, and patient communities. Patient communities can be advocates for the field, as they are a powerful group of highly motivated individuals who live daily with diseases that could be treated by regenerative medicine therapies. Learning about the needs and experiences of patients, and engaging them in early stages of the research process along with medical professionals also benefits research in a variety of ways. For example, increased engagement could result in higher recruitment rates for clinical trials and more donations of blood and tissues to biobanks. In fact, participants explained that patient-oriented research models show great promise for improving research processes and health outcomes in the future. Furthermore, patient perspectives are central to understanding and addressing the social, legal, ethical, and regulatory challenges associated with regenerative medicine. The research process may also be enhanced

Table 2.2

CellCAN Consortium of Cell Manipulation and Manufacturing Facilities

Facility	Location	Speciality	Clean Rooms (2016)
Centre d'excellence en thérapie cellulaire (CETC)	Maisonneuve-Rosemont Hospital/ Université de Montréal, Montréal	Immuno-oncology, vision health, orthopaedics, translational platform	13
Phillip S. Orsino Cell Therapy Facility	Princess Margaret Hospital, University Health Network, Toronto	Haemato-oncology, immunotherapy, mesenchymal stromal cells, bioprocessing optimization	5
Ottawa Hospital Research Institute (OHRI) – (i) Cellular Biotherapeutics, and (ii) Ottawa Virus Manufacturing Facility (OVMF)	Ottawa Hospital, Ottawa	(i) Cardio-pulmonary diseases, leukaemias (ii) Oncolytic viruses	(i) 3 (ii) 1
Centre multidisciplinaire de développement du génie tissulaire (CMDGT)	In collaboration with Laboratoire d'organogénèse expérimentale (LOEX), CHU de Québec, Université Laval Hospital, Québec City	Tissue engineering, eye and skin regenerative medicine	3
Alberta Cell Therapy Manufacturing (ACTM)	Li Ka Shing Centre for Health Research Innovation, Edmonton	Diabetes, xenografts, ocular diseases	6
Manitoba Centre for Advanced Cell and Tissue Therapy (MCACTT)	Health Sciences Centre, CancerCare Manitoba and University of Manitoba, Winnipeg	Haemato-oncology, immunotherapy, mesenchymal stem cells	2

Source: CellCAN, 2016a

by early engagement with provincial health ministries to ensure the therapies being developed will fill an unmet need, thereby supporting the early integration of novel therapies into healthcare systems.

Constraining and inefficient clinical trial and ethics environment

While there are local efforts to share best practices and support coordination of clinical trials, workshop participants concluded this is not done enough on a national level. The process for clinical trials in Canada is largely fragmented, with little coordination of ethical requirements, contracts, patient recruitment, and other logistical steps in trial development. Participants noted that the high cost and slow implementation of clinical trials can, in part, be attributed to this lack of national coordination and absence of learning across different sites. This can cause significant clinical trial constraints. For instance, multicentre trials are difficult to implement because, while ethical requirements can be similar (as stated in Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (CIHR, 2014)), the interpretation of these requirements by research ethics boards may differ depending on the location in which the trial is being performed (Rx&D, CIHR, ACAHO, 2012). The recent creation of the Canadian Clinical Trials Coordinating Centre is a positive development (CCTCC, 2016), but it represents only a first step in addressing this problem.

Coordinating clinical trials in Canada is becoming increasingly important as Canada's strong foundation in stem cell research is starting to reach patients in clinical trials. Currently, investigators in Canada may voluntarily register their clinical trials with www.clinicaltrials.gov, a database operated by the U.S. National Library of Medicine and National Institutes of Health (NIH). Health Canada encourages registration but does not require it. This makes it challenging to identify the number of clinical trials taking place in Canada. In the United States, however, the FDA mandates that all clinical trials must be registered with the database (Clinicaltrials.gov, 2016b). Dr. Sowmya Viswanathan and her research team identified 40 Canadian cell-therapy clinical trials registered in clinicaltrials.gov with a start date between 2008 and 2016 (Figure 2.4). The recent increase in Canadian clinical trials is supported by the foundation of CCRM in 2011 (KPMG, 2014) and through the manufacturing infrastructure coordinated by CellCAN (a Knowledge Mobilization Network), founded in 2014 (CellCAN, 2016a). Having said this, previous studies have indicated that there are other jurisdictions that are more active in running clinical trials: for example, since 2011 Canadian clinical trials have been 4.6% of the total global number of regenerative medicine clinical trials while California's greater share is 9.7% (CCRM, 2016b).

Importantly, Figure 2.4 underestimates the total number of clinical trials taking place in Canada, as there is no requirement that these be registered in a single common website, such as clinicaltrials.gov. Most significantly, it is probable that small clinical trials are not registered with the site. This demonstrates a data gap that makes it challenging to monitor Canada's progress in moving regenerative medicine research into the clinical trial stage.

A lack of harmonization between various regenerative medicine community members involved in the clinical trial framework in Canada is an obstacle in the subfield of clinical regenerative medicine research (KPMG, 2014). This problem relates to clinical trials for all drugs and biologics, as explained by the Senate Standing Committee on Social Affairs, Science and Technology, which stated that the “high cost and slow implementation of clinical trials was attributed to the lack of a clinical trial infrastructure in Canada” (Senate, 2012). The Committee highlighted the absence of a standardized and streamlined approach to research ethics review as one key factor implicated in

increasing the time and effort required to run a clinical trial in Canada (Senate, 2012). However, recently, a suggested framework for mutual recognition of international ethics reviews has been published which, if adopted, could lead to the acceptance of a single review by multiple research ethics boards (Dove *et al.*, 2016).

Currently, Health Canada is developing guidance on the clinical trial evaluation of cell therapies, which it classifies as a biologic (Health Canada, 2015). This grouping is problematic because living cells (used in cell therapy) behave very differently from traditional biologics such as monoclonal antibodies and recombinant proteins. This opinion was expressed in a key report that stated that, if Canada were to clarify and redefine the regulation of cell therapy, it “would not only help developers better understand the key requirements and milestones that need to be achieved for successful commercial development, but also bolster stakeholder confidence and potentially private sector investment” (KPMG, 2014).

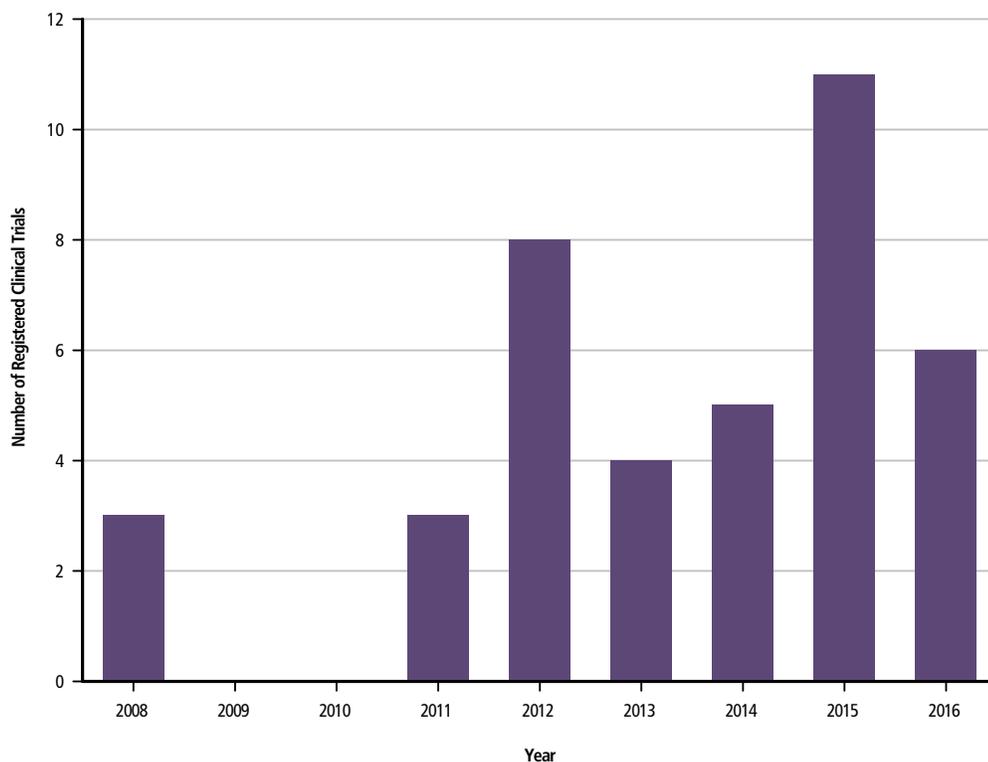


Figure 2.4

Registered Canadian Clinical Trials

Canadian clinical trials registered in clinicaltrials.gov starting from 2008 through to 2016. Clinical trials in Canada are not required to register on clinicaltrials.gov, and therefore the data presented is an underestimate of all trials currently ongoing in Canada. The number of trials registered in 2016 may increase, as this data includes only those registered through October, 2016. Data provided by S. Viswanathan (*in prep*).

Lack of international regulatory harmonization

In the opinion of workshop participants, Canada's lack of international regulatory harmonization with larger countries could make this smaller market less attractive for the development of regenerative medicine therapies. Participants noted that this may impede Canada's capacity and discourage private sector investment along the entire Canadian regenerative medicine developmental pipeline. The ISCF has been working to standardize global criteria on stem cell research and regenerative medicine therapy regulations in numerous ways, including through the International Stem Cell Initiative (ISCF, 2015a). In addition, Health Canada is a standing regulatory member of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, 2016), which seeks to achieve greater global harmonization of pharmaceuticals (ICH, n.d.).

Unrealistic expectations of short- and medium-term pay-offs

Workshop participants noted that, in Canada, some members of the public, patient groups, and investors have unrealistic expectations of the short- and medium-term pay-offs that can be achieved through regenerative medicine. This problem is exacerbated when there is an absence of transparency about the probable R&D and commercialization timelines and likely research outcomes. These unrealistic expectations could lead to a perception of failure when regenerative medicine does not meet unrealistic timelines, resulting in a loss of public and government support — as well as the premature abandoning of research programs that require risk-taking and some failures in order to advance the innovation agenda. The stuttering progress in developing novel regenerative medicine therapies may follow a similar

trajectory to that of bone marrow transplants; the first clinical applications of bone marrow transplants in the late 1950s and early 1960s had very poor results, and enthusiasm for clinical bone marrow transplantation decreased, with relatively few cases reported in the literature for over a decade (Bortin, 1970). Following these poor results, however, concentrated research in preclinical models of transplantation during the 1970s resulted in a rapid increase in the number of successful transplants performed in the 1980s and 1990s (de la Morena & Gatti, 2011).

2.3 CONCLUSIONS

In summary, workshop participants were able to pool their collective expertise and identify strengths and weaknesses in the Canadian regenerative medicine community. Importantly, participants' knowledge was earned through a range of experience in early-stage R&D, translational research, industry, ethics, funding, and the patient experience. Overall, Canada's continued success in regenerative medicine illustrates that the country's strengths, most notably the community's collaborative culture and track record of producing scientific leaders and discoveries, outweigh its weaknesses. The existence of both mature and emerging Canadian regenerative medicine companies, and the recent US\$225 million to develop BlueRock Therapeutics in Toronto, demonstrate that Canada can be a leader in the regenerative medicine field.

Following the strengths and weaknesses discussion, participants focused on identifying opportunities to help bolster Canada's leadership role in and support of the regenerative medicine field to transform Canadian healthcare systems and realize economic benefits. These opportunities are discussed in Chapter 3.

3

Opportunities to Achieve Success in Regenerative Medicine in Canada

- Opportunities
- Conclusions

3 Opportunities to Achieve Success in Regenerative Medicine in Canada

Prior to focusing on opportunities that could enable greater success in the Canadian regenerative medicine community, workshop participants considered outcomes that might result were Canada to become a global leader in the practice of regenerative medicine in 2025. The participants' discussion established four key visions that represent success:

- In 2025, Canada is a global leader in realizing the transformative potential of regenerative medicine, with its researchers and companies at the forefront.
- Ultimately, Canada is the best place in the world to bring a regenerative medicine therapy from bench to bedside, known for harmonized processes, good governance, rapid protocol reviews, innovative reimbursement models, and the most skilled HQP.
- Regenerative medicine has led to curative treatments for chronic and other types of diseases and unparalleled improvement in health outcomes, with benefits for both patients and the healthcare system.
- These changes include the delivery of novel regenerative medicine drug and cell therapies that are accessible to all.

Participants then focused on identifying opportunities that would help achieve these visions. A two-stage process was used. The first stage identified opportunities that relate to Canadian research and development and clinical trials (i.e., development and clinical translation), while the second stage identified opportunities that relate to Canada's readiness for the adoption of regenerative medicine therapies (i.e., enablement and adoption). The opportunities listed under *development and translation* are largely about funding and infrastructure and are partially within the control of the research community. This differs from the opportunities listed under *enablement and adoption*, which involve larger questions related to policy and structural change, where control is greatly dispersed across governments and various other stakeholders in Canada. These two sets of opportunities are further divided into opportunities that could be acted on in the next 1 to 2 years for immediate impact, and longer-term opportunities that could be achieved in the next 3 to 5 years. The opportunities discussed below are supported by a literature review.

3.1 OPPORTUNITIES

3.1.1 Development and Translation Opportunities: Short-Term (1 to 2 years)

Coordinating mechanism that ensures the alignment of efforts across the regenerative medicine community in Canada

Workshop participants explained that, currently, there is only informal coordination occurring among key regenerative medicine initiatives across Canada, and between these initiatives and advocacy organizations such as the Canadian Stem Cell Foundation and health charities. There is an opportunity to formalize these efforts and ensure the whole regenerative medicine community speaks with one voice and helps the community move forward with a common vision and approach. A coordination mechanism need not be started from scratch, but rather build on the strengths and cooperation of existing regenerative medicine initiatives in Canada. Participants suggested that such coordination be led by the research community and should engage and involve all relevant regenerative medicine stakeholders, including patients, clinicians, regulators, biotechnology companies, venture capitalists, researchers, and health charities. Each group is an essential part of the community and the integration of these groups' perspectives, experiences, and expertise would strengthen the field as a whole. The workshop meeting laid the foundation for improved coordination, and new collaborative efforts among a range of stakeholders have already begun.

There is also an opportunity to formalize coordination between active funding groups, ensuring support is provided to the entire regenerative medicine pipeline: from early developmental research, through translation to application, and finally uptake. Currently the available funding is piecemeal and does not always consider the entire regenerative medicine pipeline.

National coordination between regenerative medicine clinical trial sites

Clinical trial sites in Canada could improve operations and avoid repeating the mistakes of others through better national coordination that enables the sharing of best practices related to funding, design, and recruitment. Recently, a coordinating centre was set up in Canada (the Canadian Clinical Trials Coordinating Centre) through a partnership between HealthCareCAN, Innovative Medicines Canada, and the CIHR (CCTCC, 2016). However, this centre could benefit from a greater profile, enhanced publicity, and continued support from government and the regenerative

medicine research community. Coordination could also be fostered through the use of common clinical operating procedures, such as those developed by the N2 Network of Networks (N2 Canada, 2017). Coordination of clinical trial sites with patient groups could ensure that patients are connected to appropriate trials, and that their experiences are shared with researchers to inform future trials. An example of this type of coordination is the Canadian Blood and Marrow Transplant Group (CBMTG), and the operation of a registry for blood and marrow transplants (Box 3.1). Lastly, as regenerative medicine therapies may also benefit from new approaches to clinical trials, continued support of innovative research design through initiatives such as the Strategy for Patient-Oriented Research Innovative Clinical Trials initiative could be helpful (CIHR, 2016).

Box 3.1
Canadian Blood and Marrow Transplant Group

CBMTG is a Canada-wide multidisciplinary organization that supports excellent patient care, research, and education related to bone and marrow transplants (BMT). CBMTG operates a database registry that contains detailed clinical information related to patients undergoing BMT in Canada. The CBMTG registry thereby provides data on patients receiving these types of transplants at any participating location in Canada. This information allows for the determination of: Canadian patient outcomes; data that reflects Canadian clinical best practices; data about the frequency of BMT nationally (relevant to clinical trial planners); and important information about the way BMT is used in Canada (relevant to policy-makers). Additionally, the data included in the registry is available to researchers in Canada who are working at participating centres.

(CBMTG, 2016)

Long-term funding strategy

There is an opportunity to develop a clear, long-term funding strategy to provide stability for key existing national initiatives that support and encourage regenerative medicine R&D across the country (e.g., SCN, CellCAN, and CCRM). This would allow such initiatives to focus on innovation and long-term planning. Other important stakeholder groups in the regenerative medicine community, such as provincial health funders, advocacy organizations, and health charities, should also be consulted in this strategy.

Incentives for Canadian companies to build GMP facilities in Canada, and provide strategic investments for operations and the scaling up of existing facilities

There is an opportunity to build and support the infrastructure necessary to provide the materials that in turn support the growing Canadian and global regenerative medicine market. Fully operational GMP facilities that produce GMP products that support the regenerative medicine community could bring money into the Canadian economy, provide jobs for HQP, and enable researchers to purchase materials domestically. Additionally, these facilities would provide materials for the global stem cell market. Commercial facilities producing GMP products would complement the existing CellCAN GMP cell- and vector-based facilities in academic centres, where cell and tissue processing occurs (Box 3.2; for a comprehensive list, see Table 2.2). Sustained support for these GMP cell-processing facilities would also benefit the regenerative medicine community by providing stability and ensuring the facilities' continued operation. Further, workshop participants noted that there may be a need to build or expand GMP infrastructure for later-phase clinical trial and/or commercial production, similar to the U.K.'s Cell and Gene Therapy Catapult Manufacturing Centre (Cell and Gene Therapy Catapult, n.d.-a).

Box 3.2
Inside a GMP Cell Manufacturing Facility

The Philip S. Orsino Cell Therapy Facility, part of the University Health Network, offers GMP-grade cell and tissue processing capabilities, and is used for investigator-initiated clinical trials, bone marrow processing, and a range of external commercial and academic purposes. The facility is housed at the Princess Margaret Cancer Centre in Toronto, taking up 2,900 sq. ft. of space and featuring five independent clean rooms. Each clean room contains "a biological safety cabinet, incubators, refrigerators, cell processing equipment, computer work stations, and cryogenic storage." GMP conditions are controlled through a sophisticated air filter system that is constantly monitored, along with all vital aspects of the facility (e.g., particle counts in clean rooms, freezer temperatures).

(CellCAN, 2016a)

3.1.2 Development and Translation Opportunities: Longer-Term (3 to 5 years)

Infrastructure that allows for the development of Canadian regenerative medicine therapies and enables the design and execution of clinical trials

Canada could benefit from growing the infrastructure needed to fully develop regenerative medicine therapies. This infrastructure includes GMP-designated manufacturing facilities that can produce the unique materials needed to develop and use regenerative medicine therapies. Additionally, workshop participants explained that the establishment of cell banks — similar to those in Sweden, the Netherlands, South Korea, California, and Australia — would give researchers access to a large number of high-quality disease-affected and healthy cells. On a smaller scale, more specific cell banks, such as the Quebec Leukemia Cell Bank, can support targeted research areas (e.g., blood cancer) (BCLQ, n.d.). Dedicated clinical trial sites that have the full range of specialized infrastructure needed to support innovator trials would maximize efficiency and support group learning (e.g., foster accelerator/incubator contexts). This infrastructure could build on Canada's existing networks (e.g., those established through CellCAN) and supportive research hubs (e.g., those established by the Medicine by Design initiative at the University of Toronto). In some cases there may be an opportunity to integrate the clinical care of patients undergoing regenerative medicine therapies into existing healthcare systems (e.g., current clinic or inpatient resources), including leveraging the infrastructure in blood and marrow transplant programs.

Dedicated centres at the California Institute for Regenerative Medicine (CIRM) provide an example of the types of infrastructure that help expedite the translation process (CIRM, 2016). CIRM's Translating Center has the capacity to coordinate with the FDA to help with the filing of preclinical trial requirements and to develop cell manufacturing processes that are GMP-compliant. Additionally, CIRM houses an Accelerating Center that has the capacity to support multi-centre national and international clinical trials from one location; within the centre are logistical, operational, and consultative services that help accelerate the regulatory review process. CIRM intends to coordinate these two programs and the existing Alpha Clinic program (CIRM, 2016), which are three stem cell-focused clinics that operate within existing California medical centres (CIRM, 2015).

Predictable funding strategies, including stable support for platform technologies, infrastructure, and early clinical trials

Predictable funding for Canadian infrastructure related to regenerative medicine (e.g., GMP facilities and clinical trial sites) could provide consistency for the community, enabling long-term planning and a focus on innovation. Stable funding could support the significant day-to-day costs associated with regenerative medicine infrastructure, including the maintenance of equipment and facilities (e.g., the essential process of cleaning manufacturing rooms) and ongoing employment of HQP. Predictable funding strategies could also help ensure that initial start-up investments are not wasted.

Stable long-term funding for translational research and support

There is an opportunity to help move the most promising regenerative medicine therapies from late preclinical into early-phase clinical trial studies through the use of targeted support for translation research (as is now being done by SCN and OIRM). There are several promising regenerative medicine therapies in development in Canada (Box 2.1), and targeted translation funding could help ensure those that demonstrate success enter clinical practice and/or the marketplace. Workshop participants also noted that there is a lack of funding for translation to phase II and phase III clinical trials.

Other jurisdictions have changed regenerative medicine funding strategies to encourage the development of therapies as an outcome of basic research. For example, CIRM recently changed its funding from an initiative to systems-based approach, with a primary goal of providing continuous funding such that programs can progress from one development stage to the next without interruption (CIRM, 2016). The systems-based approach creates a continuum of R&D opportunities, with predictable and timely funding leading to a process that is more efficient overall. Importantly, this program could not be implemented until CIRM had the critical mass of researchers and resources needed to carry out the development of stem cell treatments from beginning to end (CIRM, 2016).

Engage and support the regenerative medicine industry in Canada

The identification of bottlenecks that hold up innovation in regenerative medicine could lead to shared strategies that address these barriers and engage important academic and industry consortia. The development and support of more consortia like the CCRM-GE Healthcare partnership in advanced manufacturing (see Section 2.2) would signal

Canadian leadership in the field, and may attract further industry to Canada. Additionally, the licensing of four STEMCELL Technologies products by GE Healthcare shows that a Canadian company is highly competitive internationally in the evolving regenerative medicine industry (GE Healthcare, 2016).

Furthermore, there is an opportunity to support Canadian industry and attract international industry to Canada by implementing new funding mechanisms, including seed funding for start-up companies, targeted infrastructure investments, and funding supports that de-risk private sector investment (e.g., incentives and tax and policy changes). An increased number of Canada-based regenerative medicine anchor companies could enable Canada to achieve return on innovation investment from multiple stages of the regenerative medicine pipeline (from R&D, through clinical trials, manufacturing and distribution, to delivery to patients). Table 3.1 outlines examples of Canada's current tax incentive structure for R&D and life sciences research, as well as those of other leading regenerative medicine countries.

Workshop participants also highlighted the importance of having strong Canadian anchor companies in the regenerative medicine space. These can build on the successful tools and technology company STEMCELL Technologies, to also include, for example, companies that develop and deliver therapies based on stem cell concepts. This could enable the scaling up of promising therapies, provide employment for Canadian HQP, and lead to new industrial R&D. The industry would include fully Canadian companies but also international companies that have headquarters or activities within Canada (e.g., Bayer AG and Versant Ventures' recent investment to form BlueRock Therapeutics). Companies from around the world have already demonstrated a desire to take advantage of Canadian R&D knowledge. For instance, Dr. Tim Kieffer of the University of British Columbia has a noteworthy collaboration with the American company Viacyte, where he acts as Scientific Advisor (CSCF, 2014).

Table 3.1

Selected Tax Incentives for R&D and Life Sciences Research in Leading Regenerative Medicine Nations

Country	Key Tax Incentive Programs
Canada	<ul style="list-style-type: none"> • There is a 15% federal tax credit for all qualifying R&D costs, excluding capital expenditures. • Refundable investment tax credits are earned by small Canadian-controlled private corporations at a rate of 35%. • Provincial tax credits are also available.
United Kingdom	<ul style="list-style-type: none"> • SMEs are eligible for a 230% superdeduction. Additionally, if an SME is in a loss position, a cash credit, equal to a maximum of 33.35% of qualifying expenditures, is also available. • Large companies can claim an 11% refundable tax credit. • A patent box regime allows companies to apply a lower tax rate (10%) on income attributable to patented technology.
Japan	<ul style="list-style-type: none"> • Tax credits worth 12% of total R&D expenditures for SMEs and 8 to 10% for all other companies are available. • Tax credits ranging from 20 to 30% are available for costs associated with collaborative research with R&D institutions. • Incremental credits of 5 to 30% are available when there is an increase in qualified research spending over prior years.
Australia	<ul style="list-style-type: none"> • Refundable tax credit worth 45% of eligible expenditure for SMEs (receipts less than AU\$20 million) is available. The credit is worth 40% for all other eligible entities. • A refundable tax credit is available for SMEs in an amount equal to 45% of the eligible R&D expenditure (but the expenditure is not deductible).
Israel	<ul style="list-style-type: none"> • Reduced tax rates are available through the Alternate Tax program, where companies pay a rate of 9% or 16% depending on the development area. • Large multinational companies can take advantage of the Strategic Program, which offers a reduced tax rate, provided they invest a minimum amount in R&D and hire a minimum number of employees.
United States	<ul style="list-style-type: none"> • Taxpayers can choose a traditional research tax credit or an alternative simplified credit. The traditional research tax credit is equal to 20% of qualified research expenses (QREs) above a base amount. The alternative simplified credit is worth "14% of the excess QREs over 50% of the average of the three previous years' QREs." • There are also a variety of local and state-wide credits and incentives, as well as specific grants to support small business technology commercialization (see Box 3.3 for more details).

Source: Deloitte, 2015

Targeted disease teams

There is an opportunity to further support targeted disease teams similar to those funded by SCN, ThéCell, and OIRM (OIRM, 2016a; SCN, 2016c; ThéCell, 2016a). Disease teams must include clinicians, basic researchers, ELSI (ethical, legal, and social implications), and other HQP focusing on the design of targeted therapies in areas that are already Canadian strengths (OIRM, 2016a; SCN, 2016c), and that are not being pursued aggressively by multiple research teams worldwide. Targeted therapies could also be those that show the most promise for feasible, cost-effective implementation in the future. However, the current funding is not sufficient to support all of those teams deemed fundable by external peer review and is not long-term. These teams could be supported by unique regulatory policies to encourage research on targeted diseases and treatments with the most potential. One example of a targeted regulatory policy is the FDA's priority review vouchers in the United States. These are designed to encourage therapies for neglected diseases or diseases particularly relevant to certain sub-populations, by allowing for accelerated review processes (Ridley, 2017).

Grow human capacity, including the support of new investigators

Having people with the right skills is essential to the success of regenerative medicine in Canada. Funding related to human capacity that targets the entire regenerative medicine pipeline would need to include translational research and support for the training of HQP in a wide variety of skills (e.g., legal, entrepreneurial). Workshop participants emphasized that, in order for the Canadian training system to be world-class, it would need to be forward-thinking and include a range of abilities beyond traditional academic skills in addition to cross-training. Importantly, this cross-training would incorporate the subjects of policy and ELSI, something that is included in some current SCN trainee sessions (e.g., SCN, n.d.). There is an opportunity to change the Canadian education system to include cross-training programs that produce convergence researchers capable of developing biologics, synthetic cells, and hybrid devices, for example, leading to a future generation of scientists who are well suited to the multidisciplinary regenerative medicine field. Furthermore, participants explained that support for young researchers entering the field would benefit the Canadian regenerative medicine community by ensuring exposure to new ideas that challenge established regenerative medicine scientists. Overall, a strong regenerative medicine community and greater support for new investigators could help Canada attract and retain the best researchers and companies from around the world, and continue to produce highly sought-after trainees who would have the opportunity and desire to work in Canada.

3.1.3 Enablement and Adoption Opportunities: Short-Term (1 to 2 years)

Embed health economic assessment in translational research to ensure feasible and practical therapies are pursued

Workshop participants identified meaningful health economic assessments as tools that can support adoption and investment decisions (e.g., payers, venture capital) and be used to inform R&D decisions. Such assessments are already required by certain funders (e.g., CCRM, SCN), but could become the norm for all translational research projects. The tools necessary for these assessments should also be readily available to investigators. There needs to be consensus on the depth required by these assessments to ensure they are always useful to researchers and funders.

Register Canadian clinical trials in a public, searchable, user-friendly, and up-to-date database

Currently, investigators in Canada may voluntarily register their clinical trials with www.clinicaltrials.gov, a database operated by the U.S. National Library of Medicine and NIH. Health Canada operates a database that "is not a registry, and therefore, it does not contain comprehensive information about each clinical trial" (Health Canada, 2016). As discussed in Section 2.2, although Health Canada encourages registration in publicly available registries like clinicaltrials.gov, it is not mandatory,¹ which makes it challenging to identify the number of clinical trials taking place in Canada. This separates Canada from the United States, where registration with clinicaltrials.gov is mandatory (Clinicaltrials.gov, 2016b). Similarly, clinical trial registration in the United Kingdom is required, and this information is used by the Cell and Gene Therapy Catapult to release an annual database of all relevant regenerative medicine clinical trials (Cell and Gene Therapy Catapult, n.d.-b; NHS Health Research Authority, n.d.). There is an opportunity to change policy and require *all* clinical trials in Canada to be registered within one registry with good searchability and usability. Further database modifications could include linking the trials database with existing communication mechanisms to inform doctors of new clinical trials.

¹ Some Canadian funding agencies, most notably the Tri-Councils, mandate that all clinical trials involving humans must be registered in a publicly available registry (Secretariat on Responsible Conduct of Research, 2014).

3.1.4 Enablement and Adoption Opportunities: Longer-Term (3 to 5 years)

Identify top opportunities for transformational impact in regenerative medicine therapies in Canada

A group of experts who take a systematic and ongoing approach to scanning the horizon could identify the most promising regenerative medicine opportunities (e.g., three per year) for transformational impact. This group could also benchmark Canada's performance in a global context. Experts in this group would need to include regulators, clinicians, researchers, and representatives from patient groups and health charities. Such a group could establish sustainable models for the adoption, governance, and dissemination of regenerative medicine therapies by bringing together all the relevant voices. It could also identify the barriers to the adoption of regenerative medicine therapies and discuss the potential impact of policy change.

Forum for policy development with a focus on the coordination of regulatory and reimbursement frameworks

An identified Canadian weakness is the lack of alignment between regulation involving decisions made at the federal level on the safety and efficacy of therapies, and reimbursement, where decisions are made at the provincial level (i.e., publicly funded healthcare systems). Coordination in reimbursement decision-making across Canadian jurisdictions could simplify applications for reimbursement for companies introducing new therapies. Such harmonization could improve uniformity of access across the country (e.g., ensure that a therapy covered in Ontario is also covered in Nova Scotia). A forum for policy development that focuses on aligning regulatory and reimbursement frameworks could help address this Canadian weakness.

One body that may be able to help with coordinating reimbursement decisions across provincial and territorial boundaries is the CADTH, an independent, not-for-profit organization that informs healthcare policy by providing objective evidence about drugs and medical devices (CADTH, 2017). In this manner CADTH could provide Canadian decision-making bodies with access to the same information for all regenerative medicine therapies. Supporting CADTH, and ensuring it has the mandate and the expertise needed to provide guidance on regenerative medicine, could support Canada's readiness for regenerative medicine.

A forum for policy development could also help address this challenge by producing policies that formalize Canada's position on conditional regulatory approval. A first step in this process would be to establish cell-based products as a separate regulatory class. In the longer term, removing the uncertainty around conditional regulatory approvals could encourage companies to introduce promising regenerative medicine therapies to the Canadian market earlier in their development.

Consider a policy whereby the cost of clinical care associated with clinical trials is paid by the existing healthcare system

While the costs associated with a new treatment in the trial stage are paid for by the funder of a clinical trial, the supporting activities (e.g., MRIs, acute care) could be paid through Canada's existing healthcare system given that these activities are covered for patients receiving established treatments. If Canadian healthcare systems were to consider covering partial costs of clinical trials, consultation with relevant stakeholders (including patient groups, health charities, and the general public) would be necessary.

Engage in public outreach, targeting patient organizations, health charities, and health practitioner groups

The general public is the main group set to benefit from regenerative medicine, through a more efficient healthcare system that provides better health outcomes. Ensuring that the public — and patients in particular — are informed of the potential benefits of regenerative medicine, as well as the challenges that need to be overcome, could boost public buy-in. Health charities and patient groups could greatly inform and improve the research process while also supporting participation in clinical trials and the donation of needed biological materials (e.g., tissues). Many of Canada's regenerative networks have this public outreach as part of their mandate. For example, SCN partners with Let's Talk Science to run StemCellTalks, an outreach initiative that facilitates information sharing between academic researchers and high school students on the subject of stem cells (CurioCity, 2017).

Tax incentives to encourage industry-academia partnership

Encouragement of private investments and partnerships may be useful for improving Canada's readiness for regenerative medicine. Policy measures, such as those instituted in Ireland and the United States, provide direct financing of research (Box 3.3), but only if those researchers form partnerships with private companies. These kinds of measures and the resulting industry-academia teams can help foster innovation and enable the commercialization of research results.

Box 3.3**Programs to Foster Public-Private Investment in Ireland and the United States**

The Centre for Research in Medical Devices (CÚRAM) is a Science Foundation Ireland (SFI) collaboration of experts from academia, industry, and clinical practice working towards designing the next generation of smart medical devices (SFI, 2016). Backed by €41.3 million in SFI and industry funding, CÚRAM has more than 150 researchers designing and manufacturing novel medical devices and implants able to react to the body's own environment. CÚRAM has 6 academic partners, and more than 24 industry partners, including Irish companies and multinationals. CÚRAM also supports product development and the formation of spin-off companies (SFI, 2016).

In the United States, the NIH's Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs are two of the biggest providers of capital for early-stage technology commercialization (NIH, 2016). These programs support U.S.-owned and operated small businesses in carrying out federal R&D for which there is a strong probability of commercialization. In 2016, SBIR and STTR planned to invest over US\$870 million into health and life science companies seeking to create innovative technologies that improve health. SBIR provides funding for early-stage small businesses working on the commercialization of innovative biomedical technologies, helping them participate in federal R&D, develop new technologies, and create jobs. While STTR is similar to SBIR, the former program requires that a business have a formal collaboration with a research institution in a phase I or phase II clinical trial (NIH, 2016).

3.2 CONCLUSIONS

Starting with a vision of future success in regenerative medicine, workshop participants identified several opportunities to accelerate Canada's advancement in regenerative medicine by using the field's strengths and addressing the identified weaknesses. Participants emphasized that the regenerative medicine research community is committed to success, and agreed that action led by the community could be taken immediately to improve coordination going forward. To ensure a comprehensive plan for the development and implementation of regenerative medicine therapies into healthcare systems, participants underscored the need for consultation and collaboration with provincial healthcare systems, healthcare provider groups, advocacy organizations, health charities, and patients. This dialogue should be ongoing because new therapies are continuously being discovered, tested, and implemented in clinical settings. The workshop highlighted that the funding framework for regenerative medicine in Canada has federal and provincial components, and a predictable and complete funding strategy — from discovery research through translation — would require coordination among all funders.

4

Conclusions

4 Conclusions

The field of regenerative medicine in Canada is built on a foundation of strong basic research; stem cells were discovered by Drs. Till and McCulloch at the Ontario Cancer Institute in Toronto, and researchers in Canada have continued to be leaders in discovery research. Canada's leadership in regenerative medicine has been supported by national organizations including SCN, CCRM, CDRD, and CellCAN, and provincial networks including OIRM (Ontario) and ThéCell (Quebec). These organizations have moved regenerative medicine in Canada forward by fostering national and international collaborations and partnerships, supporting high-quality research, and promoting public awareness. Further support is provided by the Canadian Stem Cell Foundation and various health charities. Overall, Canada has the research infrastructure and networks in place to continue to excel in regenerative medicine. Greater success and growth for the field will be supported by continued stable and strategic investment and by using existing resources to their fullest extent.

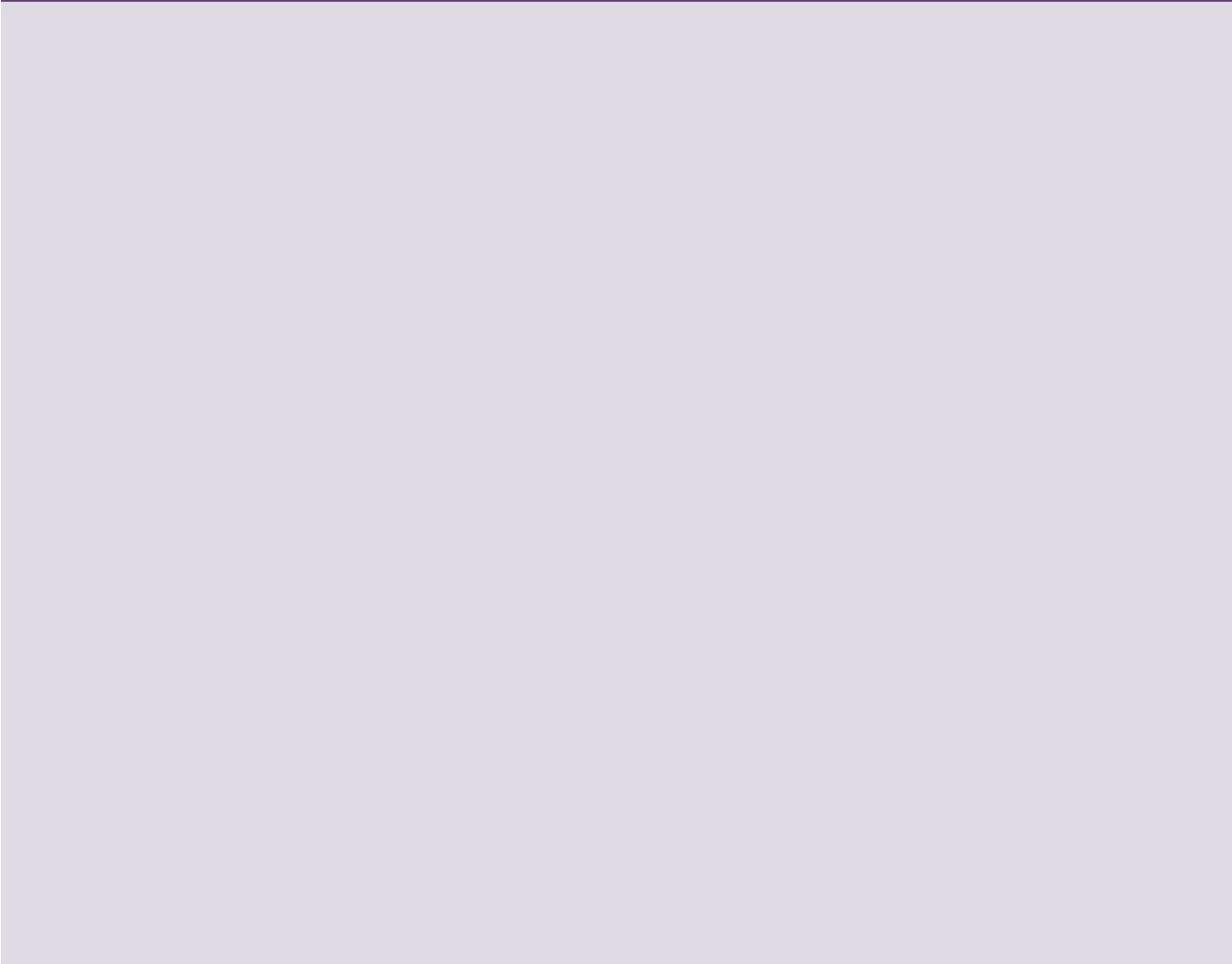
While Canada has a long history of excelling at discovery research in regenerative medicine, there is an opportunity for the country to become a leader in the translation of research discoveries to clinical and industrial settings. This opportunity has been recognized through the success of STEMCELL Technologies and the formation of CCRM and CDRD. The recent investment by Bayer AG and Versant Ventures of US\$225 million to form BlueRock Therapeutics, a regenerative medicine company based in Toronto (Bayer, 2016), indicates that international investors view Canada as a nation poised to lead the next wave of therapeutic developments in the field. Building on this momentum and continuing to foster national and international investment to create a strong regenerative medicine industry will be an important next step towards greater success.

It is clear that Canada's regenerative medicine community excels in part because of its strong emphasis on collaboration, but there is room to further take advantage of greater communication among stakeholders. For instance, coordination of efforts within the Canadian regenerative medicine community would allow Canada's world-class researchers, collaborative networks, clinicians, healthcare professionals, healthcare reimbursers, advocacy organizations, and health charities — as well as patients — to unite around a collective vision of future success in the field. Further, a long-term funding strategy, developed in consultation with all stakeholders, would bring stability to the national initiatives that support R&D across the entire regenerative medicine pipeline (including translation and commercialization), enabling these organizations to focus on innovation and long-term planning. Additionally, greater coordination between regulators (who make decisions about safety and efficacy at the federal level) and reimbursers (who make decisions about what therapies to pay for at the provincial level) could help ensure all Canadians have equal access to safe and effective regenerative medicine therapies.

In conclusion, Canada has an opportunity to leverage its strength in regenerative medicine to yield further benefits for patients, healthcare systems, and the economy as a whole. Successful regenerative medicine therapies have the potential to improve patient outcomes by opening the door to new treatments, or even cures, for many chronic diseases and genetic disorders. Developing and manufacturing novel regenerative medicine therapies would build an industry that has the potential to reduce treatment costs for some diseases, create new jobs for highly qualified personnel, and bring money into the economy.



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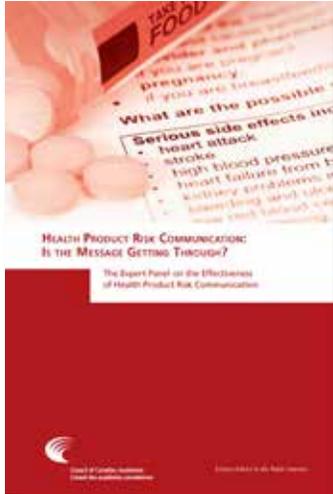
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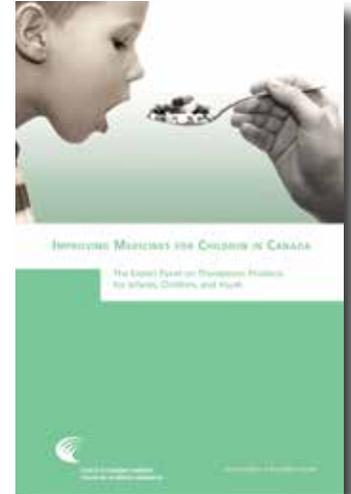
The assessment reports listed below are accessible through the CCA's website (www.scienceadvice.ca):



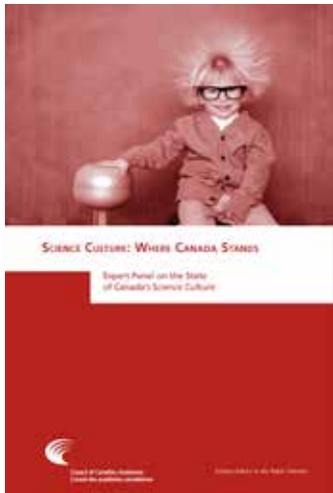
Health Product Risk Communication: Is the Message Getting Through? (2015)



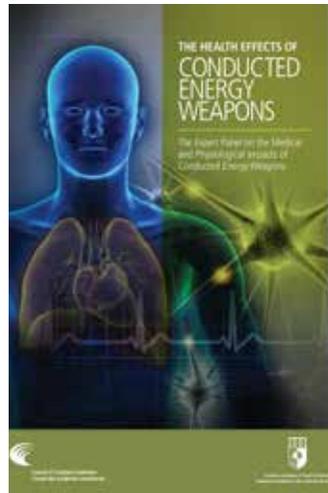
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Appendix A



Appendix A Bibliometric Analysis

This appendix details a bibliometric analysis of stem cell research, specific sub-disciplines within regenerative medicine, and clinical trials performed by researchers at Canadian institutions. While bibliometrics can provide useful information about Canada's research performance in regenerative medicine, some factors limit these insights. These include a lag time between publication and impact, as measured by citations, and the skewing of global numbers as a result of the dominance of China and the United States within the field. Furthermore, bibliometric analysis of translational research is hindered by the fact that clinical trial registration is not mandatory in Canada and cannot be used to fully examine commercialization. Therefore, the bibliometric findings provided both in this appendix and in the report should be used as only one of multiple inputs when considering the strengths and weaknesses of regenerative medicine research in Canada.

The bibliometric analysis presented in Chapter 2 and below identified stem cell research articles in Medline published between 2000 and 2014, then eliminated those that did not describe research studies (e.g., reviews, editorials, commentaries). This search included clinical studies. The analyses below focus on all articles that have at least one author from a Canadian institution (e.g., university or college, research centre, or hospital) based on affiliation data derived from the database Scopus.

A.1 RESULTS

Researchers in Canada published 8,187 stem cell-related research articles between 2000 and 2014, across the translational continuum from basic research to clinical research (including trials) (Figure 2.2). The impact of Canadian articles, as measured by citations, is high (see Chapter 2 for additional details). These results are consistent with an international comparison of stem cell research carried out by Science-Metrix (Box A.1).

The number of publications per year by researchers in Canada increased steadily between 2000 and 2012, at which point the number remains similar every year (see Figure 2.2); this trend holds true across sub-disciplines. This is consistent with global trends over the same period. The lack of increase

Box A.1 Analysis of Global Stem Cell Research

Science-Metrix's comparative analysis of global stem cell-related research articles across the translational continuum, published between 2010 and 2014, indicated that the impact of Canadian research is comparable to that of the United Kingdom, France, Germany, Sweden, and Australia. These countries have similarly strong, broad-based biomedical research support, but with targeted programs for regenerative medicine. Countries with comparable numbers of publications in stem cell research include Japan, South Korea, Italy, Germany, the United Kingdom, and France. In other words, the output of researchers in Canada is equivalent in terms of quantity and higher in terms of quality than the outputs of researchers in Japan and South Korea, despite those countries' specific focus on the field of regenerative medicine.

in the number of articles published from 2013 onwards may reflect either the maturation of the field, or a time lag in the addition of more recent articles to Scopus.

A.1.1 Regenerative Medicine Sub-Disciplines

As for most biomedical fields, clinical translation is founded on basic and pre-clinical research. As discussed in Chapter 2, while Canada continues to exhibit strength in stem cell research, translational activity has increased since 2008–2009 across (1) clinical stem cell research; (2) drug discovery research that uses or targets stem cells; and (3) cell and tissue engineering (Figure 2.2). Table A.1 summarizes the number of citations in general and the number of papers that were cited more than 100 times for all stem cell research and all of the sub-fields. These are proxies for quality, however; a limitation is that different fields have different citation patterns, especially engineering disciplines compared to clinical and basic research. The data are therefore not directly comparable.

The geographical location of co-authors for each of the sub-disciplines is similar to that of stem cell research in general (Figures A.1 and A.2, and Figure 2.1, respectively).

Table A.1
Characteristics of Canadian Stem Cell Publications, Authored Between 2000 and 2014

	Number of Publications	Number of Co-Authors	Number of Citations (Range)	Number of Articles Cited >100 Times (% of Articles)
All Stem Cell Research*	8,187	32,742	126,430 (0–63)	861 (10.3)
Drug Discovery Research that Uses or Targets Stem Cells	864	6,157	23,842 (0–1006)	82 (9.5)
Cell and Tissue Engineering Research	1,097	5,637	14,384 (0–591)	78 (7.1)

* Includes stem cell research and clinical stem cell research.



Figure A.1
Location of Authors of Articles Related to Drug Discovery Research that Use or Target Stem Cells with at Least One Canadian Author
 Location of all authors of 864 drug discovery articles that use or target stem cells published between 2000 and 2014 with at least one author from a Canadian institution.

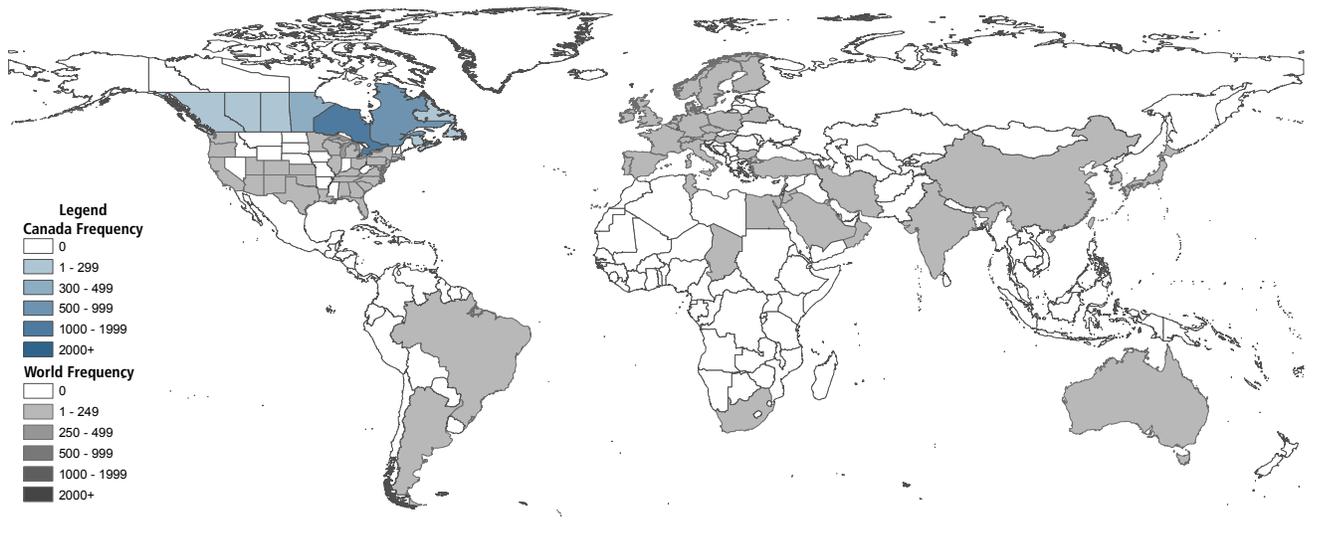


Figure A.2
Location of Authors of Articles Related to Cell and Tissue Engineering with at Least One Canadian Author
 Location of all authors of 1,097 cell and tissue engineering articles published between 2000 and 2014 with at least one author from a Canadian institution.

A.2 METHODS

A.2.1 Publication Searches

Four datasets were created for the bibliometric analysis using the search algorithms detailed in Section A.3. Search terms were developed in collaboration with field experts. All searches were conducted between November 10 and November 30, 2016, using the Ovid Databases Collection for complex queries of the resource: "Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid Medline (R) Daily and Ovid MELINE(R) 1946 to Present." The four datasets were:

1. **Stem Cell Research** (all translational stages from basic to clinical)
2. **Clinical Stem Cell Research** (Stem Cell Research with the application of clinical filters)
3. **Drug Discovery Research that Uses or Targets Stem Cells** (Stem Cell Research combined with synonyms for drug discovery research)
4. **Cell and Tissue Engineering Research**

A.2.2 Publication Record Retrieval

Each set of Medline publication records was exported from Ovid in groups of 1,000 in XML format. These files were then parsed using a custom XML to CSV parser and joined into one CSV file. This file was then imported into MySQL for storage and querying. Next, the Unique Identifier column of each set of records was converted into a search string for use in the bibliometric database, Scopus (Elsevier). The Unique Identifier column in Medline matches the PubMed ID column in Scopus. Scopus was searched using the PubMed ID search string for each of the four datasets. The full Scopus records were downloaded, parsed, and then imported into MySQL for data storage and querying. The resulting dataset sizes were as follows, indicating the number of records lost in converting from Medline to Scopus.

1. Stem Cell Research: Medline (n=212,388); Scopus (n=170,964) (searched on November 10, 2016)
2. Clinical Stem Cell Research: Medline (n=68,397); Scopus (n=42,581) (searched on November 10, 2016)
3. Drug Discovery Research: Medline (n=32,339); Scopus (n=34,145) (searched on November 30, 2016)
4. Cell and Tissue Engineering Research: Medline (n=36,707); Scopus (n=34,145) (searched on November 30, 2016)

Each of the datasets was then filtered by author affiliation — the Scopus field for "author affiliation" contained "Canada." The date range was further limited from 2000 to 2014 to account for apparent lags in indexing of records in both Medline and then in Scopus. Each dataset was additionally limited for article type to exclude editorials, reviews, and other opinion-based articles. The focus was on empirical research and therefore the only article types that were included are: clinical studies, clinical trials, comparative studies, corrected and republished articles, journal articles, observational studies, and randomized controlled trials.

These limits resulted in the following number of records:

1. Stem Cell Research: 8,187 records
2. Clinical Stem Cell Research: 1,563 records
3. Drug Discovery Research: 864 records
4. Cell and Tissue Engineering Research: 425 records

A.2.3 Author Name Disambiguation

Each of the four datasets was parsed using a custom author-name disambiguation program that relies on the Scopus Author Identifier data field.

A.2.4 Geo-Positioning of Authors

For each author, the Scopus author address field was parsed for country, state/province, and postal code information. These data were compared against U.S. zip codes, U.S. states, Canadian postal codes, Canadian provinces, and world country data to identify the most specific latitude and longitude available by importing the author-location data into a CSV to KML website (www.mapsdata.co.uk), which produced a KML file of latitudes and longitudes.

The resultant KML file of the author-location data was imported to ArcGIS Desktop 10.0 (2011, Environmental Systems Research Institute), which was used to produce maps of author locations.

A.2.5 Analysis of Medical Subject Headings (MeSH) Terms

MeSH is the (U.S.) National Library of Medicine (NLM)'s controlled medical vocabulary resource, which provides a hierarchically organized terminology for the indexing and cataloguing of biomedical information in NLM databases such as Medline/PubMed. MeSH terms were used for database searches (see Section A.3).

A.2.6 Citations

The number of citations derives from the citations field in Scopus.

A.3 SEARCH ALGORITHMS

1. Stem Cell Research (all translational stages from basic to clinical)

1. 1. Stem Cells/
2. 2. exp Cellular Reprogramming/
3. 3. exp Cord Blood Stem Cell Transplantation/
4. 4. exp Embryoid Bodies/
5. 5. exp Hematopoiesis/
6. 6. exp Hematopoietic Cell Growth Factors/
7. 7. exp Hematopoietic Stem Cell Mobilization/
8. 8. exp Hematopoietic Stem Cell Transplantation/
9. 9. exp Mesenchymal Stem Cell Transplantation/
10. 10. exp Muscle Development/
11. 11. exp Neurogenesis/
12. 12. exp Peripheral Blood Stem Cell Transplantation/
13. 13. exp Stem Cell Factor/
14. 14. exp Stem Cell Niche/
15. 15. exp Stem Cell Research/
16. 16. exp Stem Cell Transplantation/
17. 17. exp Tumour Stem Cell Assay/
18. 18. exp Wharton Jelly/
19. 19. neurogenesis.ab. or neurogenesis.ti.
20. 20. progenitor cell*.ab. or progenitor cell*.ti.
21. 21. stem cell*.ab. or stem cell*.ti.
22. 22. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21

2. Clinical Stem Cell Research (Stem Cell Research with the application of clinical filters)

To identify clinical research, we applied the following “clinical” filters² to the search in “1” to:

(humans and ("therapy (maximizes sensitivity)" or "therapy (maximizes specificity)" or "therapy (best balance of sensitivity and specificity)")

3. Drug Discovery Research That Uses or Targets Stem Cells (Stem Cell Research combined with synonyms for drug discovery research)

1. drug.mp. or exp Pharmaceutical Preparations/
2. exp Chemistry, Pharmaceutical/ or pharmaceutical.mp. or exp Technology, Pharmaceutical/
3. biologic.mp. or exp Biological Products/
4. stem cell.mp. or exp Stem Cells/
5. 1 or 2 or 3
6. 4 and 5

4. Cell and Tissue Engineering Research

1. exp Cells/
2. exp Tissues/
3. organ.mp. or exp Organ Transplantation/ or exp Organ Culture Techniques/
4. exp Bioengineering/ or exp Tissue Engineering/
5. exp Biomedical Engineering/
6. exp Bioprinting/
7. 1 or 2 or 3
8. exp Cell Engineering/
9. exp Guided Tissue Regeneration/
10. exp Tissue Scaffolds/
11. (bioengineer* or bio-engineer* or biomaterial* or bio-material* or bioprint* or tissue scaffold or cell* engineer*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
12. 4 or 5 or 6 or 8 or 9 or 10 or 11
13. 7 and 12

² See https://www.ncbi.nlm.nih.gov/books/NBK3827/#pubmedhelp.Clinical_Queries_Filters.



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