Receptor Capacity for Biotechnology Innovation in Canada

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Editor's Preface

Launched in 2009, GPS: *Where Genomics, Public Policy and Society Meet* is a series hosted by Genome Canada to facilitate a dialogue between federal policymakers and researchers exploring issues at the interface of genomics and its ethical, environmental, economic, legal and social aspects (or GE^{3}LS).

Overarching themes for the series and specific topics are selected on the basis of their importance and timeliness, as well as the "ripeness" of the underlying scholarship. Accordingly, the series focused on "Genetic information," whereas in year two, attention shifted to "Translational Genomics". Our third series, "The Innovation Continuum" broadens the discussion by casting the process of innovation in a broader societal context.

At the core of these exchanges is the development of policy briefs that explore options to balance the promotion of science and technology while respecting the many other considerations that affect the cultural, social, or economic well-being of our society.

Co-authors of the briefs are leaders in their field and are commissioned by Genome Canada to synthesize and translate current academic scholarship and policy documentation into a range of policy options. The briefs also benefit from valuable input provided by invited commentators and other experts who participate in GPS events. Briefs are not intended to reflect the authors' personal views, nor those of Genome Canada. Rather than advocating a unique recommendation, briefs attempt to establish a broader evidence base that can inform various policymaking needs at a time when emerging genomic technologies across the life sciences stand to have a profound impact on Canada.

Karine Morin
Director,
National GE^{3}LS Program

Authors:
David Castle, University of Edinburgh
John Bell, University of Ottawa
Robert Hanner, University of Guelph
Tania Bubela, University of Alberta
Peter Phillips, University of Saskatchewan
Keith Culver, University of British Columbia

Executive Summary

Biotechnology innovation and its impact on private sector growth has been an interest of the Canadian federal government for more than 40 years. Despite this perennial interest, the evidence from life science and biotechnology related funding policies and programs, as well as the extent of private sector biotechnology activity, indicates that Canada mostly remains in a 'science and technology push' rather than 'market pull' mode. Public sector investments continue to generate a strong base in the life sciences, stimulating discoveries and generating inventions, training successive generations of students and technical staff, and contributing to respectable achievements in international scientific scholarship. Yet the gap between the research base and expectations of development of commercialisable technologies remains. Many explanations of this gap have been offered, including a culture of risk aversion in Canadian businesses, a lack of direct public investment in early stage innovation, a small domestic venture capital base to bridge the innovation 'valley of death', lack of public procurement strategies for new technology, and weakness in Canadian intellectual property protection. All of these putative causes might contribute to the unchanging nature of the Canadian life science industry in which the positive feedback loops that would build and sustain growth are absent. Among the most important of these is the development of private sector capacity to absorb and exploit the new knowledge arising from inventions and discoveries. This receptor capacity is linked, theoretically and empirically, to a firm's dynamic capabilities to anticipate, monitor, and respond to new knowledge and remain competitive. As described in this policy brief, there are cases in Canadian life science innovation where dynamic capabilities have been cultivated and create desired positive feedback loops for innovation. Policy options are suggested for moving towards regionally focused smart specialisation and greater direct support for early stage innovation. Both options will foster receptor capacity and will improve the dynamic capabilities of the life science sector.

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About the Authors

David Castle's interests include innovation in the life sciences and social aspects of biotechnology. His research focuses on the interaction between science and society, including democratic engagement, regulation and governance, and intellectual property and knowledge management. He has published dozens of peer-reviewed articles and book chapters and several books on the social dimensions of science, technology and innovation. Castle has held several major research awards, and has considerable experience leading strategic research initiatives and research project management. In addition, he has consulted widely to government and industry on issues such as the impact of national technology transfer policies and programs, intellectual property strategies for the health research and development, and the role of non-scientific considerations in the regulation of science and technology.

John Bell received his Ph.D. from McMaster University in 1982. The three years that followed, he trained as a post-doctoral fellow at the University of Ottawa and then at the Medical Research Council in London, England. Dr. Bell began his independent research career at McGill University in 1986 and moved to the University of Ottawa, Department of Medicine, in 1989. He is a member of the Center for Cancer Therapeutics at The Ottawa Hospital Cancer Center, a Senior Scientist with the Ottawa Hospital Research Institute and Professor of Medicine at the University of Ottawa. He heads the Canadian Oncolytic Virus Consortium, a Terry Fox funded group from across Canada that is developing virus based cancer therapeutics and is the Director of the Biotherapeutics Program for the Ontario Institute for Cancer Research. His research program is directed towards the identification and characterization of novel viruses that specifically infect and kill cancer cells. Currently he is the Chief Scientific Officer for Jennerex Biotherapeutics, a small biotech company that performs clinical testing of virus therapeutics in patients.

Tania Bubela is an Associate Professor in the School of Public Health and adjunct professor in the School of Business at the University of Alberta. Her research program in knowledge management and knowledge translation in translational life sciences brings together her legal training and a Ph.D. in biology and expertise in genetics and molecular biology. She joined the faculty of the University of Alberta in 2004 after clerking for The Honourable Louise Arbour at the Supreme Court of Canada, articling at Field Law LLP in Edmonton, and being called to the bar (Law Society of Alberta) in 2005. She has consulted with government health and science agencies, international funding organizations, the life sciences research communities, and patient organizations. Her research program focuses on large collaborative science networks in genomics, gene therapy, and stem cell biology, addressing barriers to the effective translation of new technologies. These are varied and include ethical issues, effective communication of risks and benefits among stakeholder groups, commercialization and regulation. Her research is funded by CIHR, the Canadian Stem Cell Network, and Genome Canada. She has over 60 publications in law, ethics and science policy journals including Nature, Nature Biotechnology, Cell Stem Cell, Trends in Biotechnology, American Journal of Bioethics and Science Translational Medicine.

Robert (Bob) Hanner is an Associate Professor within the Biodiversity Institute of Ontario at the University of Guelph. He received a Ph.D. in Biological Sciences from the University of Oregon and then joined the American Museum of Natural History (AMNH) as a postdoctoral fellow and subsequently served as the Curatorial Associate of the Ambrose Monell Collection for Molecular and Microbial Research. He then joined the Coriell Institute for Medical Research, where he served as Scientific Program Director. During this time he also served as President of the International Society for Biological and Environmental Repositories (ISBER). Bob Hanner currently serves as the campaign coordinator for the Fish Barcode of Life (FISH-BOL) initiative and also as the North American Node Representative to the Global Biodiversity Information Facility (GBIF). His research program focuses on varied socio-economically relevant applications of DNA barcoding.

Peter Phillips is Professor of Public Policy in the Johnson-Shoyama Graduate School of Public Policy at the University of Saskatchewan, in Saskatoon, Canada. He earned his Ph.D. in International Political Economy at the London School of Economics and practiced for 13 years as a professional economist and senior policy advisor in Canadian industry and government. At the University of Saskatchewan he has held the Van Vliet Research Chair, created and held an NSERC-SSHRC Chair in Managing Technological Change, was a founding member and director of the virtual College of Biotechnology and was founding director of the graduate school of public policy. He was a founding member of the Canadian Biotechnology Advisory Committee, has been a member of the Board of Directors of the Canadian Agri-food Policy Institute, and is vice-Chair of Ag West Bio Inc., which operates a biotech venture fund. His current research focuses on governing transformative innovation, including regulation and policy, innovation systems, intellectual property management, trade policy and decision systems. He is co-lead and principal investigator of a $5.4 million Genome Canada project entitled Value Addition through Genomics and GE^{3}LS (VALGEN) which runs 2009–14 and has been an applicant and investigator on more than 15 peer reviewed grants worth more than $150 million. He has been author or editor of 13 books – his latest, *Innovation in Agri-food Clusters* was published in 2012 by CABI – and more than 90 journal articles and book chapters.

Keith Culver is Professor of Management, and Director of the Okanagan Sustainability Institute. Dr. Keith Culver serves as Acting Dean of Management in the absence of the Dean. In addition to his administrative role, he conducts research at the intersection of sustainability, jurisprudence, and knowledge mobilization for innovation. He previously taught at the University of New Brunswick where he was Professor of Philosophy, and in France where he held the Econoving International Chair in Eco-Innovation in the UniverSud Paris consortium of universities. Recent representative publications include Culver and Giudice, *Legality's Borders* (Oxford UP 2010) and Culver and Castle, eds., *Aquaculture, Innovation and Social Transformation* (Springer, 2008).

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I. Context

Canada's R&D and innovation performance is now back in the spotlight. Since 2008, the federal government, a number of provinces, most of the granting agencies, many firms, and a number of sectors are undergoing a period of introspection and evaluation. The federal government has signalled its impatience with a science focus that is not yielding transformative technologies that enhance Canada's economy. Backed by a wave of studies, reviews and expert panels on the state of science, technology and innovation (STI) in Canada, the federal government has begun to act.

As one of the first and arguably one of the few sustained federal instruments to advance STI in Canada, the National Research Council (NRC) has been a sentinel institution for transformations in Canada's STI policy. In recent years, the NRC has been targeted with operating cuts and a reorientation toward strategic R&D to leverage private capital and engage with industrial assistance and infrastructure programs more directly (Potter 2011). History appears to repeat itself; more than four decades ago, a Canadian federal government commission expressed concern about the gulf between Canada's science base and the interests of industry. The Glassco Commission noted the National Research Council's (NRC) tendency to serve the interests of university-based research scientists while ignoring the interests of industry. This criticism of the NRC drew upon the conviction that one of the "original purposes of government in devoting money to research was to encourage and stimulate Canadian industry" (Government of Canada (Glassco) 1962). Given that the NRC was not originally intended to have the strength of industrial linkages implied by Glassco's remark, the criticism can be viewed as a provocation to reorient public investment in scientific research in Canada. The Science Council of Canada (SCC) was formed in 1966 with this objective in mind (Wilks 2004), and, buttressed by the calls in the Lamontagne Report to improve upon and exploit the science-industry nexus (Special Committee on Science Policy (Lamontagne) 1970-3), Canadian science policy moved in the direction of state-managed publicly funded science with an industrial outlook (Atkinson-Grosjean 2006).

From the 1960s onward, Canadian science policy embraced the view that it is the 'proper business' – in the sense suggested by the Vannevar Bush report *Science: The Endless Frontier* two decades previously – of government to encourage and enable scientific and technological knowledge flows from universities to industry (Bush 1945). State-mediate coordination of university research and private sector interests intensified in the 1970s. In 1971 the Ministry of State for Science and Technology (MOSST) was formed to promote the "application and development of science and technology in Canada" (Privy Council Office 1971). Anachronistically speaking, the reorganisation of MOSST in 1975 into three coordinated Branches, one for government, industry and university, made it an early exemplar in Canada of the Triple Helix model of innovation. By 1983 MOSST took over as the Chief Scientific Advisory body to government, completing a process through which the SCC had taken over from the NRC, and was now itself usurped.

In a 1980 background paper, MOSST observed that developments in cellular and molecular biology "thrust the world onto the threshold of a new technological revolution" (Ministry of State for Science and Technology (MOSST) 1980) because the inputs of biotechnology are renewable and the outputs are generally non-hazardous – on the face of it a potentially perfect industrial system for the resource-based Canadian economy. The National Biotechnology Strategy (NBS) (1983) and National Biotechnology Advisory Committee (NBAC) focused on growing the Canadian biotechnology industry. The 1998 renewal of the NBS as the Canadian Biotechnology Strategy (CBS) described biotechnology as a "powerful 'enabling technology'" that would transform many sectors of the Canadian economy while generating jobs and making Canada more competitive (Canadian Biotechnology Strategy Secretariat 1998). This strategy was expanded through the creation of Genome Canada in 2000 to take advantage of the genomics and proteomics revolution through the translation of research results for the "benefit of all Canadians."

While explicit links between university-based research in science and technology and the private sector have existed for more than a century, the dynamics of university-industry linkages shifted radically in the post-war period toward a state-coordinated system to take advantage of university and industry roles in R&D. Canada has been slower than the United States in coordinating its system, but Canadian science policy of the last few decades reflects an aspiration to develop research and industrial capacity in biotechnology. Yet, for more than two decades there has been awareness that biotechnology capacity in Canada is nascent and needs cultivation. As the NABC Task Force remarked about its deliberations leading up to its 1984 report, it was

> *… well aware of the advantages of a "market-pull" rather than a "technology-push" approach to industrial development. However, the almost total absence of biotechnology industrial activity in Canada necessitated recommendations supporting a technology orientation, at least in the short term, for this country's development of biotechnology (National Biotechnology Advisory Committee (NBAC) 1984).*

Whereas the Swedish Paradox refers to the observed discontinuity observed between increased expenditure on S&T research and returns on innovation-led growth, the 'Canadian Paradox' is the discontinuity between the rising number of well-crafted, critical reports about Canadian innovation versus weak and declining indicators of Canadian innovation performance (Science Technology and Innovation Council 2009, 2011, 2013; Council of Canadian Academies (CCA) 2009, 2013). The Canadian Paradox led *Globe and Mail* columnist Jeffery Simpson to remark that unlike our competitors who focus on innovation issues with an "intensity that reflects the urgency they deserve," in Canada "we write reports" (Simpson 2009).

The issue that Canada should be focused on with the intensity it deserves is that while Canadian science and technology may be competitive, our innovation performance is relatively weak and not improving. Despite recent World Economic Forum promises of "major transformations to position Canada for growth over the next generation" through key investments in science and technology (Stephen Harper 2012), the federal government's long term plans for science, technology, innovation and industrial policy renewal are uncertain. Federal government investments in scientific research (GERD) have fallen over the last decade (Castle and Phillips 2011), but despite this drop, Canada momentarily maintains a strong presence in the top 100 universities ranked by the Times Higher Education and QS survey and produces around 4% of the world's scientific publications (Science Technology and Innovation Council 2011). Canada remains a competent publicly-funded producer of scientific knowledge, but is less successful at exploiting scientific and technological knowledge in the private sector.

Canadian STI performance has several well-documented aspects that are targets for potential reform:

- Canada's multifactor productivity (MFP) over the last decade raises questions about the sustainability prided social services and economic resilience in light of rising labour costs (Organization for Economic Cooperation and Development (OECD) 2012). Neither the OECD report of MFP productivity gains of just 0.28% from 1969 to 2011 nor the Statistics Canada data suggesting 1.03% growth (Diewertand and Yu 2012) are grounds for optimism relative to OECD competitors.
- Canadian business' aversion to risk, reflected in low Business Enterprise Research and Development spending (BERD) and a tendency to reinvest in personnel but not process innovation (Council of Canadian Academies (CCA) 2013), undermines business' ability to keep a virtuous cycle of interaction with venture capital firms (Science Technology and Innovation Council 2011).
- The 2013 CCA report on industrial R&D (IRD) comments on a structural mismatch between areas of research excellence (clinical medicine, historical studies, information & communication technologies, physics & astronomy, psychology & cognitive science and visual & performing arts) and sectors with respectable levels of IRD (aerospace products & parts manufacturing, information & communication technologies, oil & gas extraction, pharmaceutical & medicine manufacturing).
- Federal tax credits for industry exceed $4 billion per year with the provinces absorbing an additional $1B, but the OECD argues for a more targeted approach to improve the 'connective tissue' to translate research into commercial opportunities: "innovation might be encouraged more effectively, and risks better balanced, by reducing the importance of tax expenditures and relying more on grants" (OECD 2012).
- 80% of direct support to Canadian industry is through SR&ED (Nicholson 2009). Canada and the US spend roughly 0.25% of GDP on direct IRD supports, but in the U.S. the mix of tax credits to other forms of direct government support is inversely proportional to Canada. Direct supports in the U.S. helped American firms like Google and Apple to succeed (Mazzucato 2013) whereas Canada takes a passive but more *laissez faire* approach with SR&ED credits.

Returning to the post-war focus of improving university-industry coordination, and the multi-decade agenda of developing a Canadian biotechnology industry, the foregoing makes clear the systemic challenges to developing the commercial potential of publicly funded research. Furthermore, the Canadian biotechnology industry, while long in the making, is certainly far from mature. Notably, among Canada's research and industrial strengths, biotechnology continues to receive very little attention in the reports already cited – for example, life science innovation is not prominent in the most recent Council of Canadian Academies report on industrial R&D capacity.

The basic but largely undefined problem is whether/how Canada can generate appropriate absorptive and receptor capacity to translate our competitive performance in bio-based science and technology into industrial innovation.

II. Background and Theoretical Underpinnings

The linkage between risk aversion, BERD, the role of SR&ED credits, and innovation performance can be linked to business' ability to become a better receptor for knowledge flows arising in particular from universities. Commenting in *The Globe and Mail*, two now-former university presidents said:

Universities, colleges and hospitals could all do better at turning discoveries into marketable services and products. But Canada's total R&D spending as a percentage of GDP is middle of the pack in the OECD, primarily due to Canada's low and falling level of spending in business R&D. Thus, while researchers in public institutions will continue to push out ideas and inventions, it's the receptor capacity in the private sector that needs urgent attention (Naylor and Toope 2010).

Direct discussion of 'receptor capacity' in Canada is relatively uncommon, which is puzzling given that it is a widely recognised critical attribute of the private sector in innovation scholarship and policy making. In three STIC reports for example, there are two mentions of 'receptor capacity.' These refer to potential improvements to internships and cooperative programs that would make firms better receptors of new knowledge (STIC 2009; 2011), development of firm research programs to assimilate new knowledge more easily (STIC 2011), and a comment about the "weak receptor capacity to take advantage of and exploit science, technology and innovation opportunities" (STIC 2013). Yet 'receptor capacity' is the concept that underpins the idea that firms will have the resources and ability to help co-develop and benefit directly from scientific research and technology development in a 'pull' rather than a 'push' model. Genome Canada's five-year plan, for example, describes the desired transition:

There appears to be strong interest in moving from a "push" based approach wherein scientific discoveries are used to fuel downstream activities to a "pull" based model wherein science is conducted in the context of a defined challenge. This is not the same as emphasizing one or the other in the term "R&D". Rather it is growing recognition that there is no point in solving a problem without a need to solve it. Increasingly, downstream expertise is required to apply the knowledge gained through science to create something of significant impact. It is about innovation (Genome Canada 2012).

'Downstream expertise' can be articulated in terms of the 'receptor capacity' that enables firms to take advantage of new knowledge.

In ordinary speech, 'receptor capacity' refers to the presence of a firm that is potentially able to use new knowledge. In the technical sense, 'receptor capacity' refers to the specific characteristics and abilities of firms that make them not only able, but also willing, to seek, adapt, adopt and use knowledge. In contrast with large firms that are capable of buying-in and retaining knowledge and expertise through mergers and acquisitions, many smaller firms exploit external knowledge without necessarily increasing their size or scope or diversifying their operations. The ability to "recognize the value of new information, assimilate it, and apply it to commercial ends" is a firm's 'absorptive capacity,' and the central idea is that firms that undertake their own R&D, or have experience exploiting external R&D, will have the "prior knowledge to assimilate and use new knowledge" (Cohen and Levinthal 1990). Absorptive capacity is therefore at once a function of the experiences of the people and the collective memory of a firm, especially if it is engaged in IRD and complements its own activity with exogenous knowledge exploitation. Absorptive capacity also creates path dependencies in which accrual of new knowledge is conditioned by the type of knowledge and sources previously encountered.

Teece and Pisano (1994) contrast 'resource-based strategy,' in which firms accumulate technology assets and seek aggressive intellectual property stances to protect them, with firms that deploy 'dynamic capabilities.' Dynamic capabilities are defined as:

…the firm's ability to integrate, build and reconfigure internal and external competencies to address rapidly changing environments. Dynamic capabilities thus reflect an organisation's ability to achieve new and innovative forms of competitive advantage given path dependencies and market positions (Teece, Pisano, and Shuen 1997).

A firm's dynamic capabilities are analyzable in terms of processes (organizational and managerial, learning, reconfiguration and transformation), positions (complementary, financial and locational assets) and paths (dependencies, opportunities). The assessment of dynamic capabilities is difficult, however, and does not admit of easy metrology because behaviour and performance are firm-specific and are difficult to replicate or imitate. Like all intangible assets, dynamic capabilities such as firm experience and organisation are not captured on balance sheets or company reports, and therefore "generally cannot be bought; they must be built" (Teece and Pisano 1994). The process of building capabilities can take decades to achieve (Teece, Pisano, and Shuen 1997), which explains why attempts to emulate, imitate or replicate success observed elsewhere are doomed – particularly in the case of cookie-cutter approaches to cluster formation promulgated in the 1990s.

Absorptive capacity has been conceived as a dynamic capability with two modalities – realised and potential absorptive capacity – and four routines or processes: acquiring, assimilating, transforming and exploiting knowledge (Zahra and George 2002). This approach focuses primarily on the potential for absorptive capacity, since this relates most directly to firm strategy in dynamic environments. Importantly, the ratio of realised to potential absorptive capacity, which is called an 'efficiency factor,' indicates the extent to which a

firm can draw on the kind of learning and experiences described by Cohen and Levinthal as it identifies, absorbs and uses exogenous knowledge. Some of this learning can be developed through partnerships with universities. Recent scholarship on university-industry partnerships emphasises the over-arching importance of relationships that foster innovation, rather than focusing on metrics of technology transfer (Perkmann and Walsh 2007). This is particularly important from the firm standpoint in which learning or absorptive capacity and the development of dynamic capabilities influence organisational culture and behaviour.

III. Case Studies

The following five condensed case studies demonstrate the range of biotechnology receptor capacity in Canada, and to give real examples of positive and negative experiences that can serve as guides for the future. The case studies confront directly the view that the private sector in Canada is unable or unwilling to adopt new technology so as to explore presumptions about the lack of 'receptor capacity,' including: a) the lack of 'absorptive' capacity in Canadian firms leading to low levels of firm learning and innovativeness; b) lack of enabling developer-user interfaces; c) culture of risk-aversion in Canadian firms; d) absence of innovative funding models; e) relative lack of direct supports to technology intensive firms by government. Each case study illustrates commercialisation performance with which a Genome Canada related technology has been commercialised, and each emphasises the development and exploitation of private sector receptor capacity or the exploitation of existing receptor capacity.

3.1 Investments in Canadian Aquaculture

Canadian aquaculture of marine and freshwater finfish, shellfish and plants had a production value of $926.5 million in 2010 (Department of Fisheries and Oceans 2012), making it relatively small in global terms. Canadian aquaculture has nonetheless benefited from nationally subsidized R&D programs including the AquaNet Network of Centres of Excellence (1999–2006), a 2008 NSERC Strategic Grant (NSERC 2008) and the current Department of Fisheries and Oceans Aquaculture Collaborative Research and Development Program (Fisheries and Oceans Canada 2013). Completed genomics R&D projects include the 2001–2005 $6.2 million Genomic Research on All Salmon Project (GRASP) and 2006–2010 $15 million cGRASP (consortium GRASP) projects investigating salmon; the 2004–2007 $4.1 million Pleurogene project investigating halibut; and the 2006–2010 $18.4 million Atlantic Cod Genomics and Broodstock Development Project (Fisheries and Oceans Canada 2013). Through GRASP and cGRASP widely used microarrays were developed (Genome British Columbia 2013), the technology and underlying knowledge formed the basis of international partnerships, (Davidson et al. 2010), and commercial collaborator Mainstream Canada use the knowledge (Gutierrez et al. 2012). The Pleurogene project's commercialization partner Scotian Halibut diversified its activities as a result of the project (Scarratt 2012). By contrast, the Atlantic cod genomics project's did not lead to Cooke Aquaculture to farm Atlantic cod (CBC News 2010) and the remaining elite Atlantic cod broodstock are now maintained for Genome Atlantic at the International Aquaculture Innovation Centre (www.huntsmanmarine.ca).

3.2 A Decade of DNA Barcoding: The Technology and its Uptake

DNA barcoding is the sequencing of sequencing a short, standardized mitochondrial gene region for all animals to build a comparative sequence database (Ratnasingham and Hebert 2007) that could support the rapid, accurate and cost-effective identification of species (Hebert, Cywinska, and Ball 2003). Investments of more than $80M into barcoding infrastructure and direct costs of research include Genome Canada sponsors the International Barcode of Life (iBOL.org) project, the largest biodiversity genomics initiative ever undertaken. Barcoding's applications have been recognized (Stoeckle 2003): for parasites and vectors of zoonotic diseases (Besansky, Severson, and Ferdig 2003); agricultural and forestry pests (Armstrong and Ball 2005) (Floyd et al. 2010); other species of socio-economic importance (Schander and Willassen 2005); authentication of cell lines used in research (Lee et al. 2011); detection of seafood fraud (Wong and Hanner 2008); illegally traded wildlife products (Eaton et al. 2010); forensics (Dawnay et al. 2007); and environmental metabarcoding (Shokralla et al. 2012). While Canada leads the world in DNA barcoding research, and despite the fact that public sector 'receptor capacity' has been cultivated in federal government departments and agencies, low levels of policy uptake means that the Canadian public benefits less from its research investment than other nations like the U.S. and New Zealand where barcoding uptake is stronger. Moreover, this lack of policy uptake also means that private sector jobs created in this sector are emerging in other markets and that Canadian-trained experts are leaving the nation in order to capitalize on them.

3.3 Genetics and Genomics in Canadian Crop Biotechnology

Canada's agricultural sector had the highest growth in labour productivity in 2000–2010, is one of only three sectors posting rising competitiveness versus the US and, as a precursor to future change, has the highest ICT use per hour worked in Canada relative to the US (Science Technology and Innovation Council 2013). In short, agriculture in Canada seems to have a winning formula. An example of Canadian agri-food innovation capacity was development in the 1990s of herbicide tolerant canola, which by 2007 became the world's third most important source of edible oils.

Developed in the Saskatoon 'entrepot' (Bathelt, Malmberg, and Maskell 2004) (Phillips 2002), canola development started in the 1980s (Phillips and Webb 2013; Phillips and Khachatourians 2001). With interest in exploiting new techniques in plant biotechnology and a desire to adopt plant variety protection (Malla, Gray, and Phillips 2004), the NRC recruited top biotechnologists to its newly repurposed Plant Biotechnology Institute while Agriculture Canada developed a Saskatoon oilseeds research centre. Local expertise was further concentrated as Monsanto, AgrEvo and Dow relocated research staff to access the capacity in the local public institutions. Between 1985 and 2000, joint investment by industry and government of more than C$200M globally (much of it in or linked to Saskatoon) produced five new traits expressed in more than 60 varieties that generated more than C$240M benefits annually in 2000 (Phillips 2003). Canadian share of the global market has risen correspondingly. After 2000, the innovation focus turned to differentiation with quality enhanced traits and plant-made products, but changes in federally-funded research has changed how attractive plant biotechnology is to foreign investors. Meanwhile market access for new traits and overall canola profitability are dampening enthusiasm for continued investment in canola innovation.

3.4 Innovative Cancer Therapies

Dr. John Bell, Director of the Ontario Institute for Cancer Research in Biotherapeutics, and San Francisco-based biotech entrepreneur, Dr. David Kirn (currently of Johnson & Johnson, 4D Molecular Therapeutics) formed a clinical trials company, Jennerex Biotherapeutics (www.jennerex.com) in 2006, to test oncolytic virus based therapeutics in cancer patients. Dr. Bell contributed his *Rhabdovirus* platform and associated intellectual property to the company and Dr. Kirn brought a license for a *Vaccinia* virus platform, developed by scientists supported by the National Institutes of Health (NIH). An initial round of Canadian seed funding enable Jennerex to commence clinical trials in the United States, Korea and Canada. Dr. Bell established a manufacturing facility at OHRI using funds provided by the Canadian Foundation for Innovation, the Ontario Institute for Cancer Research, and private donations from local benefactors. Jennerex established regional partnerships in Korea, China and Europe to help provide further funding for the company. Initially, Jennerex was majority owned by Canadian investors, but to mature the company from phase I through phase III clinical trials and commercial launch required the company to move to the U.S. An appeal to the Government of Ontario to establish domestic manufacturing capability did not succeed. Bell and one of the Jennerex Board members approached the Ontario government with the idea of establishing a commercial manufacturing facility in Ontario. At present Jennerex is sponsoring 11 clinical trials, with one recruiting and three completed. Despite returning Jennerex intellectual property to the Ontario research institutes where it was discovered and developing a collaborative agreement between McMaster University, OHRI and the Children's Hospital of Eastern Ontario, Jennerex products are manufactured outside Canada, and GLP cerified laboratories suitable for animal model testing of virus products are located in the U.S. Dr. Bell and colleagues remain committed to developing an Ontario based company, and international pharmaceutical companies have expressed interest in their technology, but it remains to be seen whether a successful, innovative biotechnology company for cancer therapeutics can be created and sustained in Canada.

3.5 Regenerative Medicine

Stem cell research is considered by some to be a Canadian export following the Till and McCulloch demonstration of the existence of multipotent stem cells published in *Nature* in 1963. The Canadian Stem Cell Network (SCN) has supported stem cell researchers in Canada since 2001. The calibre of Canadian stem cell science is high, with 14 SCN investigators among the one hundred most highly cited researchers in the entire field (Bubela et al. 2010). Now in its final round of funding, further commercialization initiatives will be developed by the Centre for Commercialization of Regenerative Medicine, supported under the Centres of Excellence for Commercialization and Research (CECR) Program. This replaces the original commercialization model of Aggregate Therapeutics Inc. (ATI: 2006–2009), a company charged with licensing stem cell technologies developed by SCN investigators and supporting commercialization through specialized business, legal and financing services. In Canada, the most successful regenerative medicine company is STEMCELL Technologies Inc., (http://www.stemcell.com/en/About-Us.aspx) a privately owned Vancouver-based biotechnology company. In 2011, it reported an operating revenue of $20,387,440 (USD), down from a peak of $29,117,880 in 2007, and employed 400 individuals. Its United States subsidiary reported $15,867,000 (USD) operating revenue in 2012 with 80 employees. A second company is Verio Therapeutics Inc., an Ottawa based privately held company founded in 2008. In April 2010, San Diego-based Fate Therapeutics acquired Verio Therapeutics for undisclosed financial terms, and formed a Canadian subsidiary. In 2011, Orbis reports Fate Therapeutics operating revenue as $2.2 M (USD) with 20 employees. Much cutting-edge stem cell research is conducted in Canada, but significant barriers exist to its commercialization and clinical translation. Risk averse global investors expect a secure patent estate combined with positive data from phase 2 clinical trials, yet Canada lacks the capacity to manufacture clinical grade material (cGMP) and funding for the conduct of early-stage clinical trials. Success in Canadian clinical

research capacity point to commercialization success in streams of research that either do not require clinical trials, or involve the export of innovative Canadian research and IP to biotechnology companies in larger, less risk-averse markets.

IV. Policy Options

Option 1: Promote Smart Specialization for Regional Innovation and Growth

As the aquaculture and crop biotechnology case studies demonstrate, the combination of science, technology, people and regional context can be a winning formula for innovation. Smart specialisation refers to the ability of regions to use their specialised abilities to absorb, disseminate and exploit general purpose technology (McCann and Ortega-Argilés 2013), and to promote innovation and enhance productivity according to the region's unique needs and economic strengths (Aghion et al. 2009), increase receptor capacity, and remove impediments to knowledge flows. Given Canada's size, geography, and regional concentrations of populations, research organisations, and business, smart specialization is an approach to the prioritization and concentration of effort. Although increasingly adopted in Europe and recommended by the OECD, smart specialisation has yet to make policy inroads in Canada.

Option 2: Develop Programs to Support Domestic Early Stage Innovation

The cases of regenerative medicine, novel cancer therapeutics, and DNA barcoding are situations where Canada is either the leader, or among the leaders, in an emerging field of science and technology, yet where technology development and commercialization occurs beyond Canada's borders. In these cases, the intellectual capital that is created is either moved by legal means as patent portfolios are bought up and exploited across borders, or where trained personnel have to move to follow the potential for job creation in other jurisdictions. As the Council of Canadian Academies has pointed out, the direct investment in early stage innovation characteristic of the U.S. innovation system is responsible for the retention of intellectual capital as well as the retention of business and their employees. The United Kingdom might provide a useful model for Canada to consider, since the Department for Business, Innovation and Skills and the Technology Strategy Board make strategic investment decisions based on an appraisal of the Technology Readiness Level of emerging technologies (NASA 2013).

V. Future Research or Future Action?

Instead of further prospective research, the solution is staring us in the face. As a continental economy with highly segmented regional economies and differentiated sectoral strengths, Canada is a natural living laboratory for implementing regional specialization through targeted and purpose-built programs for early stage innovation. In the past Canada has pursued national programs, albeit tailored to regional necessities through industrial and regional benefits. As those initiatives have wound down, provinces, communities and key sectors have emerged as innovators of programming for early stage innovation. Providing incentives for more innovations and comparing, contrasting and evaluating their respective success in advancing STI outputs and outcomes offers a valid and appropriate response to the needs of the Canadian bioeconomy (and undoubtedly other sectors). Piloting, prototyping and learning-by-doing (Sanderson 2002) offer one credible response to the Canadian paradox, by replacing action for perpetual study.

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