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UNDERSTANDING OPEN VERSUS PROPRIETARY RESEARCH AND INNOVATION: A CASE STUDY OF CANADA'S PHARMACEUTICAL SECTOR

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A DISSERTATION SUBMITTED TO
THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

Graduate Program in
SCIENCE AND TECHNOLOGY STUDIES

York University
Toronto, Ontario

November 2019

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Abstract

With decreasing public funding for scientific research and innovation (R&I) in Canada, the onus has fallen on public research institutions to partner strategically with industry to ensure that research generates innovative socio-economic gains. As a result, R&D has become *more* prescribed and *more* restricted, as private contracts and other proprietary intellectual property (IP) mechanisms regulate and often limit avenues of inquiry. This push towards commercialization has extended upstream into the process of research itself, and is not limited solely to product development (Mirowski and Van Horn, 2005).

In response to the restraints on R&I imposed by commercialization and proprietary IP measures, concepts of open science and innovation have become increasingly prominent, particularly in discussions of pharmaceutical development. The push towards openness in R&I has offered a potential solution to navigating through complex networks of proprietary IP licenses and patents, primarily by releasing project data into the public domain and ensuring broad user access, expanding participation in R&I, and reducing commercial barriers (Gitter, 2013; Feldman & Nelson, 2008). Though open science initiatives offer low entry costs and increased methodological transparency, there is significant debate within the STS and innovation studies literature regarding the role of open and proprietary IP in R&I. While some, such as Lezuan and Montgomery (2015), argue proprietary mechanisms are necessary for collaboration and provide incentives for investing in research, others, such as Mirowski (2011), highlight the aforementioned roadblocks to innovation and collaboration brought about proprietary IP. In both cases, open and proprietary mechanisms are often presented as dichotomous and incompatible.

This dissertation builds on the argument that, contrary to this dichotomy presented in current STS scholarship, these open and proprietary mechanisms may be complimentary at particular stages of R&I. I extend my focus to intermediary organizations established to facilitate the translation of basic research into marketable pharmaceutical products, in addition to public research institutes, small- to medium-sized private pharmaceutical firms, and incubator labs in Toronto. In doing so, this research aims to unpack how these mechanisms operate in the R&I process, as well as their role in facilitating or hindering collaboration and pharmaceutical R&I more broadly.

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Acknowledgements

First and foremost, my endless gratitude to my advisor, Kean Birch, whose guidance has made my time at York as rewarding an experience as I had hoped. Thank you for your mentorship, for supporting me with patience and kindness, and for generously sharing your expertise and including me in your own research. I am overwhelmingly grateful to Kean for challenging me, encouraging me, and giving me every opportunity to become a better scholar and pursue new avenues of inquiry.

I am grateful for financial support over the last several years from the Social Sciences and Humanities Research Council of Canada, the Government of Ontario, and York University. To James Williams, thank you for sharing your immense wealth of knowledge and insight with me, and for your guidance and compassion over the last five years. To Conor Douglas, thank you for stepping in to offer your feedback and incredibly valuable insight. To Fiona Murray and Lars Frølund at the MIT Innovation Initiative, thank you for giving me the opportunity and resources to pursue my research, and for your mentorship over the last year. I would also like to acknowledge the invaluable contributions and perspective given by Stacey Ivanchuk, Jeff Coull, Marc Gibson, and Aled Edwards.

I would be at a loss the last five years were it not for the encouragement, support, endless dinners and drinks, and [nearly] constant hilarity offered by my friends in Toronto and abroad. To Rob Guay, Sam Rogers, and Lee Nelson in particular, thank you for always responding to my histrionics calmly and pragmatically, for humouring me, and for always showing up to brunch. To Erin Grosjean, thank you for your patience, advice, and support, and for mitigating so much of my STS-induced anxiety over the last few years. To Chad, thank you for making the home stretch so wonderful. I'm also incredibly lucky to have the most remarkable group of women who have motivated me, kept me grounded, and changed my life immeasurably over the last decade. To Mel Parchment, Kristina Groeger, Vanessa Lumahaan, Elena Vukosa, and Rachel Nagy, thank you for your love and wisdom, and for making the last few years as joyful and painless as possible. To Emily Johnson, my most brilliant and inspiring friend, to whom I credit with making the last five (but actually eighteen) years infinitely magical – thank you. All the wine in Bellwoods, the late nights, the long walks, the countless letters and emails and texts added up to something after all.

Finally to my parents, who have challenged me to learn and better myself, and given me every opportunity to do so with generosity and love – my expression of gratitude does not suffice. Thank you.

Dedication

To Gianni – my brother, best friend, and the person I look up to most in the world. Thank you for everything.

1. Introduction

In asserting the linear progression of scientific and technological innovation, Vannevar Bush's *Science: The Endless Frontier* (1945) argued that technological progress was founded on well-funded, independent fundamental scientific research. For the United States to prosper from its scientific enterprise, according to Bush, basic research had to be undertaken without any pressures of commercial application or necessity. Following the emergence of the biotech sector in the late 1970s, however, the biological and biotechnological sciences witnessed a dramatic shift away from idyllic "Big Science" designs towards an increasingly commercialized, entrepreneurial technoscientific enterprise. Organizational practises and institutional arrangements were reconfigured to accommodate new means of knowledge transfer, as demonstrated by the changes in university-industry-government relations and the emergence of national innovation systems in particular (Etzkowitz & Leydesdorff, 2000). New relational networks between government agencies, private industry, and academic institutes coincided with an increasing emphasis on application value, particularly as it related to issues of funding and investment in fundamental research. In effect, scientific research came to be seen as a primary wealth-creating mechanism in national research and development (R&D) systems, and subsequently came under pressure to give more obvious and proportional value for dollars invested (Ziman, 2002b: 73). Major policy and legislative changes in the United States during this period paved the way for new practices in techno-scientific and academic capitalism. For instance, the passage of the *Bayh-Dole Act* (1980) in the United States saw the creation of a new marketplace for scientific knowledge and its byproducts, as public research institutes such as universities and national laboratories were able to attract investment from private industry by patenting research results and funding projects with wealth-creating potential (Mirowski, 2011). Scientific research, in essence, became a commodity:

with the ability to patent knowledge and data, legal "owners" were entitled to claim payments for its use (Ziman, 2002a: 335).

At the same time, biomedical research and innovation (R&I) practices saw a dramatic transformation with the emergence of the *–omics* era in the late 1980s, shifting the focus of research from objects (e.g. the gene, the protein) to systems (e.g. the genome, the proteome). As a result, scientific inquiry became largely data-accelerated and interdisciplinary, with R&D becoming dependent on the availability of and access to numerous databases to an increasing extent. For example, gene therapy in cancer research has become increasingly reliant on the collaborative development of sequence data (i.e. gene, protein, or other transcript sequences), wherein researchers rely heavily on databases to interrogate nucleotide sequences of interest, compare protein sequences, and search for sequence data in particular disease contexts. This shift in research practices, coupled with the increasing commodification, commercialization, privatization, and marketization of R&I itself, has led to the reorientation of public funding in universities towards public/private partnerships. This in turn has resulted in the reconfiguration of research agendas emphasizing both intellectual property (IP) and open science initiatives that increasingly impact how scientific knowledge is produced and shared, as well as the reshaping of R&I itself in accord with the commercial or social interests of the groups subsidizing it (Lave et al., 2010). With decreasing public funding of science in Canada (Science and Economic Development Canada, 2018), the onus has fallen on public research institutions to forge partnerships with private industry to ensure that research generates innovative socio-economic gains (such as much-needed novel pharmaceutical products). The Canadian Government has also encouraged the collaboration between universities and industry as a means of bridging this funding gap (NSERC, 2018b).

1.1. Key Challenges in Pharmaceutical R&D

This dissertation focuses primarily on pharmaceutical R&D and the development of novel clinical products in this sector. Drug development is notoriously expensive, slow, and precarious. From initial laboratory target discovery through regimented clinical trials to U.S. Food and Drug Administration (FDA) approval, pharmaceutical R&D averages 13 years and roughly $1.5 billion per new chemical entity (NCE) (Collins, 2011). These costs continue to rise. Table 1 below, adapted from DiMasi et al. (2016), demonstrates the growing costs of developing novel pharmaceutical products. The studies included in this table focus primarily on products developed in the United States and include the costs from all stages of development, however it nonetheless provides some clarity of the monetary scale associated with developing a new pharmaceutical product:

Table 1: Costs of new drug development, 1983 – 2015

Study	Study Period	Inflation Adjustment	Cost Estimate (USD)
DiMasi et al. (2003)	First-in-humans, 1983–1994	2000 dollars	$802 million
Adams & Brantner (2006)	First-in-humans, 1989–2002	2000 dollars	$868 million
Adams & Brantner (2010)	Company R&D expenditures, 1985–2001	2000 dollars	$1.2 billion
DiMasi & Grabowski (2007)	First-in-humans, 1990–2003 (large molecule)	2005 dollars	$1.2 billion
Gilbert et al. (2003)	2000–2002 (launch)	2003 dollars	$1.7 billion
O'Hagan & Farkas (2009)	2009 (launch)	2009 dollars	$2.2 billion
Paul et al. (2010)	≈2007	2008 dollars	$1.8 billion
Mestre-Ferrandiz et al. (2012)	In clinical development, 1997–1999	2011 dollars	$1.5 billion
DiMasi et al. (2016)	New drug and biologic development	2013 dollars	$2.8 billion

*adapted from DiMasi et al., 2016

According to a 2015 report by the Pharmaceutical Research and Manufacturers of America, the likelihood that a drug entering clinical testing would eventually be approved by the FDA was estimated to be less than 12 percent (PhRMA, 2015). At the same time, though basic research often produces promising results upstream, research outputs lag far behind associated costs and the

number of new medicines has not increased proportionately with investments made in basic pharmaceutical R&I. Attrition rates in late stage clinical trials are especially high and contribute to the risk and unpredictability associated with investing in pharmaceutical R&I (Gassman and Reepmeyer, 2005). Similarly, the paradigm of the "Blockbuster drug" (e.g. the one-disease-one-drug-one-target era, where products with broad, simple applications netted colossal revenues for firms) is seemingly over, and the shift to personalized medicine has presented new challenges for firms seeking to profit from their innovations (Jorgensen, 2011).

Moreover, issues related to the lack of financing for R&D have also negatively impacted innovation in the Canadian pharmaceutical sector. A 2013 report by Industry Canada noted that market growth in this sector has continued trending down, while brand-name pharmaceutical firms have experienced "record levels of revenue losses" in Canada and elsewhere (Industry Canada, 2013: 4). Further, these losses and their resulting poor pipeline productivity have required firms to re-examine investment strategies and adopt new business models "built upon external networks and third-party partnerships" – essentially outsourcing large portions of their business functions (e.g. development, testing, and manufacturing of new drug products) (ibid). The same report also noted that inadequate access to capital has also had a profound and negative impact on the ability of small- to medium-sized biopharmaceutical firms to flourish in Canada,

In terms of the Canadian pharmaceutical landscape, the 2017 Patented Medicine Prices Review Board (PMPRB) reported that total business expenditures on R&D by Canadian pharmaceutical firms have fallen below $1 billion since 2011 and industry R&D spending from 2001 to 2017 fell by 20% (PMPRB, 2017). Moreover, contract research organizations (CROs) are undertaking growing share of R&D in this sector, as new medicines and drug candidates are "increasingly being developed externally via partnerships with academia, small and medium sized enterprises (SMEs), government and research centres as well as contract research organizations

(CROs). Drug research and development is increasingly done via external partners, as over the past decade, 60% of innovator small molecules and 82% of innovator biologics have their roots outside of big pharmaceutical companies" (Industry Canada, 2019). The country's major biopharmaceutical clusters are located in Toronto, Montreal, and Vancouver. Canada's pharmaceutical pipeline is predominantly oriented towards oncology (with 35% of new pharmaceutical products specializing in this category), diseases of the central nervous system (17%), infectious diseases (12%), and cardiovascular diseases (7%) (Industry Canada, 2017a). The majority of these products currently being developed (76%) are in early stages of R&D (i.e. target discovery and validation through phase I/II clinical trials), while the remaining 24% are in mid- to late-stages of development. The PMPRB report (2017) also documents 80 new patented medicines first reported to the PMPRB in 2017 (compared to 128 in 2016). The PMPRB (2017) also noted that since 2010, 82.1% of patented medicines introduced offer "Slight or No Improvement" in therapeutic benefit over existing therapies (p. 12). However, sales of patented medicines in Canada rose by 7.6% between 2016 and 2017, from $15.6 billion to $16.8 billion (ibid: 22). As a share of overall medicine sales, patented medicine sales in Canada have been trending upward from 55.8% in 2010 to 61.5% in 2017, while non-patented and generic medicines have grown at lower rates (ibid:23). Stemming from this, sales of patented medicine as a portion of Canada's GDP tripled from 0.25% in 1990 to 0.78% in 2017 (ibid). More broadly, Canadian pharmaceutical sales account for a 2% share of the global market, making Canada the 10th largest world market (Industry Canada, 2019). Stemming from this, brand-name products account for 79.3% of Canadian sales and 30% of prescriptions, while generics account for the remainder (ibid).

Setting aside issues related to drug sales or the difficulties of creating drugs in the era of personalized medicine, the issue at stake in this dissertation stems from the fact that commercialization threatens to enclose crucial knowledge and information and restrict its access

behind IP protection, slowing drug development even further. The rationale for the widespread use of proprietary IP tools such as patents is, essentially, to allow firms recoup the growing costs associated with development, regulatory application, and marketing by charging a high cost for the drug based on market exclusivity granted via the patent (Barton and Emanuel, 2007). As will be discussed in greater detail in ensuing chapters, however, patents tend to have an anticommons effect (Heller and Eisenberg, 1998; Murray and Stern, 2007). This has wide-ranging implications, as the need for novel diagnostic and therapeutic drugs able to combat increasingly insidious and prevalent diseases has grown in recent years. Meeting these needs has been hindered by bottlenecks in the development process stemming from aforementioned issues of funding scarcities to high attrition rates in clinical trials to slow translation times associated with pharmaceutical development. As will be discussed in more detail in Chapters Four and Six, while the industry presence in Canada is significantly smaller, and the legal architecture underlying the Canadian patent system differs somewhat from its American counterpart, pharma R&I in Canada is similarly hindered by these bottlenecks (Science and Economic Development Canada, 2018).

Given that research in *–omics* fields relevant to pharmaceutical R&D often relies heavily upon collaboration and access to diverse knowledge, duplication of research is prohibitively costly for institutions lacking access to significant datasets or findings generated via contract-based research. The enclosure and restriction of scientific research behind proprietary barriers – for instance through broad upstream patenting or the use of material transfer agreements (MTAs) – is constitutive of the commercialization process and is, more often than not, a requisite in public/private research agreements. Proprietary IP devices, however, generally result in increased R&D costs (from associated legal fees to royalty fees etc.). Basic research projects deemed to be unprofitable or unable to be captured via proprietary IP rights might also be defunded (Caulfield et al., 2011). For example, both the Canadian Institutes of Health Research and the National

Sciences and Engineering Research Council of Canada require an explicit demonstration of application value as part of grant applications (NSERC, 2018a). Moreover, demands for commercialization and the subsequent expansion of broad proprietary IP rights further upstream in the research process necessarily impedes R&D further downstream, as even the most commercially irrelevant research can be encumbered by MTAs and broad patent claims (Scherer, 2002).

In response to the restraints on R&I imposed by commercialization and proprietary IP measures, practices and concepts of *open science, permissive licenses,* and *translational R&I* have become increasingly prominent, particularly in discussions of pharmaceutical development (Getz and Kaitin, 2012). The push towards openness in R&I has offered a potential solution to navigating through complex networks of proprietary IP licenses and patents, primarily by releasing project data into the public domain and ensuring broad user access (Gitter, 2013). Likewise, open science initiatives aim to make use of data through non-proprietary devices (e.g. through creating open source databases), expanding participation in R&I, and reducing commercial barriers (Feldman & Nelson, 2008). While open science initiatives offer low entry costs and increased methodological transparency, they do not necessarily offer a remedy for the impediments arising from conventional, proprietary forms of IP management (Birch et al., 2018). There is significant debate within the science and technology studies (STS) and innovation studies literature concerning open and proprietary IP devices (such as patents, research agreements, open access databases, permissive licenses, etc.) and their effect on the processes and products associated with R&I. While some, such as Lezuan and Montgomery (2015), argue proprietary devices are necessary for outlining collaborative research relationships and provide incentives for investing in research, others, such as Mirowski (2011), highlight the aforementioned roadblocks to innovation and

collaboration brought about by patents and MTAs. In both cases, open and proprietary devices are often presented as dichotomous and incompatible.

This research builds on the argument that, contrary to the dichotomy presented in current STS scholarship, open and proprietary devices may be complimentary at particular stages of R&I and that their respective net effect on the commercialization of research is context-dependent. Furthermore, this research seeks to tease apart how these devices operate within the R&I process, and to understand the impact they have on collaboration efforts more broadly. My aim is to highlight the substantial gaps between existing theoretical discussions of innovation and intellectual property and the strategies and practices employed in pharmaceutical R&D; gaps that potentially skew our understanding of innovation ecosystems and impede sound policy decisions. Namely, as will be discussed further in Chapter Seven, a primary argument of this dissertation is that scholars of STS and innovation studies fail to discuss the nuances of pharmaceutical development, largely in terms of differentiating between *tools* and *products* and the ways in which this distinction impacts the efficacy of certain IP tools. I endeavour to parse the relationship between innovation and entrepreneurship in the pharmaceutical sector and analyze the ways in which open and proprietary devices help to turn pre-clinical or early-stage research into a revenue producing asset. Moreover, I situate these devices within the larger context of corporate strategy, scientific competition, technology transfer, and academic and government policy. In doing so, I intend to highlight the variations in innovation strategies between industry and academia as well as the varying role and efficacy of open versus proprietary devices in each environment. Unpacking the R&I process – focusing specifically on the mechanisms that enable disparate actors to collaborate, that facilitate or hinder innovation and investment in R&D, that engender groundbreaking advancements in the pharmaceutical sector, and so on – is of critical importance

not only for scholars of STS, but for scientists, policymakers, entrepreneurs, and venture capitalists alike.

1.2. Background

This research analyzes and critiques the parameters of open and proprietary devices and their respective roles Ontario's rapidly changing R&D landscape, specifically addressing the network of actors and institutes shaping Canada's pharmaceutical sector. I extend my focus to intermediary organizations established to facilitate the translation of basic research into marketable products, in addition to public research institutes, small- to medium-sized private pharmaceutical firms, and incubator labs in Toronto. Specifically, I focus on MaRS Innovation and its affiliate firms and public research hospitals, the Ontario Institute for Cancer Research (OICR) and the Fight Against Cancer Innovation Trust (FACIT), Johnson & Johnson's incubator space JLABS @ Toronto and its affiliate firms, the Structural Genomics Consortium (SGC). This section provides a brief overview of these organizations, to be elaborated upon more significantly in Chapter Three.

1.2.1. MaRS Innovation, the OICR, and FACIT

MaRS Innovation (MI) is a pan-provincial non-profit organization created in 2008 as a Centre of Excellence for Commercialization and Research by the Networks of Centres of Excellence (NCE). As such, the purpose of MI is to accelerate the translation of academic discoveries to marketable products and services by providing researcher groups with capital, industry networks, and laboratory space (MaRS Discovery District, 2016). As Canada's largest research cluster, MI works in conjunction with academia and other public research institutes, industry partners from a range of sectors, venture capitalists and angel investors, and government agencies. MI's commercialization model identifies early-stage inventions with high market or

patent potential and provides support to its members through the licensing of intellectual property, funding, the development of business plans, and/or the creation of startup companies (NCE, 2017a).

Likewise, the OICR is a non-profit translational research organization established in 2005 by the Government of Ontario, focusing primarily on "the prevention, early detection, diagnosis and treatment of cancer" (OICR, 2016). As "receptors" to translational pharmacology research, OICR and MI work in partnership, connecting researchers in fields like genomics and bioinformatics from their public partners with private organizations to facilitate innovation in cancer medicine. FACIT, a provincial business trust working in conjunction with MI and OICR, funds and licenses early stage research through its Intellectual Property Development and Commercialization (IPDC) fund (FACIT, 2016).

1.2.2. JLABS @ Toronto

In 2012, Johnson & Johnson (J&J) opened JLABS @ Toronto, an incubator space housed in the MaRS Tower and the first JLABS site operating outside the United States. Working in collaboration with J&J Innovation, Janssen Inc., the Government of Ontario, and the University of Toronto, JLABS leases wet and dry laboratory space to its residents, the majority of which are early-stage companies focused on therapeutic or medical device technology development (JLABS @ Toronto, 2017). As an incubator, the purpose of JLABS is to help catalyze innovation, particularly for small firms (ibid).

1.2.3. The Structural Genomics Consortium

As a non-profit public-private consortium, the SGC undertakes basic scientific research "…of relevance to drug discovery. [Its] core mandate…is to determine 3D structures on a large

scale and cost-effectively – targeting human proteins of biomedical importance and proteins from human parasites that represent potential drug targets" (SGC, 2017a). Operating out of the University of Oxford in the UK and the University of Toronto in the MaRS Tower, the SGC works in collaboration with a network of academic, industry, and government partners in Canada, the US, and the UK (ibid). Research at the SGC is focused on determining the crystal structures of proteins that act as "targets" for drug therapies for various types of cancer, diabetes, and psychiatric disorders. Importantly, the SGC releases its crystal structures into the public domain with no strings (i.e. proprietary IP rights) attached.

Each of these three groups – MI and the OICR, JLABS, and the SGC – and their affiliated firms and organizations has a unique approach to innovating and collaborating. Some, in particular the SGC and a number of affiliate firms of MI and JLABS, have embraced open devices and openness broadly speaking as a means of forming broad working relationships outside the confines of their respective firms, and of navigating around what some scholars of STS and innovation studies see as a cost-prohibitive web of proprietary IP rights and their associated legal architecture and personnel issues. Others, namely the OICR, FACIT, MI's in-house IP office and many of its affiliate firms have been reluctant to fully embrace the push for openness previously discussed (e.g. through increased methodological transparency, increased use of open IP tools, and low transaction costs and barriers to entry), and have maintained a more traditional, proprietary commercialization model. The point of this dissertation is to unpack the innovation process and the role played by open and proprietary mediating devices in the pharmaceutical sector. To do so, it is necessary to explore why some institutes or firms embrace openness and others do not, why some actors see open devices as facilitating innovation in theory but not in practice, why others are able to successfully form commercial partnerships on the basis of using open devices and others aren't, and why the success of open devices is dependent on what's being produced and in what

context. These three groups provide an interesting case study, as they are located in close proximity to one another, have similar broad mandates (to accelerate the development of novel pharmaceuticals), and are all subject to the same provincial and federal laws and regulations. As will be discussed in further detail in chapter five, however, open and proprietary devices play markedly differing roles for each group in terms of enabling collaboration, attracting investment in early-stage research, and bringing profit-generating innovations to market.

1.3. Theoretical Overview

1.3.1. Mediating Devices

In terms of a theoretical framework, this research builds on the premise that particular open and proprietary mechanisms enable public and private research groups, government regulators and policymakers, and investors from a broad range of organizations to interact, collaborate, and bring innovative research forth from the lab to clinical practice. I theorize these mechanisms as *mediating devices*. For the purposes of this research, mediating devices consist of patents, MTAs, NDAs, reach-through license agreements, copyrights, open-source licensing (such as copyleft), and open-access databases. In essence, I argue these devices are the linchpins that enable collaboration, commercialization, and knowledge transfer, and/or determine valuation of the products and processes of R&I.

Notions of "mediating instruments" have been have been discussed at length in the accounting and economic sociology literature, largely in the context of the broad range of financial and economic models (Morrison and Morgan, 1999), instruments, metrics, and mechanisms related to practices of calculation, valuation, budgeting, and computation (Miller, 1992; Miller and O'Leary, 1987). Others have similarly outlined *market devices* as "the material and discursive assemblages that intervene in the construction of markets," suggesting these objects encompass

"analytical techniques to pricing models, …purchase settings to merchandising tools, …trading protocols to aggregate indicators" (Muniesa, Millo, and Callon, 2007, p. 2; see also Muniesa, 2007). However, the concept of *mediating devices* as outlined above has yet to appear in the STS or innovation studies literature, and I argue that this concept both adds nuance and sheds a political economic and epistemic light on these debates.

Mediating devices are particularly salient in the context of pharmaceutical development. As discussed above, scientific research has become progressively more data-accelerated, internationally collaborative, and interdisciplinary in recent decades. At the same time, however, the ability to rapidly and cost-effectively translate innovative research findings from the lab to the clinic is limited by the increasingly complex entanglement of science and capitalism and the commercialization of science itself (Chiappetta and Birch, 2018). On the one hand, "duplicating research findings is prohibitively costly, creating an imperative for ('pre-competitive') collaboration; on the other hand, enclosing research results behind IP rights provides incentives for private investment in R&I" (ibid: 68). I argue these mediating devices, situated within complex networks of researchers, investors, incubators, labs, patent offices and so on, play a crucial role in configuring the organization, process and products of pharmaceutical R&I. Patents, MTAs, NDAs, open-access libraries (among numerous other devices) shape the ways in which information and data are diffused and circulated, and help to frame collaborative networks of disparate actors. Moreover, they attach value to the interactions of actors within these networks (e.g. by stipulating potential royalties), determine how and when innovative research is translated across disciplinary boundaries, and regulate how value may be appropriated from the products of these interactions (ibid).

Further, this work draws primarily on the existing body of literature relating to knowledge production and translation, commercialization and valuation, business and innovation models,

intellectual property, and innovation strategies. The literature underpinning this research is divided into three broad sections focusing on the following areas: firstly, STS and innovation studies; secondly, economics of science and the political economy of science; and finally, intellectual property.

1.3.2. STS and Innovation Studies

STS scholars have debated the nature of *science* as an epistemic enterprise to the point of exhaustion. While my intention with this dissertation is to avoid esoteric debates surrounding the properties of scientific knowledge itself, it is necessary to provide an overview of critical works in the field that inform this dissertation, however tangentially.

Regarding knowledge production more abstractly, the work of Michael Gibbons et al. (1994) extensively detailed a "new" mode of knowledge production in contemporary science – that is, knowledge produced *in the context of application* (versus "pure" or "basic" scientific knowledge). The *mode 1* and *mode 2* distinction has been criticized as promoting a reductive and inadequate basic/applied dichotomy (Whitley, 2001), as scientific knowledge production has historically never been free from the pressures of commercial necessity. In an attempt to move beyond stereotypical basic/applied distinctions, John Ziman (2005) coined the term *post-academic science*, referring to the research paradigm that emerged following the birth of the biotech industry in the 1970s wherein knowledge is constructed by heterogeneous groups "in accord with the commercial, political, or other social interests of the bodies that underwrite its production" (p. 174). Ziman's concept is an especially useful descriptor, as the science to be examined and discussed in this project does not fit under the mode 1/mode 2 or basic/applied umbrellas: the R&D in question in this research is not undertaken solely with the objective to produce theoretical knowledge about natural phenomena, nor is it intended solely to produce marketable products.

Rather, it is mission-based, oriented to market principles (ibid), and guided by the desire to solve particular social and economic problems. The solutions to these problems may be tangible artifacts (e.g. a marketable therapeutic agent) or something more abstract (e.g. a digital technology, such as a drug screening platform, or improved clinical trial expediency).

Innovation and technological change have been discussed extensively in historical and economic literature. As a standalone discipline, innovation studies evolved from two existing frameworks in the 1960s: one, a sociological perspective concerned with inventions and cultural lags, and the other a historical approach that came to be called the linear model of innovation (Godin, 2010a). Early works in the field of innovation studies highlighted the need for proprietary research, particularly in terms of "gales of creative destruction" (Schumpeter, 1942), natural trajectories and selection environments (Nelson and Winter, 1977), technological paradigms and trajectories (Dosi, 1982), and regimes of appropriability (Teece, 1986). These works emphasized the role of proprietary market forces as necessary determinants of techno-scientific change. Recently, some (Nightingale, 1998; Fagerberg and Verspagen, 2009; Martin, 2012a, 2012b) have sought to provide a conceptual framework of the field, highlighting its intellectual and organizational characteristics. Others (Godin, 2015, 2010a, 2010b) have been critical of innovation studies as a field, critiquing the conflation of innovation with commercial invention and technological change by its scholars, as well as the overly broad focus of the discipline.

In terms of examining business and innovation models in the biotech sector, there has been a flurry of publications focusing on the emerging field of open innovation in recent years (Chesbrough 2003a, 2003b, 2004, 2006; Gaul, 2006; West et al., 2006). In particular, Chesbrough (2003b) focuses on the paradigm shift from closed to open innovation models, arguing that ideas and technologies hold no inherent value, but rather that business models used to bring them to the market that determine their value. He highlights the need for a combination of open and proprietary

measures in order for firms to achieve market success. Some have been critical of Chesbrough's definition of openness. Hayden (2010) argues that the public domain extends only so far as property regimes do and serve to prop up existing IP monopolies, and thus open innovation nonetheless remains neoliberal in nature. Looking to the success of openness in the field of software development, Hope (2008) proposes a "bazaar" model as a means of increasing openness in scientific R&D, wherein decision-making and resource control are autonomous, and participation is voluntary. Gassman and Reepmeyer (2005) have written specifically about open business models in the context of pharmaceutical development, making the case for increased openness as a means of combating the growing lag between research output versus its associated costs. Of particular importance for this research is the work of Elmquist et al. (2009), who argue that the *locus* of innovation (i.e. within or outside the confines of a single firm) affects our understanding of how the innovation process actually occurs. Foray (1997) and Etzkowitz and Leydesdorff (2000) have also made the case for increased openness in the properties and distribution of scientific knowledge, particularly as it relates to university-government-industry interactions.

While these works play a critical role in outlining a conceptual foundation for this dissertation, there are critical gaps in this literature that need to be addressed. Namely, there is a noticeable lack of discussion in the STS and innovation studies literature on the role of open and proprietary *devices* (versus strategies) in the innovation process. Chesbrough's (2003b) notion of open innovation simply extends R&I beyond the confines of a single firm and makes little room for the material and notional objects that control the flow of knowledge across these organizational boundaries (such as contracts, research agreements, databases, etc.).

1.3.3. Economics of Science and the Political Economy of Science

This section focuses on the evolving political economy of science and technology and the current entanglement of science and capitalism. To understand the state of today's pharmaceutical R&I paradigm, it is necessary to outline its evolution in the last four decades. Regarding the changing political economy of science and technology, Mirowski (2011) has extensively discussed the science-business model that emerged following the birth of the biotech sector in the 1970s, wherein for-profit enterprises engaged in basic scientific research and universities actively sought to profit from it. The passage of the Bayh-Dole Act (1980) affirmed the right of universities to patent government-funded inventions, while the landmark case of Diamond v. Chakrabarty (1980) ensured that microorganisms could be patented. As a result, discovery and application became increasingly integrated, and the marketplace for scientific knowledge and its biproducts extended beyond a single university or firm laboratory to include technology transfer offices, funding agencies, policymakers, venture capitalists, and so forth (Popp-Berman, 2012).

Mirowski (2011) has been particularly critical of proprietary R&I, extensively detailing notions of commercialization, commodification, privatization, and marketization that have continued to shape research and innovation since 1980 and discussing the ways in which proprietary demands on R&I actually hinder innovation. Lave et al. (2010) have also discussed the entanglement of neoliberalism and science, specifically emphasizing the consequent narrowing of research agendas at public institutions, while Mirowski and Van Horn (2005) have the commercialization of scientific research in the current paradigm. Moreover, Mazzucato (2012) has also discussed the critical (and increasingly challenged) role that universities play in conducting basic research, highlighting the importance of government investment in fundamental R&I. Mirowski and Sent (2002) and Radder (2010) have been critical of the ways in which proprietary, commercialized R&I is inherently self-limiting, while Stephan (2012) has examined the negative

changes to academic science brought about by market systems. Much like the case with innovation studies, there have been a number of works attempting to outline the theoretical and organizational framework of the economics of science (Dasgupta and David, 1996; Sent, 1999; Ballandonne, 2012; Tyfield, 2012b, 2012c).

1.3.5.. Intellectual Property

The existing STS and innovation studies literature concerning intellectual property has been largely framed as a debate around open versus proprietary R&I. In the legal context, Posner (2002, 2003) has been particularly critical of the ways in which expansive, proprietary property rights limit the production of intellectual property itself. Heller and Eisenberg (1998) have also argued against the use of certain proprietary devices in biomedical research, such as material transfer agreements and reach-through license agreements, while Caulfield et al. (2012) have discussed at length the potential for bottlenecks in the R&I process that result from broad IP claims upstream. Conversely, Lezuan and Montgomery (2015) have argued that proprietary devices are necessary for outlining collaborative research relationships and provide incentives for private firms to invest in basic research. In his discussion of the tension between science and business in the biotech sector, Pisano (2006) argues that the monetization of IP has shaped the process of R&I itself, resulting in an inherently corporate model of innovation.

Feldman and Nelson (2008) and Hope (2008) have provided detailed accounts of the birth of *open science*, particularly as an extension of the growth of *open source* software in the mid-1990s. As the sharing of data and information is paramount in the *–omics* era, there have been a number of works examining the impact of openness on the scientific knowledge and its byproducts as well as the changing practices of research itself in this era. For instance, one aspect of open science is the idea of *open access* (OA), specifically as it relates to publishing. As Wellen (2013)

and Harnad et al. (2008) note, OA journals offer one solution to navigating around the prohibitively costly user fees traditionally associated with academic journals so that published data is, in theory, broadly and freely available. Gitter (2013) and Rhoten and Powell (2007) have discussed open approaches to licensing in the context of scientific R&I, specifically highlighting the ways in which non-proprietary licensing arrangements such as *Creative Commons*, copyleft or *GNU Public Licenses* (GPL) help to navigate around issues of data ownership by ensuring that users may freely use, modify, and distribute data or information on the condition that its derivatives are bound by the same conditions (see also Birch et al., 2018).

Again, though these works form a crucial component of the theoretical skeleton of this research, there is nonetheless a significant gap in this literature that has yet to be addressed: scholars in STS and innovation studies have yet to analyze how proprietary *and* open devices vary in terms of their efficacy when they are employed in academic versus industrial settings. Moreover, there is little nuanced discussion in the existing literature regarding why open and proprietary devices operate effectively at different stages in the innovation process, or how they can be employed to facilitate collaboration. Existing works have yet to analyze how open and proprietary devices may be used *together* in the context of interdisciplinary pharmaceutical research and public/private collaborations, and *how* researchers might navigate through IP gridlocks when potentially competing or conflicting interests are guiding knowledge translation.

1.4. Research Objectives

This dissertation addresses the following research questions:

1. *How do social actors in the pharmaceutical sector understand innovation? By extension, how can we theorize open and proprietary devices?*

My aim here is to provide a conceptual outline of mediating devices as the linchpins that enable

collaboration, commercialization, and knowledge transfer, and/or determine valuation of the products and processes of R&I. In doing so, I endeavour to highlight the substantial gaps between existing theoretical discussions of innovation and intellectual property and the strategies and practices employed in pharmaceutical R&D; gaps that potentially skew our understanding of innovation ecosystems and impede sound policy decisions. This is discussed at length in Chapter Five, where I examine what it means to innovate, how innovation is measured and valuated, the factors drives certain actors to invest in the development of innovative new biotechnologies, and the factors that accelerate or inhibit the commercialization of these innovations.

2. *Which proprietary and open devices are used in pharmaceutical R&I? For whom, and why?*

Here I examine the ways in which patents, NDAs, MTAs, reach-through license agreements, open licenses, and open libraries and databases are used by actors at the institutes overviewed in section 1.2. This is examined in Chapter Six, where I discuss MTAs as they relate to academic TTOs, emphasizing the difficulties and costs associated with executing MTAs and the impact of these costs on pharmaceutical research and innovation. In this chapter I also discuss how mediating devices configure collaboration agreements, focusing specifically on the effects of proprietary contracts and open databases and libraries on research and innovation. Finally, I discuss patents and their role in the legal architecture of research and innovation, highlighting how they (re)configure the commercialization of new pharmaceutical products in Ontario and the implications this has for the use of open devices. In situating these devices within the larger context of corporate strategy, public policy, and technology transfer, I analyze the ways in which these devices are incorporated into innovation strategies and business models at these institutes.

3. *How do different devices facilitate or hinder collaboration and knowledge translation in this sector? At what stage in the innovation process are they most effective, and why?*

I examine this question at length in Chapter Seven, where I evaluate the impact of broad versus narrow patent claims and their impact on innovation. Here, I argue that the efficacy of open and proprietary devices, both in terms of accelerating the translation of pharmaceutical research and encouraging collaboration, is dependent on: firstly, when they are employed in the innovation process (i.e. upstream versus downstream); and secondly, what they are applied to (i.e. tool compounds used to develop candidate drug products versus the products themselves). More often than not, the implementation of proprietary devices too early in the R&I process, particularly in the case of broad upstream patent claims, results in bottlenecks that slow down or stop knowledge translation entirely. Conversely, the use of open devices downstream in the commercialization process of new drug candidates is likely to derail private investment. Moreover, the role of open versus proprietary devices in facilitating or hindering innovation is dependent on several variables: namely, collaborative arrangements and the nature of the IP in question (e.g. a tool used in the development of drug candidates versus a pharmaceutical product itself).

4. *How can they be employed in the development of innovation strategies so as to streamline the process of drug development?*

This final question is also addressed in Chapter Seven, where I conduct a case study of the open molecule JQ1, a tool compound used in the development of therapeutic products for certain types of cancer. Building off observations made previously in the chapter, I highlight the issues associated with broad proprietary IP claims and the limitations (particularly related to funding and investment) associated with open devices in certain cases. I argue that, contrary to the dichotomous and incompatible image of open and proprietary devices that is presented in the STS and innovation studies literature, these devices may be complimentary at particular stages of R&I, and, when used together, can accelerate advancements in the pharmaceutical sector.

These questions are summarized in Chapter Eight, where I endeavour to draw policy implications from the previous three chapters. My overall aim is to parse the relationship between innovation and entrepreneurship in the pharmaceutical sector and analyze the ways in which open and proprietary devices help to turn pre-clinical or early-stage research into a revenue producing asset. The results of this project are relevant to public research institutes and private firms, and are applicable in cases of less commercially oriented projects in addition to late-stage product development. My hope is that this research may be used in part to form an explanatory model for sustainable pharmaceutical R&I and can be used to help shape institutional R&I policies in Canada so as to streamline the drug development process.

1.5. Methodology

Data for this research was collected via database and literature analyses, and semi-structured qualitative interviews. This will be elaborated upon significantly in Chapter Three. In light of the research questions outlined above, data collection and analysis was divided into three stages: firstly, a theoretical synthesis of the existing literature on open innovation, commercialization, and knowledge translation in the life sciences, outlined in Chapter Two. Secondly, an analysis and secondary literature review of existing provincial and federal policy regarding pharmaceutical innovation and technology transfer, outlined in Chapter Four. Finally, an analysis of qualitative interview data on the use of mediating devices in pharmaceutical R&I in Ontario, with interviewees drawn from the organizations outlined in in section 1.2. This analysis occurs in Chapters Five through Seven.

Following transcription and prior to analysis, interview data was coded using NVivo. The coding process involved describing, classifying, and connecting (Blaikie, 2011). Primary coding categories included innovation, collaboration, business models, funding and investment in R&I,

and open and proprietary devices (among others), with sub-categories including definitions, metrics, and strategies (of innovation), barriers to and facilitators of (collaboration), and so on. Classification also entailed an evaluation of the causal and intervening conditions behind the use of each mediating device (ibid).

1.6. Contribution to Knowledge

In terms of contributions to theory, this research seeks to fill gaps in the existing STS, innovation studies, and political economy of science literature concerning the relationship between intellectual property and open innovation. As discussed in section 1.3., while notions of "mediating instruments" have been discussed at length in the accounting and economic sociology literature, the concept of *mediating devices* as outlined has yet to appear. I argue that situating and analyzing these devices within the broader context of corporate strategy, technology transfer, scientific competition, and academic capitalism sheds light on the ways in which information and data are diffused and circulated in the context of pharmaceutical development and helps frame collaborative networks of disparate actors. Moreover, examining mediating devices in this context may help to the refine and streamline institutional innovation strategies, and may help to rapidly and cost-effectively translate innovative research findings from the lab to the clinic, particularly by highlighting which devices work for whom, and when. Ultimately, by examining the context in which pharmaceutical innovations develop as well as the devices that enable innovations to be rapidly and cost-effectively diffused to clinical settings, Canada will be better suited to solving salient health policy issues (e.g. how to foster a sustainable and efficient environment for pharmaceutical R&D) and to answering the demand for novel diagnostic and therapeutic drugs.

1.7. Conclusion

This chapter provides an overview of the issue at hand – namely, the limitations posed to pharmaceutical R&I by proprietary IP and the commercialization of science itself. This research examines the development of new drug candidates at public research institutes and private firms in Ontario, focusing specifically on MI and its affiliate firms and research hospitals, the OICR and FACIT, JLABS and its affiliate firms, and the SGC. I introduce the concept of mediating devices and their role as intermediaries within the broad network actors and institutes shaping Canada's pharmaceutical sector and provide a brief overview of the scholarly works informing this dissertation. Finally, I outline the objectives of this research and hypotheses associated with each research question. The remainder of this dissertation is organized as such:

Chapter Two provides an in-depth theoretical and conceptual framework, focusing on key works in STS, economics of science, and innovation studies. Specifically, this chapter begins broadly with a theoretical discussion of how knowledge is produced and the role of interdisciplinarity in the sciences, before moving on to detail the commercialization of knowledge and academic entrepreneurship. I then discuss business and innovation models and strategies, before focusing finally on intellectual property and mediating devices. In addition to providing a theoretical foundation for the remainder of this dissertation, the purpose of this chapter is also to situate this research within the broader existing body of relevant work in STS.

Chapter Three is a comprehensive overview of the methodological approach undertaken in the collection and analysis of qualitative data. Here I discuss in detail the approach to interviewing that was undertaken, the coding and analysis process, and potential limitations to this research.

Chapter Four offers a background of the landscape of pharmaceutical R&D in Ontario, providing a more detailed discussion of the institutes and actors involved in this study as well as the legal and regulatory architecture behind drug development research in Canada. This chapter

also examines relevant international legal agreements, such as the *General Agreement on Tariffs and Trade* (GATT) and the agreement on *Trade-Related Aspects of Intellectual Property Rights* (TRIPS) agreement.

Chapter Five focuses on the concept of *innovation* itself and attempts to unpack what the term meant to interview participants. Stemming from this, this chapter also seeks to analyze how the concept of innovation and the ways it is measured sheds light on funding and investment decisions. Here I highlight the role of mediating devices in driving pharmaceutical R&I in Toronto's innovation ecosystem and assess the relationship between the lack of public funding for research in Canada and the consequent profit-driven nature of research. I also evaluate the role of mediating devices in attracting external investment, in addition to the ways in which these devices affect the commercialization of new technologies.

Chapter Six focuses on the embeddedness of mediating devices in the architecture of Canadian research and innovation. I begin by discussing MTAs in the context of university TTOs and unpacking the difficulties and costs associated with the execution of these devices. Secondly, I evaluate the ways in which these devices configure collaboration agreements, focusing specifically on the effects of proprietary contracts and open databases and libraries on R&I. Finally, I examine the case of patents and their role in the legal architechture of R&I in Ontario, highlighting the ways they (re)configure the commercialization of new pharmaceutical products.

Chapter Seven examines the impact of broad versus narrow patent claims and their effect on innovation. Here, I evaluate the ways in which broad upstream patent claims on tool compounds results in bottlenecks that slow down or stop knowledge translation entirely. I also analyze the use of open devices downstream in the commercialization process of new drug candidates, and the impact of this on private investment. This chapter concludes with a case study of the open molecule JQ1 as a means of highlighting the importance of distinguishing between research *tools* versus

marketable *products* when attempting to understand the overall impact of open and proprietary mediating devices on pharmaceutical innovation.

Finally, Chapter Eight summarizes this dissertation and offers concluding remarks concerning the state of pharmaceutical development in Canada and future research areas.

2. The Business of Pharmaceutical R&I: A Review of the Literature

Pharmaceutical development has grown to be a business in its own right in recent decades, and the process of developing new pharmaceuticals has become an engine of wealth creation for national economies, particularly in the United States, Canada, and the UK. Aided by a series of policy and legislative reforms in the early 1980s, the rapid growth of biotechnology presented the opportunity for both universities and private firms to commodify research projects with wealth-creating potential and subsequently capitalize on the results (Mirowski, 2011). The expansion of intellectual property rights further upstream into the research process has ensured that universities play a more active role in reconfiguring research agendas toward more commercial and social interests (Lave et al., 2010). Whether or not the net effect of this expansion has been to hinder innovation in the pharmaceutical sciences remains to be seen.

This chapter is divided into five broad sections and provides an overview of the existing body of scholarly work in the following areas: firstly, science and technology studies (STS), specifically in the context of knowledge production and interdisciplinarity; secondly, economics and the political economy of science; thirdly, innovation studies; fourthly, intellectual property; and finally, mediating instruments and mediating devices. This research is focused specifically on pharmaceutical R&D and the development of novel clinical products. However, a significant component of R&D nonetheless involves the production of knowledge, and as such this chapter begins with a broad overview of the properties of scientific knowledge and a discussion of interdisciplinarity and collaboration in the sciences. Following this, I provide a historical overview of major changes to the political economy of science in recent decades affecting the pharmaceutical R&I in question, focusing on academic capitalism and commercialization. Next, I discuss innovation studies as a discipline and innovation models used to bring research results to the

market. Subsequently, I provide an overview and analysis of intellectual property and open science, concepts at the center of drug development policy today. Finally, I introduce the concept of mediating devices that will play a critical role in the remainder of this dissertation.

2.1. Science and Technology Studies

As a discipline, STS emerges from the intersection of history and philosophy of science (HPS) and sociology of science, borrowing theoretically and methodologically from these fields, and, recently, economics and policy studies. Given its transdisciplinary orientation, STS theory – particularly as it relates to interdisciplinary collaboration and knowledge production – is well-suited to shedding light on the ways in which the epistemic enterprise of *science* shapes and is shaped by social, political, and economic factors, and further provides a useful lens through which to understand how these elements affect the translation and commercialization of scientific research.

This section focuses on seminal discussions of knowledge [co]production and interdisciplinarity in STS; more specifically, on the works of Merton (1942), Shapin (1984), Shapin and Schaffer (1985), Gibbons et al. (1994), and Etzkowitz and Leydesdorff (2000). While these works may seem abstract or too theoretically removed to be relevant, I argue there is a link worth briefly exploring between these works and the topic at hand. In particular, between knowledge production for Shapin and Schaffer and the idealized version of science articulated by Merton, and how the arguments of these authors contrast with the realities of how knowledge is enclosed behind proprietary barriers, how commercialization affects interdisciplinarity and inhibits the movement of knowledge across interdisciplinary barriers. Further, discussing these works (however briefly) helps to situate this research within the significantly broader field of STS. Understanding *science* not as a representation of an objective reality, but rather as the product of

social processes, requires an unpacking of the *things* that fall in between an experiment and the knowledge it produces, and by extension, unpacking the *things* that mediate the interactions of those responsible for producing that knowledge and ultimately bringing it to market (e.g. in the form of a clinical product such as a drug). It necessarily involves closely examining the tangible and intangible *devices* that enable scientific knowledge to move from the laboratory through a clinical trial, or that prevent scientific data from being circulated and shared beyond the confines of a single firm. Thus, while notions of knowledge production and interdisciplinarity seem abstract, the development of new pharmaceutical products begins in the lab and extends across a global network of firms and institutes, incorporating varying methodologies and expanding upon past experiments. At its core, pharmaceutical R&D ranges a broad array of disciplines and incorporates a similar diversity in its actors. To that end, understanding *innovation* in and of itself – either to streamline the process, to interrogate the mechanisms that enable it, and so forth – requires discussion of the abstract before an examination of the finer details of drug development specifically. This section focuses firstly on scientific knowledge production as discussed by STS scholars, before discussing "new modes" of knowledge production, and finally interdisciplinarity and collaboration in scientific R&D.

2.1.1. Knowledge Production

The social nature of *science* has been discussed at length by sociologists, historians, and philosophers of science, and the argument that scientific knowledge is a product of the actions and interactions of social actors is not particularly novel. In fact, arguably the most prominent vein of early STS scholarship focused almost exclusively on the epistemics of the scientific enterprise, with scholars seeking to understand how scientific *matters of fact* are generated and solidified (see Shapin, 1984; Shapin and Schaffer, 1985), how scientific knowledge results from the actions of

complex groups of actors and institutions (see Galison, 1985), and the notion of social construction in the broad context of the scientific enterprise (see Pinch and Bijker, 1987; Latour, 1987; Hacking, 1999).

For Shapin (1984) (and later Shapin and Schaffer [1985]), producing and disseminating matters of fact amongst a community of scientists – essentially creating *knowers* – involves a distinct set of practices unique to scientific disciplines, the first being the *standardization of methodology*. The scientific method, he argues, ensures a uniform process in which experiments are conducted, demands consistency, allows for replication, and creates trust amongst the scientific community at large (Shapin, 1984). The basis of this method lies in the consistent, regimented repetition of steps and observations in each investigation, which reduces the potential insertion of personal biases and the serendipitous reoccurrence of experimental outcomes. Secondly, Shapin and Schaffer (1985) highlight *the use of mimetic devices* as a means of creating matters of fact. Pictorial representations (i.e. schematic diagrams, anatomical drawings, infographics showing patterns or trends in large amounts of data etc.) generally functioned to establish matters of fact by communicating ideas, results, and information, and "[serve] to announce…that 'this [experiment] was really done' and that 'it was done in the way stipulated'" (Shapin and Schaffer, 1985: 61-2). Finally, creating scientific knowledge involved the *extension of experience from the few to the many*. Given the elaborate, and costly nature of scientific experimentation, the need for multiple testifiers to validate experimental results becomes problematic, and thus the multiplication of witnesses was an integral step in producing matters of fact. Providing complex and heavily detailed testimonies "to be taken as undistorted mirrors of complex experimental outcomes" (i.e. publishing and reporting experiments) creates a virtual witness in the reader, thereby facilitating trust in the knowledge claims being made (Shapin and Schaffer, 1985: 64). Moreover, as Jasanoff (2005) notes, scientific matters of fact hold weight not necessarily because they objectively reflect nature,

but because they have been certified as true by those with the authority and competence to do so. For now, the general consensus appears to be that the notion of a lone scientist in noble pursuit of an abstract truth is both outdated and false.

In 1942, Robert Merton outlined what he saw as the *normative structure of science* – that is, the non-codified rules and customs informing the behaviour of scientists, determining what counted as "good" science, and, broadly, shaping the scientific ethos (Merton, 1973). Merton's norms, neatly encapsulated by the initialism CUDOS, are as follows: if scientific knowledge were to be accepted as legitimate and incorporated into the "communal stock" by the scientific community, and by extension, trusted as a matter of fact by society at large, it had to be *communal* in its availability, *universally* assessed on the basis of established impersonal criteria, *disinterested* in nature, and evaluated with *organized scepticism* (ibid).

As it relates to pharmaceutical innovation, the authors discussed above all (indirectly) touch on notions of openness. For Merton (1942), "legitimate" scientific knowledge was communally available. As will be discussed in the ensuing sections of this chapter, the notion that scientific knowledge must be communal in nature (and thereby that scientific findings cannot be owned exclusively by any group or individual) is debatable, to say the least, and the realities of knowledge production (particularly in the context of developing new pharmaceutical products) contrasts significantly with Merton's views (Shapin, 2008). Moreover, given the increasing involvement of private, for-profit research institutes and firms in fundamental research, the norm of *disinterestedness* holds increasingly less weight. For Shapin and Schaffer (1985), the "extension of experience from the few to the many" (p. 64) was a critical component of objective scientific fact-making – a task made especially difficult today when knowledge and data are enclosed behind proprietary barriers.

In light of the growth of industry-funded R&D and the expectation that scientific research

produce results with direct commercial value, the abbreviation PLACE may be more appropriate in the context of research conducted by means of public-private partnerships. In contrast to what he describes as academic science, wherein Merton's norms hold true at least in part, Ziman (2002a) argues *industrial* science,

> …produces *proprietary* knowledge that is not necessarily made public, it is focused on *local* technical problems rather than on general understanding, [its] researchers act under managerial *authority* rather than as individuals, their research is *commissioned* to achieve practical goals, rather than undertaken in the pursuit of knowledge, [and] they are employed as *expert* problem solvers, rather than for their personal creativity (78-79).

Ziman's distinction between academic and industrial science is significant here: whether or not scientific inquiry can be neatly classified as one or the other, the contrast between Merton's idyllic view of science as an independent pursuit of fundamental truths about nature versus Ziman's somewhat more pragmatic vision highlights the importance of interrogating the social processes that underpin scientific practices. While Merton's norms highlight the social nature of scientific knowledge production, their relevance today is disputable. Nevertheless, they continue to affect scholarship in cognate fields such as the economics of science (see section 2.2), perpetuating an impractical version of scientific research that has negatively impacted science policy and research in recent decades.

2.1.2. Mode 1/Mode 2: A Useful Distinction?

While traditionally speaking, scientific knowledge is often considered to be produced under and reflect specific disciplinary identities, in recent years research projects have been undertaken in "…the 'context of application,' that is, [emphasizing] the growing importance of the socio-economic environments of knowledge production" (Heimeriks, 2013: 98). The work of Michael Gibbons et al. (1994) was an important attempt to extensively detail a "new" mode of knowledge production in contemporary science – that is, knowledge produced *in the context of application*

(versus "pure" or "basic" scientific knowledge). Gibbons et al.'s distinction between what is described as *Mode 1* and *Mode 2* science is intended to illustrate the varying and elaborate methods, values, theories, and communities in which scientific research occurs and in which knowledge is produced and disseminated. Though the Mode 1/Mode 2 distinction is reductive and overly simplistic, it is worth unpacking the terms, particularly as they apply to pharmaceutical development.

Scientific knowledge derived in Mode 1 generally upholds the Mertonian norms discussed above and highlights the principles of "pure science" put forth by Merton and reinforced by Vannevar Bush in 1945. According to Gibbons et al. (1994), "Mode 1 is identical with what is meant by science. […]Its cognitive and social norms determine what shall count as significant problems, who shall be allowed to practice science, and what constitutes good science" (3). The locus of Mode 1 science is the university: it is characterized by its homogenous, discipline-based focus and practitioners, and occurs in the absence of specific practical goals (ibid: 3-4). It is, in essence, *pure* science: neutrally conducted research intended to produce universal knowledge about natural phenomena to be used to test theories in specific discipline-based contexts.

Conversely, Mode 2 knowledge is produced *in the context of a specific application* and is motivated by real-world concerns. With the advent of "Big Science" following the Second World War, scientific research became "socially accountable and reflexive," and was produced in industrial settings by a "more temporary and heterogeneous set of practitioners, collaborating on a problem defined in a specific and localised context" (ibid: 3). According to Gibbons et al. (1994), Mode 2 knowledge production blurs disciplinary boundaries and is inherently *trans*disciplinary. Its focus is practical and application-based, though *application* is not necessarily synonymous with *product development*; rather, the production of Mode 2 knowledge involves an attempt to solve real-world problems. Unlike in Mode 1 where members of a specific discipline determine the

legitimacy and integrity of knowledge, the value of Mode 2 knowledge is determined by a broad range of stakeholders extending beyond the core research group (ibid). Importantly, it is the product of specific *supply and demand factors*: as a result of the rapid growth of scientific and technical "professionals" and the subsequent proliferation in specialised knowledge since the 1950s, "…the market for knowledge – the number of places where it is wanted and can be used – is now wider and more differentiated than it has ever been" (ibid: 49). There was (and is) now a greater opportunity than ever before for scientists of disparate backgrounds to temporarily come together to solve a particular problem. For instance, for Gibbons et al., developing novel cancer therapeutics would constitute Mode 2 knowledge production: research in this context is conducted to solve a particular real-world problem. It isn't carried out *solely* by pharmacologists or *solely* by molecular geneticists, but rather it *applies* the knowledge and expertise from multiple disciplines, from biochemistry to applied mathematics to biomedical ethicists. Its value is assessed not only by those who those who produce it, but by those who fund it and make use of the products or solutions it may yield.

While the notion of supply and demand factors for knowledge production is a useful one in the context of this work (to be discussed), the Mode 1/Mode 2 distinction has been criticized as promoting a manifestly reductive and inadequate basic/applied dichotomy. Whitley (2001) is particularly critical of the lack of consideration given to the changes to organizational characteristics scientific disciplines have experienced in recent decades. He notes certain fields (particularly the biological sciences) have developed increasingly "fluid and overlapping organizational boundaries," in part due to the development and generalization of molecular biology and to "…the expansion of funding by mission-oriented agencies on a project basis" into the academic sphere (Whitley, 2001: xix). The focus on disciplines and discipline-based knowledge production inherent in the Mode 1/Mode 2 distinction (recall, Mode 1 is discipline-based while

Mode 2 is interdisciplinary) overlooks the social nature of scientific knowledge production, even the most fundamental sort. What Gibbons et al. would describe as Mode 1 science is not immediately supplanted by Mode 2 at the suggestion of application or interdisciplinarity. Scientific research *across* the basic/applied spectrum, Whitley argues, has long been "entrenched in educational institutions and employment markets" that shape how it is conducted and determine the products it yields (2001: 9). The advent of Big Science did not precipitate a chasm between academic ("pure") and industrial (applied) science, as Fuller (2000) notes, and the Mode 1/Mode 2 distinction mischaracterizes universities as autonomous institutions free from external pressures of industrial or commercial influence. Moreover, it ignores the relationship between science and technology on the one hand, and enterprise and society on the other (Shinn, 2002). For centuries, the majority of scientific discoveries have been motivated by attempts "to solve problems in navigation, mining, etc.," and the "solution of practical problems through scientific means has been an important factor in scientific development, whether in German pharmaceutical science in the 17th century…or in the British-sponsored competition to provide a secure basis for navigation" (Etzkowitz and Leydesdorff, 2000: 116). What is described as Mode 2 science is not a "new mode of knowledge production," rather,

> it is the original format of science before its academic institutionalization in the 19th century… Mode 2 represents the material base of science, how it actually operates. Mode 1 is a construct, built upon that base in order to justify autonomy for science, especially in an earlier era when it was still a fragile institution and needed all the help it could get (ibid).

As an additional explanatory model for the current state of scientific R&I, Etzkowitz and Leydesdorff (2000) describe the *triple helix model* of knowledge production. In this particular model, universities, industry, and government are argued to be the primary, co-equal helices the scientific enterprise, largely due to the increasingly prominent role played by scientific knowledge

in society broadly speaking, and the growing importance and variety of non-academic collaborators (ibid). The significance of these institutions in the triple helix model is determined by the dynamics of wealth generation in the economy, novelty generation by scientific research, and the governance of both via policymaking in the public sphere and corporate management in private industry (Leydesdorff, 2010). As will be discussed in ensuing sections of this chapter, interactions between these institutes often produce entrepreneurial intermediary organizations such as incubator labs, spin-offs or startups, science parks (such as MI, for instance), and venture capital firms (Etzkowitz, 2007). Innovation in the triple helix model generally takes place when collaborative, reciprocal relationships are established between each of the three helices: for instance, enhancing the R&D performance of universities "often becomes the key issue as part of a strategy to renew an older economy or create new economic activity on the basis of intellectual capital" (ibid: 11). Once this policy strategy is established, government and industry may then become involved in supporting academic R&D, often through the establishment of research centres and funding initiatives (ibid). Unlike the Mode 1/Mode 2 model, the triple helix model does not erase or ignore the historical relationship between the scientific enterprise and the state; rather, it posits a co-evolution of these institutions and their organizational structures such that knowledge production is inextricably linked between each helix (Shinn, 2002).

In yet another attempt to navigate around the limits of the Mode 1/Mode 2 distinction, Ziman (2002a) coined the term *post-academic science*, referring to the research paradigm that emerged following the birth of the biotech industry in the 1970s wherein knowledge was constructed by heterogeneous groups "in accord with the commercial, political, or other social interests of the bodies that underwrite its production" (174). What differentiates Ziman's post-academic science from the Mode 1/Mode 2 notion of science put forth by Gibbons et al. is the emphasis on *utility* versus *application*. Post-academic science, however theoretical or applied in nature, is evaluated

based on its utility. Even the most commercially "useless" sciences (i.e. cosmology) are required to demonstrate short- or long-term utility (though not necessarily immediate application) to institutions outside academia to justify funding and are seen as being in service of the nation. Science, in the post-academic paradigm, is a "…driving force in a national R&D system, a wealth-creating techno-scientific motor for the whole economy" (ibid: 73).

But why is all of this useful in a discussion of the open and proprietary dimensions of pharmaceutical innovation? Are Merton and the Mode 1/Mode 2 distinction not outdated by now? A quick scan of papers published in *Social Studies of Science* and *Science, Technology and Human Values* – two of the highest impact journals in STS – since 2009 reveals several dozen citations of Gibbons et al. (1994). These works cite the Mode 1/Mode 2 debate largely in discussions of the blurring of boundaries between industry and academia (Tuunaienen and Knuuttila, 2009; Parker and Crona, 2012), science as a public good (Stengel et al., 2009), the epistemics of scientific knowledge and current technology (Hoffman, 2015), and entrepreneurial science (Lam, 2010), among numerous others. Ziman's *post-academic science* is an especially useful descriptor here: the Mode 1/Mode 2 ("pure"/applied) delineation seems to depict science as though all theory-directed, explanatory, or classificatory research occurs in a vacuum, unaffected by the politics of funding bodies or institutions, while anything outside this bubble is intended solely to produce marketable products. The science examined and discussed in this dissertation does not fit under either the Mode 1 or Mode 2 umbrellas; it is *inter*disciplinary, mission-based, market-oriented, and situated within the broader context of corporate strategy, scientific competition, and government policy. It is *useful*, commercially and otherwise. Regardless, it bears examining the ways in which the production of scientific knowledge has come to be understood by STS scholars, and how these discussions contrast with the complex realities of pharmaceutical R&D.

2.1.3. Interdisciplinarity, Collaboration and the Organization of Science

Whether the Mode 1/Mode 2/post-academic distinctions are generally useful or relevant today, these discussions nevertheless highlight one crucial characteristic of contemporary scientific R&D: *interdisciplinarity*. Heimeriks (2012) differentiates between *multidisciplinarity* ("a conglomeration of disciplinary components"), *transdisciplinarity* ("an application-oriented type of heterogeneous knowledge production"), and *interdisciplinarity* ("a more synthetic attempt at mutual interaction") (1). *Interdisciplinary* is a subjective concept and a slippery one to pin down. Interdisciplinary research may be narrow in nature and include fields that are conceptually close to one another, in which interaction between participating fields "is not exceptional or particularly challenging in epistemological terms, since the concepts, theories and/or methods are relatively similar in their epistemological presuppositions," such as in the case of systems biology (Huutoniemia et al., 2010: 82). Conversely, it may be broad in nature, wherein conceptually heterogeneous fields covering broad intellectual areas interact (e.g. medicine and law, molecular biology and history). It may refer to skillsets, infrastructures for research designs, application of methodologies, knowledge bases, and/or tools for data acquisition and analysis (Heimeriks, 2012).

This dissertation employs a general, somewhat generic definition, in that "research becomes interdisciplinary whenever the research activity involves several fields" (ibid). In the *–omics* era, knowledge production is no longer inwardly oriented, and disciplinary boundaries have become increasingly difficult to draw, while knowledge flows have become increasingly fluid. Historically, drug development was primarily based in chemistry. Today, studying the complex interactions of biological systems to develop new drugs and medical technologies and to understand diseases and population dynamics necessarily extends beyond the confines of any particular discipline and includes in part the methods and tools of genomics, proteomics, metabolomics, mathematics, physics, computational biology, and statistics (Pisano, 2006).

Disciplinary interests, constraints, and methodologies are constantly dissolving, merging, and overlapping in response to external challenges. Knowledge production has also become coupled more directly to broad social and economic problems, involving fluid organizational structures of disciplines "mediating between knowledge and knowledge markets" (Weingart and Stehr, 2000: xiv).

Interdisciplinarity is now synonymous with *innovation* and *progress* (ibid) and it has become increasingly difficult to justify funding for research that is not interdisciplinary to some degree. Heimeriks (2012) argues that in fields with high commercial potential such as nanotechnology, biotechnology, and genomics, there is a strong incentive for government R&D policies that promote and fund interdisciplinary research. This is evident in the growth of government-funded interdisciplinary research institutes across North America and Europe. For instance, in 2007 the U.S. National Institutes of Health (NIH) launched an interdisciplinary research consortia consisting of nine institutes (including the Broad Institute of MIT and Harvard University, and the Oncofertility Consortium at Northwestern University), the aim of which was not only to address complex health challenges, but to dissolve departmental boundaries within institutions, forge "inter-disciplines," and provide training for students in multiple disciplines (NIH, 2007). In contrast to *multi*disciplinary research, in which researchers approach particular problems from their own disciplines, *inter*disciplinary research conducted by consortia members

> integrates elements of a wide range of disciplines, often including basic research, clinical research, behavioural biology, and social sciences so that all of the scientists approach the problem in a new way. The members of interdisciplinary teams learn from each other to produce new approaches to a problem that would not be possible through any of the single disciplines. Typically, this process begins with team members first learning the language of each other's discipline, as well as the assumptions, limits, and valid uses of those disciplines' theoretical and experimental approaches. Experiments are then designed in ways that cut across disciplines, with, for example, an experiment based in one discipline producing data that can be correlated — or otherwise connected to — data generated in experiments based in

> another discipline. The common understanding by the team of the disciplines involved assures that this tight linkage across the disciplines is valid (ibid).

Likewise, Canada's primary federal funding bodies for research in the sciences – the Canadian Institutes of Health Research (CIHR) and the Natural Sciences and Engineering Council (NSERC) – both explicitly emphasize the need to adapt research practices in the post-disciplinary paradigm by promoting and advancing a national interdisciplinary research program (CIHR, 2018; NSERC, 2018a). Since 2012, both agencies have offered funding for multidisciplinary training and collaborative health research projects, the purpose of which is to "encourage the NSERC and CIHR research communities to collaborate and integrate their expertise" and to "train highly qualified personnel in collaborative and interdisciplinary research relevant to health" (NSERC, 2018b). Institutes such as the European Molecular Biology Lab (EMBL) and the UCL Centre for Computation, Mathematics and Physics in the Life Sciences and Experimental Biology (CoMPLEX), for instance, again demonstrate the push for researchers to move away from "reductionist" discipline-focused and engage in collaborative, interdisciplinary R&D (EMBL, 2018). Interdisciplinarity has evidently become a key component of scientific knowledge production in this particular research paradigm, one that is now tied directly to funding opportunities.

As R&D has become more interdisciplinary in nature, it has become more collaborative – a product of the growing access to human capital offered by new communication technologies, in addition to the rising costs of R&D and the increasing complexity of science itself. The "burden of knowledge" as described by Jones (2009), has necessitated more collaborative efforts among scientific researchers. Knowledge begets new knowledge, Jones argues, and as the total stock of knowledge (about cancer, targeted therapies, and so on) accumulates and individuals "know an increasingly narrow fraction of it," a growing breadth of expertise is needed to undertake scientific R&D (Jaffe and Jones, 2015: 3). Scientific R&I is an aggregate process of producing new

knowledge and the narrowing of expertise, argues Jones (2009), reduces the capabilities of the individual scientist, and, by extension the scope of their methodologies, research tools, and knowledge base. To continue making advancements in biotechnology or pharmaceutical sciences, then, increased numbers of researchers are required to collectively pool their skills and expertise (Freeman et al., 2015; Raasch et al., 2013). Further, the advancement of information and communication technologies since the 1990s has coincided with the rapid growth of STEM PhDs and researchers around the world – essentially, the growth of human capital has been coupled with an increased ability to tap into it (Freeman et al., 2015). As a result, there has been a marked increase in international collaborations, particularly in the biotech sector, as demonstrated by a rise in international research collaborations and co-authorships of scientific papers (ibid), particularly between graduate students, post-docs, and faculty (Conti and Liu, 2015). Freeman et al. (2009) argue the growing number of international scientific collaborations suggests a positive link between authorship, interdisciplinarity, and collaboration; essentially "…the greater the knowledge that goes into a paper, the greater the scientific contribution of the paper – at least to the extent that these measures are a valid 'paper trail' of flows of knowledge" (43). Increasingly, research across all disciplines – including STEM fields, the social sciences, and the humanities – is conducted as a collaborative effort, particularly high-impact research (Wuchty et al., 2007). Naturally, communication barriers arise when disparate and physically distant groups with varying expertise come together, however the rise of "team"-based R&D suggests that collaboration offers researchers growing returns (in reputational and intellectual property markets), and is demonstrative of the fundamental changes to both the organization of scientific activity and the production of scientific knowledge that have occurred since the early-2000s (Agrawal et at., 2015).

As discussed briefly in chapter one, the *–omics* era brought about a shift in the focus of research from objects (e.g. the gene, the protein) to systems (e.g. the genome, the proteome). As

noted above, R&D is now increasingly interdisciplinary and collaborative, particularly in the context of drug development. By extension, the *–omics* era has been accompanied by a rise in the cost of R&D itself, compounding the push towards interdisciplinary collaboration. The average cost of clinical trials for new chemical entities, from initial protocol approval to final clinical trial report was "US$3.4 million for phase I trials involving patients, $8.6 million for phase II trials and $21.4 million for phase III trials" in 2017, with everything from the number of subjects randomized per trial to strategic choices (e.g. the selection of country in which to conduct trials) affecting overall costs (Martin et al., 2017: 381). Towards the upstream end of the R&D spectrum, the costs of early-stage research can also run quite high. In the case of structural genomics for instance, high-throughput technologies employed to determine the three-dimensional structure of proteins used in drug targeting and discovery are expensive to run and maintain, with the average cost of deciphering a protein structure estimated to be roughly US$300,000 (Chandonia and Brenner, 2006; Sá and Tamtik, 2011). As Stephan (2015) notes, while some of the equipment used in contemporary R&D, "…although expensive, [is] still affordable at the lab or institutional level. Some, however, such as nuclear magnetic resonance (NMR), [carry] sufficiently large price tags *to encourage, if not demand, collaboration across institutions*" (339, emphasis added). R&D in certain fields (notably drug discovery and development) is, more often than not, prohibitively costly to duplicate. As discussed previously and outlined in table 1, DiMasi et al. (2016) estimate the cost of drug development to be roughly $2.8 billion. and requires research groups to pool resources (either tangible or intangible) at every stage of the R&I process. Thus, in addition to it being interdisciplinary in nature, R&D generally relies heavily on collaborative efforts both within and across institutional boundaries.

The purpose of highlighting the various modes of knowledge production discussed in STS scholarship in this literature review is to shed light on the relationship between the consideration

given to contextual application at the outset of research projects and the consequent interdisciplinarity of practices in the sciences. Knowledge production extends beyond the technical work occurring within the laboratory and is a product of the ebb and flow of information across disciplinary boundaries. If, as discussed, the internal structure of science is a social formation (Ziman, 2002b) and scientific collaborations have extended to broader and more heterogenous networks over time, it is important to examine the *devices* that facilitate or impede social interactions and collaborations in the process of scientific research – that is the aim of this work. Moreover, it is worth examining these devices not only in the lab, but also in the intermediary institutions (e.g. science parks and tech transfer offices) that have grown from the interactions between universities, industry, and government, as this research aims to do.

2.2. The Changing Political Economy of Science

If the economy is socially embedded, and the scientific enterprise is a complex social institution with a *politics*, it must therefore also have an *economics* (Nelson, 1959). As Ziman (2002b) has argued, it is based on a system of financial and notional *markets*, driven by competition and based on the exchange of commodities for currencies. The relationship between science and economic growth is impossible to disentangle: today, science is seen "as an economic engine, a source of innovation that can create new products, firms, or even industries" (Popp-Berman, 2012: 6). Scientific research frequently tasked with "kick-starting the moribund economy," the idea being that innovations stemming from research will provide opportunities for dynamic investment, offer commercial solutions for societal problems to a broad consumer base, and create new markets, services, and jobs (Birch et al., 2018: 596). This section focuses on the changing political economy of science in recent decades, focusing first on the economics of science broadly, before discussing the current paradigm of academic capitalism and the commercialization of scientific

research.

2.2.1. The Economics of Science and Technology

It has become a truism to argue that economic growth in industrialized nations is rooted in part in the exploitation of scientific knowledge (Dasgupta and David, 1994). In fact, there is a long history of economic studies of science and technology focusing on theoretical and empirical explanations of the sources and trajectories of technological innovation, science as a process of production, the relationship between technological innovation and economic power, research funding, the commodification of knowledge, and so on (for example, see Arrow, 1962; Nelson, 1959; and Polanyi, 1969).

Sent (1999: 97-98) identifies six groups endeavouring to analyse the economic structure of science and the effects of economics on the conduct and content of science, noting there is little movement or dialogue between any group: first are the *orthodox economists* seeking to understand the economic drivers of research funding and the incentives driving scientific research. Second, the *historians of science and technology* attempting to historicize the pure/applied dynamic of science. Third, the *sociologists of science* producing "micro-studies" of laboratory activity and the social operations of science. Fourth, the *philosophers of science* analyzing the construction of scientific knowledge via economic processes. Fifth, the *science policy experts* analyzing funding and organizational patterns of science as they relate to market models. Finally, there are actual *working scientists* discussing funding conditions in the sciences. As Tyfield (2012b) notes, "there are almost as many definitions of the 'economics of science' as there are practitioners" (13), and while the organizational structure of the field has undergone significant changes since in recent decades, there is no dominant paradigm of an economics of science that has emerged since.

The growth of Mertonian sociology of science coincided with the work of economists and

philosophers of science such as Nelson (1959), Arrow (1962), Popper (1963), Polanyi (1962), and Feyerabend (1975) that rose to prominence shortly following the Second World War, marking the first wave (or historical phase) of an "old" economics of science (Sent, 1999). Favouring a simplistic basic/applied dichotomy, this cohort of scholars focused predominantly on measuring the impact of scientific research on economic growth, understanding the reward structures embedded in the scientific enterprise, institutional structures, and funding and grant patterns (Ballandone, 2012). During this time, a "concertedly nationalized system of science" was established in the United States, wherein antitrust laws were strengthened while IP was weakened, universities were generously funded, and the notion of science as a public good was dominant (Mirowski, 2011: 114).

The National Science Foundation (NSF) became the face of "pure" science, while the military acted as the primary managers for research universities and national laboratories and promoted basic science as a means of protecting national security (ibid). As the Cold War intensified, a new paradigm emerged in the early 1980s, marking the second phase of the "old" economics of science that lasted until the mid-1990s. At this time, scientific knowledge was deemed to be a commodity in a generic market that was seen as the general model for all social organization, and science itself was implicitly treated as just another market phenomenon (Mirowski and Sent, 2009). Moreover, economists of science had "essentially abandoned the field to philosophers of science and science studies scholars," as evidenced by the dominance of works by Latour and Woolgar (1982), Collins (1984), and Fuller (1988) examining the social and socio-economic foundations of science during this period (Sent, 1999: 102). The linear model of techno-scientific innovation, in which basic scientific knowledge flowed sequentially from discovery to applied contexts to the development and diffusion of a commercial good, dominated this paradigm in both theoretical discussions and policy practices (Godin, 2006).

Since the mid-1990s, the political economy of science has been shaped largely by the rise of neoliberalism and characterized by a growing entanglement of science and capitalism. The primary outcome of this entanglement has been the push towards increased commodification, commercialization, privatization, and marketization of scientific research (Lave et al., 2010). Science is seen as an engine of prosperity, where the value of research and its byproducts is qualified in terms of returns on investment (Chiapello, 2015). Moreover, it has become fundamentally market-oriented, in that profit and cost are prioritized over other (ethical) considerations.

The effect of market considerations on the scientific enterprise is exemplified by pharmaceutical development and drug pricing. In this particular case, economic returns are increased when knowledge contributes directly to solving problems affecting large population percentiles. Diseases such as diabetes, chronic hypertension, and hyperlipidemia have large target populations, and thus offer a greater opportunity for drug manufacturers to earn a higher return on their investment. Conversely, rare diseases that may, in fact, be easier to target (e.g. those with single gene defects) are extremely costly, both for pharmaceutical manufacturers as well as for health insurance providers – this is reflected in drug pricing. In the current free market economy, rather than the price of a new drug inversely reflecting its worth (i.e. if a product has a higher life-saving potential it should be more readily available), prices generally reflect what the market bears (Abboud et al., 2013). Recall, it costs roughly USD$1-1.5 billion per NCE, from initial laboratory target discovery through clinical trials and including all other ancillary costs such as advertising and salaries (Collins, 2011). Following those figures, drug manufacturers net profits after roughly a billion dollars in sales. However, drug prices for diseases with small target populations continue to be prohibitively high even after production costs are recouped, and compromise access to live-saving therapies (Abboud et al., 2013).

The case of imatinib is a particularly interesting example of mediating devices (to be discussed at length in section 2.5) negatively impacting the clinical application of new medicines in this new era of commercialized science. Patented by Novartis and marketed under the brand name *Gleevec*, imatinib was the first successful treatment (and the most successful targeted cancer therapy developed at the time) for chronic myelogenous leukemia (CML), a particularly aggressive blood cancer (Pray, 2008). Unlike with other solid cancers, with treatment CML is "more similar to indolent disorders like diabetes, hypertension, and cardiovascular disorders, where daily therapy is required indefinitely to produce the anticipated benefit of long-term survival" (Abboud et al., 2013: 4440). Despite the extremely promising results imatinib offers to patients, the population of those affected with CML is quite small (~90,000 patients in the United States), and the price per annual treatment course fluctuates between $90,000 and upwards of $138,000 depending on the brand name product versus the generic with insured patients in the United States paying on average 20% out of pocket (ibid). In 2012, annual revenues for imatinib for Novartis were roughly USD$4.7 billion, long exceeding its original development cost, as monthly costs continue to grow (Johnson, 2016).

The case of imatinib demonstrates both the negative impact of a market monopoly granted via a patent as well as the primacy of market considerations (over other considerations) in terms of shaping scientific research and its biproducts in this current paradigm. As will be discussed in Chapters Five through Seven of this dissertation, these market considerations shape not only what kind of research is conducted, but also the IP tools that are used to bring that research to market in the form of new drug products.

This paradigm has also seen a rollback of public funding for scientific research, as the end goal of scientific knowledge production in this paradigm has primarily been to yield profits (Lave et al., 2010). The production of science (or scientific knowledge) for specific commercial actors

and markets has led to a consequent narrowing of research agendas and has limited the ability of researchers to pursue tangential and potentially fruitful avenues of inquiry (Mirowski, 2011). Given that it is especially difficult to appropriate returns from basic scientific research, "which is at best years away from contributing to products that may or may not be of value to the market," the commodification of scientific knowledge and the push to commercialize research has potentially significant implications for upstream R&D in this paradigm (Stephan, 2012: 111). Specifically, as noted in chapter one, basic research projects deemed to be unprofitable or unable to be captured via proprietary IP rights run the risk of being defunded (Birch et al., 2016). Correspondingly, this phase has also seen a weakening of antitrust legislation and a strengthening of IP rights as a means of commercializing knowledge produced in both the public and private sphere (Lave et al., 2010). As will be discussed in the ensuing section on intellectual property, while fortifying proprietary IP helps in part to navigate around previously mentioned issues of appropriability, various forms of IP protection (e.g. patents or copyrights) may actually hinder the production and dissemination of scientific knowledge by preventing others from building on and translating knowledge. As public funding for basic research and public research institutes has fallen, this particular political-economic phase has also seen the collapse of in-house corporate research labs and the growing practice of outsourcing corporate research (Mirowski, 2011).

In terms of scholarship during this phase, by the mid-1990s the economics of science turned in a new direction with the publication of the seminal paper "Toward a New Economics of Science" by Dasgupta and David (1994). In outlining a framework for research and policy development, the authors identify three key areas of focus in the "new" economics of science (NES): the production, dissemination, and use of scientific knowledge. "Science" is defined and analyzed according to Mertonian norms, and the NES

> …has the two-fold ambition of (1) exposing the underlying logic of salient institutions of science, and (2) examining implications of those differentiating institutional features

> for the efficiency of economic resource allocation within this particular sphere of human action (ibid: 492).

In defining science along sociological lines, NES then endeavours to provide explanatory economic models for the emergence, stability, and problems of the [Mertonian] norms of science (Tyfield, 2012b). Although science here is seen as a social phenomenon that includes tacit elements, Sent (1999) is particularly critical of the tendency of theoretical work in NES to conflate *science* with *knowledge*, and *knowledge* with *information* by "presuming that the treatment of 'knowledge' is unified in economics" (115). Moreover, knowledge in NES is treated as an uncomplicated commodity to be exploited, overlooking the complex ways in which knowledge and research agendas are shaped by both funding arrangements and the economy broadly (Mirowski, 2011; Mirowski and Nik-Kaah, 2016).

Further still, the Mertonian sociology of science and its associated norms (CUDOS) have essentially been invalidated by a generation of work in STS and the sociology of scientific knowledge (SSK) demonstrating the inextricable relationship between social factors and scientific knowledge production (Tyfield, 2012b). While the current political economy of science remains market-oriented for the time being, the economics of science as a field remains poorly defined. An effective approach to studying the economics of science would incorporate a broader examination of the reciprocal interaction between science and economics, in addition to reflecting the contributions of science to the production of economic goods (ibid). As Mirowski and Sent (2009) point out, the notion that there is even a *singular,* monolithic economics of science is misleading. The economics of science, they argue, has evolved in tandem with the sciences, and thus the field should reflect the complexity of social and cognitive networks that shape the scientific enterprise. Much like the field of innovation studies (see section 2.3), economic studies of science as a discipline leaves many questions unanswered.

2.2.2. Academic Capitalism

With the growing entanglement of neoliberalism and science since the end of the Cold War, the scientific enterprise was seen as an economic engine. By neoliberalism, I refer simply to the political economic ideology favouring market fundamentalism, increased competition (via the opening of domestic markets to foreign competition), and deregulation and privatization of state enterprises (Ostry et al., 2016). During this time, universities began focusing on the commercial impact of science, a move that coincided with both the stagnation of government funding for academic science in the 1970s and the decline of in-house corporate R&D, in turn leading industry to rely on universities to conduct basic research (Rosenberg and Nelson, 1996). It was therefore determined that the market "[was] the best way of getting university breakthroughs into the hands of the public, and patents create the incentive that [made] that happen" (Popp-Berman, 2012: 6). Prior to the birth of the biotech industry in the late 1970s, there was a clear boundary between the university and industry. While faculty served as advisors and consultants to industry, academic entrepreneurship was relatively limited – a result of a dearth of capital for early-stage industry developing academic inventions (ibid: 58). However, following the emergence and rapid growth of the biotech sector in the 1970s and a relaxed regulatory environment towards the end of the decade, a series of legislative reforms in the United States ushered in a new era of academic capitalism (see Hackett, 1990; Slaughter and Rhodes, 2004). Specifically, the U.S. Supreme Court decision in *Diamond v. Chakrabarty* (1980) and the passage of the *Bayh-Dole Act* (1980) led to an explosion of patent filings by American universities (Sterckx, 2010). After the loosening of recombinant DNA research regulations in 1977, the landmark case of *Diamond v. Chakrabarty* in 1980 determined that genetically modified microorganisms could be patented (Mirowski, 2011). That same year, the passage of the *Bayh-Dole Act* affirmed the right of universities to patent government-funded inventions (ibid). Both created an opportunity for public research institutes to

attract investments from private industry, thus expanding the marketplace for scientific knowledge and its byproducts.

As will be discussed in more detail in Chapter Five, after *Bayh-Dole* became law, universities began to develop technology transfer offices (TTOs) with the idea that patenting research was necessary to attract investment in research projects. TTOs operated (and continue to operate) under the idea that "universities had a responsibility to patent to prevent publicly funded research from languishing unused. […]Simply creating knowledge and making it accessible was not enough. Universities needed to harness the power of the market" (Popp-Berman, 2012: 95). Further, universities "were urged to help revitalize U.S. technological competitiveness by taking steps to transfer technology to industry," and the number of patents awarded to universities continued to rise – doubling between 1991 and 1997, while licensing revenues tripled (Geiger and Sá, 2008: 12). Through the fortification of its national patent regime and the enactment of patent policies and research regulations founded on the bedrock principles of ownership and profiting from one's ownership, the U.S. government ensured a means of return on public capital investment in scientific research (Kraemer, 2006). As it relates to the Canadian landscape of innovation, the period of the Mulroney administration (1984-1993) in particular saw the rise of neoliberal ideologies in Canadian public policy, especially as Canada became a signatory to several international trade agreements (discussed further in Chapter Four) (Warner, 2002). Canadian universities similarly began to develop TTOs to commercialize academic research, though on a much smaller scale with significantly less revenue than their American counterparts (Thon, 2018).

Ziman (2002b) argues that it is the market-like mechanisms currently in place that ensure scientific research remains flexible, open, progressive, relatively impartial, and self-critical. The market "is a social institution for the systematic exchange of commodities for currencies between vendors and customers" (ibid: 323). Prior to 1980 and the rise of patenting at American

universities, primarily notional commodities and currencies were traded on a *reputational* market: scientists presented their contributions to knowledge (i.e. published papers) in exchange for communal recognition. In this notional market, "the vendors are individual researchers, the commodities are research results, the customers are 'invisible colleges' of other researchers, and the currency is simply a public sign of personal esteem" (ibid: 331). However, as the end goal of scientific knowledge production in the current paradigm has primarily been to profit, scientific knowledge cannot only be traded for recognition but can also be sold for cash. As Ziman (2002b) notes, once research has been disclosed publically (i.e. in the form of a published paper), it is essentially a public good and appropriating rent becomes difficult. A *good* in economic terms is defined by two characteristics: rivalry and excludability. In this particular case, "a good is appropriable (or exclusive) if it is possible for the person using or consuming it to prevent any other potential user or customer from doing the same," and it is rivalrous when two or more actors are competing for its use (Callon, 1994: 399). Conversely, a *public* good is both non-rivalrous and non-excludable: it can be accessed and put to use by all members of the public with no particular group benefiting from its exclusive use or property rights, and without its usefulness being undermined.

As will be discussed in section 2.4 of this chapter, while debates in STS regarding the status of scientific knowledge as a public good remain ongoing, knowledge (i.e. research results) is made both rivalrous and excludable when enclosed behind proprietary IP rights. For instance, patenting a chemical compound ensures its excludability, prevents others from freely mobilizing that knowledge, and establishes a legal owner with the power to demand payment for its use. Ziman (2002b) points out that the financial value of basic research is speculative at best, as estimates of the value of knowledge claims are conjectural and the majority of early-stage discoveries are ultimately commercially worthless. However, even if this is the case, the extension of the

commercial market into academia and the ability to commodify research results via patents that followed has permanently ensured "the orientation of academic research toward technological advancement and socioeconomic priorities" (Radder, 2010: 13).

2.2.3. The Commercialization of Science

As discussed previously, basic scientific research has traditionally been funded almost exclusively by government, while private industry has taken on translational- and late-stage development. The state has historically been less productive than the private sector in terms of commercialization, however it has also taken on the bulk of funding for the riskiest, path-breaking research (Mazzucato, 2013). This occurs namely because the market value of fundamental science is often difficult to forecast, and the "realization of economic rents ('profits') from a basic research advance…are intrinsically difficult to establish and defend," making private returns to investment highly uncertain (Dasgupta and David, 1994: 490). The commercialization of pharmaceutical research is especially difficult given the associated sizeable upfront costs and high risks, and further requires marketing, manufacturing, distribution, and regulatory compliance assets that are generally unavailable to university researchers (West, 2008). Moreover, a significant amount of time, investment, and know-how is needed to translate the majority of [early-stage] research conducted at universities into marketable goods – it is *industry*, not academia, that excels in doing this, as *development* has long been a product of industry (Stephan, 2012).

With that said, however, commercialization (in the pharmaceutical sciences) today is a product of the relationships between universities and biotechnology firms, and biotechnology firms and large pharmaceutical companies (ibid). In fact, the majority of NCEs emerging from biotechnology firms originated in public research institutes, as universities have become active participants in the commercialization process and the primary recipients of biotech patents (Edwards, Murray, and Yu, 2003). Extending from this, in a 2017 survey of 34 Canadian academic

and non-profit research institutions, the Association of University Technology Managers (AUTM) found that patent disclosures increased by 10.9% since the previous year, to 1,882 in 2017 (AUTM, 2017a: 3). The AUTM's survey of American academic and non-profit research institution similarly found 7,459 US patents issued in 2017 – the highest number reported in the survey's history (ibid, 2017b). Therefore, if "economists measure productivity by comparing the amount of input into production with the amount of output that emerges," then large private pharmaceutical companies have arguably not been particularly productive in recent years (Mazzucato, 2013: 72). In this model, universities play an active role in the commercialization process by establishing large patent portfolios (particularly in the life sciences) and providing a ready supply of knowledge and data to industry, after which point small- to medium-sized biotech firms continue to develop products, often licensing them to large pharmaceutical firms.

Mirowski and Sent (2008) argue the root cause of the new model of 20th century commercialization can be found in the spreading practice of outsourcing corporate research: with the weakening of antitrust laws and the strengthening of intellectual property in the early 1980s, an unfettered corporate sector was now free to contract research to external firms (such as research parks and academic start-ups) as a cost-reduction measure. The decline of public research funding and demise of in-house R&D in fact corresponded to a rise in both the private funding for R&D and the volume of research conducted outside of the corporation funding it (ibid: 659-660). Contract research organizations (CROs) grew to prominence following the implementation of higher efficiency and safety standards by the FDA in the late 1980s (Mirowski and Van Horn, 2005). Originally offering narrowly focused outsourcing services to their clients, CROs such as Charles River Laboratories and Covance have grown to dominate nearly all stages of drug development (i.e. from basic research through discovery phase, pre-clinical nonhuman trials, and clinical trials) while manufacturing, commercialization, and marketing generally remains the

purview of the firm itself. Offered services range from "initial screening of molecules for biocompatibility, in vitro screening, pharmacokinetic modeling, chemical synthesis and analysis, all phases of clinical testing, dosage formulation and pharmacy services, to all aspects of the regulatory process" (ibid: 507). In a particularly interesting example of the growing significance of the CRO, a 2017 study conducted by the US Department of Agriculture (USDA) and published by the National Institutes of Health (NIH) evaluated the supply and demand for nonhuman primates used in pharmaceutical research and testing at NIH-funded National Primate Research Centers and other academic institutions, federal facilities, and private firms (NIH, 2017). The study found that of the total 38,799 nonhuman primates used in pharmaceutical research and testing by private firms in 2017, Charles River Labs and Covance accounted for 11,179 and 8,412 (or 12.2% and 9.3%) respectively (ibid). Merck and Pfizer, two of the largest pharmaceutical firms in the world, accounted for 1,432 and 1,157 (or 1.8% and 1.5%) respectively (ibid). What can be inferred from this is that CROs are indeed bearing the brunt of pharmaceutical development outsourced by large firms, as evidenced by the scale of preclinical nonhuman testing managed by Charles River Labs and Covance above. Arguably, as Mirowski and Van Horn (2005) note, CROs are paradigmatic of the current "regime" of industrialized/privatized science: the imperative of commercialization that has been injected into R&D has fundamentally changed how innovations are filtered through from the university to the market, as well as the extent to which scientific research is contracted out to external firms.

As discussed in the previous section, science has always been motivated by some practical application or socio-economic supply and demand factors (Shapin, 2008). However, the growth of university patenting practices and the increasing interconnectedness between universities and industry is indicative of more sweeping changes to the practices and organization of science in this paradigm. As will be outlined in more detail in Chapter Five, universities have become

increasingly entrepreneurial since the 1980s, while industry has relied more heavily on external firms to help bring products to market. Research and its byproducts have increasingly become market-oriented and shaped by the tenets of neoliberalism in this paradigm, often to the detriment of its end-users (in this case patients/consumers of pharmaceutical products). Further, the ubiquity of intellectual property rights (discussed further in section 2.4 and 2.5 of this chapter) represent a clear extension of the market into academia, and have become a linchpin in the R&D process.

2.3. Innovation Studies

Much like the economics of science, innovation studies has followed a circuitous path to becoming a discipline in its own right. Despite lacking any distinct methodological tools, designated journals, or field-wide associations, innovation studies is centered on a cognitive platform that extends from early studies of technological change and invention. It is composed of networks of communities of scholars in cognate fields (e.g. geography, policy studies, management studies, industrial economics) bound together by strong working relationships (Fagerberg and Verspagen, 2009). This section focuses first on the establishment of innovation studies as a discipline before discussing recent changes to biotech business and innovation models specifically.

2.3.1. Innovation as a Discipline

As a discipline, innovation studies is rooted in three stages of early economic thinking; namely invention, technological change, and finally technological innovation (Godin, 2010a). Innovation studies is considered to have stemmed from early work by the economist Joseph Schumpeter, and a large majority of core works in the field proceed from his discussions of evolutionary economics (Coriat and Weinstein, 2002). In distinguishing entrepreneurial

innovations from inventions, Schumpeter argued innovation followed organized patterns whereby entrepreneurs innovated primarily by introducing new means of production (Schumpeter, 1942). Capitalism, he asserted, "is by nature a form or method of economic change and not only is but can never be stationary," and thus economic structures are revolutionized from *within* through what he described as *creative destruction* (ibid: 82). Entrepreneurial innovation, fueled by competition, therefore plays a role in the "perennial gales of creative destruction:" new consumer goods, new modes of production, new markets, and new forms of industrial organization created by the capitalist enterprise sets and keeps the capitalist engine in motion (ibid: 83-84). Innovation in the capitalist system upsets job markets, caused old technologies and ideas to become obsolete.

Decades later, "mainstream" economists shifted their focus to economic studies of technical change, concentrating largely on innovation as technological invention, factors of production, market structure, and economies of scale (Godin, 2012). At the time, Nelson and Winter (1977) were especially critical of this economic turn to innovation studies, arguing there was no coherent intellectual structure to the field and as a result its body of work was either shallow or theoretically disjointed. Building off Schumpeter's discussion of capitalism and innovation, Nelson and Winter (1977) argue innovation follows a set *natural trajectory*, which determines how technologies change over time and are affected by economic parameters. Dosi (1982) is also highly critical of the lack of theoretical unity in economic studies of innovation. Extending the *natural trajectory* argument, Dosi describes innovation as a product of both continuous change along a *technological trajectory*, and radical change following the emergence of a *technological paradigm* (1982: 152). Broader economic and social factors, he argues, affect technological development and innovation namely by selecting the direction of change (i.e. shaping the technological paradigm) and selecting among changes (through competition between old, new, and alternative technologies) (Dosi, 1988, 1997). Later, Nightingale (1998) uses the term *technological tradition* to extend Dosi's concept

and acknowledge the social construction and socially embedded nature of technological production.

A number of publications in recent years have offered empirical studies, models, and historical explanations of economic growth fueled by technological change (see Freeman, 1994; Nelson, 1995; Coriat and Dosi, 1995, Dosi et al., 2006). These works, produced by a small number of academics, have provided the core literature and cognitive platform on which innovation studies is currently based (Fagerberg and Verspagen, 2009). As Fagerberg et al. (2012) note, there are two main poles in the innovation studies literature today, one focusing on innovation in firms and the other focusing on the role of technology and innovation in facilitating economic and social change. Godin (2015) has been critical of categorizing innovation studies as a discipline, particularly of the absence of reflexivity among its scholars (namely in assuming all innovation is good), and of the dominant (quantitative) framework of neoclassical economics in the study of technological innovation. He argues the field of Schumpterian innovation studies has essentially constructed a tradition of research on technological innovation as the commercialization of technical inventions, focused almost exclusively on firms, rather than examining innovation as a cultural force affecting social, political, and economic thought (Godin, 2015). As will be discussed in Chapter Five, the disjointedness of the field – particularly the conflicting definitions of innovation offered by its scholars – pose significant problems for policymakers attempt to guide the innovation process.

2.3.2. Biotech Business and Innovation Models

The emergence and rapid growth of the biotech sector in the late 1970s essentially created today's science-business model. Three technologies emerged in the same decade that expanded knowledge targets and by extension the landscape of drug development; specifically, recombinant DNA for the production of proteins, hybridization for the production of monocolonal antibodies,

and combinatorial chemistry for mass chemical synthesis (Pisano, 2006). As discussed in section 2.1, the emergence of these technologies resulted in an increased complexity of practice and heterogeneity of practitioners in the field of drug development. In 1976, the firm Genentech was founded Robert Swanson (a venture capitalis) and Herbert Boyer (a biochemist) specifically to capitalize on recombinant DNA technology (Mirowski, 2011). Aided by the strengthening of intellectual property laws at the time, Genentech (and later Biogen and Amgen) established a model for monetizing intellectual property that remains in place today. The model consists of three connected elements: firstly, technology transfer from universities to the private sector through the creation of new firms (versus selling technologies to existing companies); secondly, venture capital and public equity markets that provide funding at critical stages and reward founders for the risks they have taken; and finally, a market for know-how in which young companies provide their intellectual property to established enterprises in exchange for funding (Pisano, 2006). Today, the majority of biotech firms are university spin-offs, and the biotech model "amounts to…the outsourcing of many of the upstream R&D functions that had previously been performed in-house by Big Pharma," with small-to medium-sized firms often negotiating temporary joint R&D projects with large pharmaceutical firms (Mirowski, 2011: 203). In fact, they do not actually produce drugs or marketable products; rather, they undertake commercial science via contract and equity agreements (Coriat et al., 2003). Stemming from this, a 2018 survey by Deloitte and BIOTECanada found that Canada's biotech sector is composed primarily of early-stage start-ups and spin-offs, the majority (67%) of which identified as undertaking either discovery or emerging phase R&D (Deloitte, 2018).

Following the coinage of the term "open innovation" by Chesbrough (2003b), there has been a flurry of publications focusing on the emerging field of open innovation (Gassman and Reepmeyer, 2005; Chesbrough, 2003a, 2003b, 2003c, 2006; Gaule, 2006; West et al., 2006;

Dahlander and Gann, 2010; Getz and Kaitin, 2012). As Teece (2010) notes, it is the business model that determines how value is both delivered to the customer and captured. Focusing on the paradigm shift between [pre-1970s] closed and [post-1980s] open innovation models, Chesbrough (2003b) further argues that ideas and technologies hold no inherent value – rather, it is the business models bringing them to market that determine their value. Recall, an element of the current neoliberal era of scientific R&D has been the collapse of in-house corporate research labs and the growing practice of outsourcing corporate research (Lave et al., 2010). Chesbrough (2006) as argued this has led to the proliferation of *open innovation* in response – defined as "the use of purposive inflows and outflows of knowledge to accelerate internal innovation, and expand the markets for external use of innovation, respectively" (1). Prior to this paradigm shift, firms were inwardly focused and developed, marketed, financed innovations without external input. Open innovation, however, is the phenomenon of "firms making greater use of external ideas and technologies in their own business, and letting unused internal ideas and technologies go outside for others to use in their business" (Chesbrough and Bogers, 2014: 9-10). Two emerging factors eroded the closed innovation paradigm that allowed a near monopoly condition to exist in many industries throughout most of the 20th century, namely: the mobility of skilled workers who were no longer tied to one company for the duration of their career, and the growth of the venture capital market allowing startups to commercialize new technologies (ibid). To capitalize on the open innovation model, firms often license their innovations out externally.

Criticisms of the open innovation model have argued Chesbrough (2003b) creates an oversimplified and false open/closed dichotomy, and that his description of open innovation is not a new phenomenon (Trott and Hartmann, 2009; Mowery, 2009; Bonvillian, 2013). Following this, Nightingale and Martin (2004) argue there has not actually been a paradigm shift in terms of the innovation model that followed the birth of the biotech sector, and the notion of a paradigm shift

in this particular sector has created unrealistic expectations regarding the rate of development for new technologies. Instead, the development and transmission of innovations in medical biotechnology continues to follow a "well-established pattern of slow and incremental diffusion" (ibid: 564). Elmquist et al. (2009) argue that *innovation* as a process remains a black box in Chesbrough's discussion of open innovation (and in subsequent publications on the subject), and these works neglect to answer how the process of innovation occurs, if its locus is anywhere on a field of collaboration between the firm and outside actors. In criticizing the use of the term *open* in open innovation, Hayden (2010) argues Chesbrough's model is not *truly* open; rather, it simply circulates knowledge within monopolistic IP regimes.

The work of Chesbrough and others on open innovation plays a critical role in outlining a conceptual foundation for this dissertation. However, whether it is novel in quite the same way as it is sold is debatable. Chesbrough's (2003b) not-particularly-open notion of open innovation is traditional business model employing proprietary intellectual property tools and maintaining high barriers. It simply extends R&D beyond the confines of a single firm and makes little room for discussion of the material and notional objects that enable and control the flow of knowledge across these organizational boundaries (such as contracts, research agreements, databases, etc.).

2.4. Intellectual Property and Open Science

Various forms of intellectual property (IP) have become critical tools in the commercialization of scientific research, determining how universities and firms capture value and shaping the interactions between each. As will be discussed, there is significant debate in the STS and innovation studies literature regarding the impact of enclosing research and information behind proprietary intellectual property rights, and whether or not the expansion of IP upstream negatively affects downstream development. This section first defines intellectual property rights

and examines the role played by patents and various forms of contracts before discussing their open counterparts.

2.4.1. What is Intellectual Property?

Simply put, intellectual property rights (IPRs) afford proprietary legal protection to any original intellectual creation (e.g. ideas, inventions, creative expressions, logos, etc.), whether it is artistic, literary, technical, or scientific in nature (Brown, 2003). IPRs are a means of protecting and rewarding innovators and are generally granted as trademarks, copyrights, or patents – the latter two are particularly important in the context of this dissertation. Copyrights are property rights in *expression*, essentially giving the author or artist of any creative works (from music and literature to scientific publications to computer software) the legal right to determine whether and how copies of their work are made and distributed (ibid). Patents are property rights in *useful ideas* and are awarded for inventions that "satisfy the criteria of global novelty, non-obviousness, and industrial or commercial application," and may be granted for either products or processes (Saha and Bhattacharya, 2011: 89). Unlike rights of physical property, both patents and copyrights are limited in duration due to the fact that IP presents a more serious issue of "rent seeking" than physical property does (with *rents* defined as "excess revenue over cost") (Posner, 2002: 9). If IP is created rather than found, then by defining IPRs too broadly "the rents generated by them will be so great that excessive resources will be drawn into efforts to be the first to create a valuable piece of intellectual property and thus to obtain the property right to it" (ibid). Moreover, limiting the duration of IPRs ensures the distribution and use of that IP is not hindered. For instance, in the context of science and scientific innovation, the fruits of basic research (such as Planck's constant or $e = mc^2$) are not patentable, thus ensuring that research building off basic scientific findings is not subject to related costs (e.g. royalty fees) (ibid).

2.4.2. Proprietary IP and the Tragedy of the Anticommons

Paradoxically, limiting IPRs may, in fact, be necessary to facilitating the production of knowledge and ensuring its widespread use. Heller and Eisenberg (1998) identify what they describe as the *tragedy of the anticommons* in biomedical research, whereby "a proliferation of intellectual property rights upstream may be stifling life-saving innovations further downstream in the course of research and development" (698). Privatization holds both risks and rewards: although patenting may offer incentives for researchers to undertake risky research projects, too many owners holding property rights in previous discoveries may present barriers to future research (Cohen, 2004). An anticommons may inadvertently be caused by three mechanisms in particular: firstly, requiring "bundles" of patent rights with more than one owner (such as multiple protein structures for the development of a therapeutic), often compounded by the lengthy delays between the filing and issuance of patents, slows down the innovation process (Heller and Eisenberg, 1998). Secondly, the expansion of broad proprietary IP rights further upstream in the research process may also impede R&D further downstream, as even the most commercially irrelevant research can be encumbered by MTAs and overly broad patent claims (Scherer, 2002). As will be discussed in Chapter Seven, broad upstream patent significantly limit the ability of researchers to freely pursue potentially fruitful avenues of inquiry that may arise over the course of their research. Finally, stacking licenses through the use of reach-through license agreements (RTLAs) may also cause an anticommons effect, as it gives the owner of upstream patents rights in subsequent downstream discoveries. In effect, the employment of RTLAs "gives each upstream patent owner a continuing right to be present at the bargaining table as a research project moves downstream toward product development" (Heller and Eisenberg, 1998: 699). Given that drug development involves a high volume of patent filings and license negotiations, these are legitimate concerns in the pharmaceutical sciences. The oncomouse, a genetically modified mouse used in

cancer research and originally patented by DuPont, is an especially interesting example of the pitfalls of RTLAs: initially, DuPont offered sublicenses requiring licensees to seek approval before passing on new discoveries that resulted from use of the oncomouse, thereby granting DuPont the right to participate in future negotiations concerning the development of commercial products falling outside the scope of their patent claims (ibid).

Like RTLAs, material license agreements (MTAs) are proprietary license agreements that offer similar impediments to pharmaceutical R&I. MTAs make up "all species of contracts between parties engaged in the same or similar scientific research, which [aim] to legally encumber that research in some fashion" (Mirowski, 2011: 140). They have become the primary means of imposing restrictions on the dissemination and disclosure of research, limitations on actual use, and liability indemnification (Ku and Henderson, 2007). For instance, Party A transferring a proprietary cell line or reagent to Party B may dictate the terms of Party B's use of that material through an MTA. MTA restrictions often lead to onerous and prohibitively costly negotiations over research materials and also carry hidden associated costs. Rodriguez (2007) notes that MTAs, like patents, may also lead to an anticommons, as they essentially bring research to a halt – creating bottlenecks as legal departments and tech transfer offices representing each party are inundated with thousands of MTAs each year and the bureaucracies at each institute and associated paperwork add time to the execution of each contract. The widespread use of proprietary IP "devices" such as patents, MTAs, and RTLAs in university and industry research is a product of the previously discussed changes to R&D brought about in the 1980s. As will be discussed further in Chapter Five, patents and the MTA ("accessories to the patent system") have become crucial tools in the commodification and commercialization of research, particularly in the case of academic research (Mirowski, 2011: 143).

2.4.3. Open Licensing, Open Access, Open Science

In response to the potential restraints on R&I posed by proprietary IP devices such as patents and MTAs, concepts and practices such as *open science*, *open access*, and *permissive licensing* have become increasingly prominent, particularly in discussions of pharmaceutical development (Getz and Kaitin, 2012). The perceived negative impact of proprietary research tools by some has led to a push towards openness in R&I, which has consequently offered a potential solution to navigating through complex networks of proprietary IP licenses and patents, primarily by releasing project data into the public domain and ensuring broad user access (Hope, 2008; Gitter, 2013). Open science initiatives aim to make use of data through non-proprietary devices (e.g. through creating open source databases), expanding participation in R&I, and reducing commercial barriers (Feldman & Nelson, 2008).

Open science grew out of the *open source* movement in the field of computer science and was founded on the principle of *open access* to technological information (Gitter, 2013). As in Hope's (2008) bazaar model, *open source* meant information (such as source code) was freely accessed (i.e. unhindered by proprietary restrictions), altered, and shared; barriers to entry were lowered or removed; decision-making was relatively autonomous; resources were self-controlled; and participation was voluntary. The issue of ownership within the open source movement is solved by open licensing arrangements such as *copyleft, Creative Commons*, or *GNU Public Licenses* (GPLs). In contrast to their proprietary counterparts, these open licensing arrangements ensure that users may freely modify and share work on the condition that its derivatives are bound by the same conditions (Rhoten and Powell, 2007; Hope 2008). In the case of GNU GPLs, licensees may choose to charge an initial fee, allowing for commercial redistribution of the licensed product but forbidding the redistribution of that product under a contract or non-disclosure agreement. Both copyleft licenses and GNU GPLs make use of copyright law essentially to

accomplish the opposite of its ordained purpose: that is, rather than imposing restrictions on the use of the licensed work, copyleft and GNU GPLs *grant* legally enforceable distribution rights (Rhoten and Powell, 2007). In response to criticisms of openness in terms of property protections and questions raised as to how firms are to profit if they embrace openness, Hope (2008) argues that

> open source licenses are not inherently anti-intellectual property; rather, they are a legitimate, if unconventional, form of intellectual property management. Nor are open source licenses inherently anticommercial; on the contrary, they enable an economically significant class of commercialization strategies, known as "free-revealing" or "nonproprietary" strategies. By choosing an open source license, a licensor demonstrates a credible commitment to allowing his or her technology to be treated as a contribution to bazaar-style production, whether on academic/permissive or copyleft/reciprocal terms (186).

Moreover, she argues that the primary objective of implementing proprietary IP rights in the biotech sector is to protect existing corporate monopolies, while employing strategies to offset the value of a competitor's IP. Hope (2008) focuses largely on the successes of open licensing in the context of software development, however she argues these successes may extend to biotech development as open IP tools simply articulate the terms of collaboration (p. 156). Moreover, she argues the principles and practices of open science can be applied successfully to the development of biological derivatives (ibid). This will be discussed further in Chapter Seven, particularly in the context of tool and scaffold compounds.

In the field of biotechnology (and particularly in subfields like computational biology) where the sharing of information and data is paramount, open licences have become particularly salient tools in R&I. Building off the open source movement, *open science* "means that data from [a] project is released rapidly into the public domain, subject to certain conditions, including that users not exercise their intellectual property rights in a way that would preclude other users' access to the basic data" (Gitter, 2013: 623). Releasing reusable scientific data into the public domain

encourages methodological transparency and facilitates interdisciplinary collaboration by ensuring ease of engagement. Open science initiatives "tend to involve collaborative projects that pool the work of many participants and make advances available to a broad community," ensuring that research results are non-proprietary (Feldman and Nelson, 2008: 25). Further, they provide researchers from non-profits "who may not have the financial capacity to navigate the maze of patent rights and licensing" the opportunity to conduct less commercially appealing research (ibid). The SGC, as outlined in Chapter One and discussed in Chapters Five and Six, is an example of an incredibly successful open science initiative, in addition to the International HapMap Project and the Human Genome Project. Each of these initiatives is an example of openness facilitating interdisciplinary, international endeavours wherein participation extends beyond a single lab or instititute and participation is not limited by user fees or other proprietary restrictions (Birch et al., 2018). The voluntary participation and task selection that characterizes open source initiatives is made possible by "transparency, exploitation of peer review and feedback loops, low cost and ease of engagement, and a mixture of formal and informal governance mechanisms built around a shared set of technical goals" (Gitter, 2013: 623). Access to data and information within the open science model is advanced by the growing prevalence of open access journals, where traditionally costly subscription fees are either non-existent or minimal, offering a solution to the prohibitive costs traditionally associated with academic journals (Wellen 2013).

While open science initiatives undoubtedly offer low entry costs, increased methodological transparency, and interdisciplinary research opportunities, they do not necessarily offer a remedy for the impediments arising from conventional, proprietary forms of IP management (Birch et al., 2018), and whether they are viable options in the commercialization of novel pharmaceutical products remains debatable. This will be discussed at length in Chapter Seven. In response to the growing push for more "open" innovation, Ettlinger (2014) states "…a closer look reveals that,

rather than being a strength of American capitalism, the openness paradigm is a symptom of its problems: profit gouging without sustained investment and squeezing labour to sap already week, and credit-dependent, demand" (89). Indeed, despite its move away from proprietary property rights, research in the open science paradigm is nonetheless valued in terms of returns on investment and is produced such that it generates assets and serves the market demands of corporate and individual customers (Birch et al., 2018).

There is significant debate within the science and technology studies (STS) and innovation studies literature concerning open and proprietary IP devices and their net effect on the processes and products of R&I. A study of patent-paper pairs by Murray and Stern (2007) examined the citation rate for scientific publications before and after formal IP rights associated with the publication were granted. The study found an anti-commons effect that becomes more pronounced over time, notably for researchers with public sector affiliations (ibid). More specifically, the authors found that citation rates after a patent grant decline by approximately 10 to 20 percent (ibid). This suggests intellectual property rights do, in fact, have an impact on the diffusion of scientific knowledge. Some scholars argue proprietary IP impedes innovation in the biological sciences by limiting avenues of inquiry, excluding certain groups from R&I, and creating bottlenecks through patent thickets (Heller and Eisenberg, 1998; Mirowski, 2011; Caulfield et al., 2011). Others, such as Lezuan and Montgomery (2015), argue it is necessary for outlining collaborative research relationships and provide incentives for investing in research. In both cases, however, open and proprietary "devices" are often presented as dichotomous and incompatible. A key finding of this research points to the contrary: these devices can, in fact, complement each other when employed at particular junctures of the R&I process. Moreover, their respective overall effect on the commercialization of research is context-dependent, but when used in tandem may potentially streamline the innovation of new pharmaceutical products.

2.5. Mediating Devices

In terms of its theoretical framework, this research builds on the premise that the open and proprietary "tools" or mechanisms outlined above enable public and private research groups, government regulators and policymakers, and investors from a broad range of organizations to interact, collaborate, and bring innovative research forth from the lab to clinical practice. Previously, I have theorized these mechanisms as *mediating devices* (Chiappetta and Birch, 2018). This section outlines cognate concepts of *mediating instruments* and *market devices*, before discussing *mediating devices* as it will be employed in the remainder of this dissertation.

Callon (1991) outlines the concept of *techno-economic networks* as "a coordinated set of heterogeneous actors…interact more or less successfully to develop, produce, distribute and diffuse methods for generating goods and services" (133). As discussed in section 2.2, the passage of the Bayh-Dole Act in 1980 (in addition to other notable legal cases and legislative reforms) created a new marketplace for the products of scientific research and led to a growth in scientific entrepreneurship and a diversification of the practitioners, funders, vendors and consumers of science. Techno-economic networks grew to include technology transfer offices, funding agencies, policymakers, venture capitalists, and so forth (Popp-Berman, 2012), and have continued to increase in complexity given the interdisciplinary and data-accelerated nature of contemporary R&I in the biological sciences. Miller (2007) notes that these networks extend beyond simply a heterogeneous group of actors: "a whole set of intermediaries circulates among them. These [intermediaries] give material content to the links uniting the actors. They may be written documents, technical artefacts, human beings, or money" (710).

The notion of *mediating instruments* has been discussed at length in the accounting and economic sociology literature, largely in the context of the broad range of financial and economic models (Morrison and Morgan, 1999), instruments, metrics, and mechanisms related to practices of

calculation, valuation, budgeting, and computation (Miller, 1992; Miller and O'Leary, 1987). These instruments serve to mediate the interactions between science and economics, shaping the ways in which science is governed and regulated, as well as the means by which the products of R&I may be exchanged (Miller and O'Leary, 2007: 708; see also Power, 1994). For example, *mediating instruments* such as accounting practices or capital budget models "can help connect science to the national economy, by making visible and quantitative the responsibility of individual managers for science and technology" (Miller and O'Leary, 2007: 708). These instruments work to establish a connection between R&D (as the measure of science and technology) and ways of economic calculation located at the firm level, thereby helping to reconcile technoscience with ideals of economic growth and financial prosperity (ibid). Others have similarly outlined *market devices* as "the material and discursive assemblages that intervene in the construction of markets," suggesting these objects encompass "analytical techniques to pricing models, …purchase settings to merchandising tools, …trading protocols to aggregate indicators" (Muniesa, Millo, and Callon, 2007: 2; see also Muniesa, 2007). Examples of market devices include focus groups in market research, consumer tests that help to impact supply and shape market demand, consumer credit scoring practices, and financial derivatives that allow for the rapid growth of increasingly complex markets (Muniesa, Millo, and Callon, 2007).

I expand this concept of intermediaries to include various forms of open and proprietary mechanisms (Chiappetta and Birch, 2018). Building on the premise that particular open and proprietary mechanisms enable public and private research groups, government regulators and policymakers, and investors to interact, collaborate, and bring innovative research forth from the lab to clinical practice, I theorize these mechanisms as *mediating devices*. I differentiate these from the *market devices* and *financial instruments* outlined above, largely given that *market* implies a necessarily commercial nature to the device in question. Moreover, the term *instrument* tends to

imply an object distinct from the techno-economic network in which it is situated – Miller and O'Leary (2007) point out that "by its nature, an instrument is independent of the thing it operates on" (709) – I argue mediating devices are embedded within techno-economic networks. The word *devices* also suggests "a bifurcation of agency: the person on one side and the machine on the other" (Muniesa, Millo, and Callon, 2007: 2). For the purposes of this research, mediating devices consist of patents, MTAs and RTLAs, copyrights, open licenses (such as copyleft), and open-access databases. Essentially, these mediating devices "are the linchpins in contemporary techno-economic networks that enable collaboration, commercialization, and knowledge transfer, as well as the management of value in the development and commercialization of assets and products in the life sciences" (ibid: 67). Situated within complex techno-economic networks, mediating devices play a critical role in configuring the organization, governance, and valuation of biological R&I, and dictate the ways in which research results are circulated and disparate groups collaborate. Moreover, they determine at what point in the R&I process actors within these networks interact, attach value to these interactions (e.g. by stipulating potential royalties), and regulate how value may be appropriated from the products of these interactions (Birch et al., 2017).

Mediating devices are particularly salient in the context of pharmaceutical development, as will be discussed at length in Chapters Five through Seven. As this chapter has endeavoured to highlight, scientific research has become increasingly data-accelerated, internationally collaborative, and interdisciplinary in the –omics era. Proprietary IP is a ubiquitous feature of drug development, while the push for increased openness has only escalated. This research seeks to tease apart the concept of the *mediating device* as the instruments, situated within the larger context of corporate strategy, scientific competition, technology transfer, and academic and government policy, that enable (or hinder) interaction and collaboration throughout the process of pharmaceutical R&I.

2.6. Conclusion

In its attempt to unpack the notion of science as a social enterprise, this chapter has provided an overview of the existing body of literature relating to the properties of scientific knowledge and its production, research commercialization and academic capitalism, innovation studies and innovation models, intellectual property and open science, and mediating devices. While the works discussed form a crucial component of the theoretical skeleton of this research, there is nonetheless a significant gap in this literature that has yet to be addressed: despite much discussion of their significance as *tools* of commercialization, scholars in STS and innovation studies have yet analyze how proprietary *and* open devices vary in terms of their efficacy when they are employed in academic versus industrial settings. Moreover, there is little nuanced discussion in the existing literature regarding why open and proprietary devices operate effectively at different stages in the innovation process, or how they can be employed to facilitate collaboration. Existing works have yet to analyze how open and proprietary devices may be used *together* in the context of interdisciplinary pharmaceutical research and public/private collaborations, and *how* researchers might navigate through IP gridlocks when potentially competing or conflicting interests are guiding knowledge translation. These are gaps that potentially skew our understanding of innovation ecosystems and impede sound policy decisions.

3. Research Design and Methodology

To recap, this research is focused broadly on pharmaceutical R&D and the development of novel clinical products. More specifically, this dissertation endeavours to unpack the innovation process and the role played by open and proprietary mediating devices in the pharmaceutical sector. As discussed in Chapter One, the issue at stake in this dissertation stems from the fact that commercialization threatens to enclose crucial knowledge and information and restrict its access behind IP protection, slowing drug development even further. While proprietary IP tools such as patents is in theory allow firms recoup the growing costs associated with development, regulatory application, and marketing by charging a high cost for the drug based on market exclusivity granted via the patent (Barton and Emanuel, 2007), they may also have an anticommons effect (Heller and Eisenberg, 1998; Murray and Stern, 2007). This has the potential to significantly and negatively impact innovation in the pharmaceutical sector.

In unpacking the impact of open and proprietary devices on pharmaceutical innovation, this research takes both an *inductive* and *retroductive* approach. As Blaikie (2010) notes, "the aim of the inductive research strategy is to establish limited generalizations about the distribution of, and patterns of association amongst, observed or measured characteristics of…social phenomena" (83), while "the aim of the retroductive research strategy is to discover underlying mechanisms that, in particular contexts, explain observed regularities" (87). In this case, pharmaceutical innovation constitutes the "social phenomena" in question, while the use of particular mediating devices constitutes the observed regularities to be explained. The *inductive* research strategy involves collecting data on characteristics or patterns (e.g. patterns of use in the context of mediating devices), while the *retroductive* strategy involves documenting and modeling a regularity (e.g. regarding the employment of particular mediating devices) (ibid).

Fully dissecting the relationship between innovation and entrepreneurship in the pharmaceutical sector and analyzing the role of open and proprietary mediating devices in research commercialization therefore requires an empirical study of innovation in action: namely, of the social actors involved in pharmaceutical development, the points of interaction between them (e.g. the signing of a collaborative research agreement or an NDA), and the devices that shape these interactions. Thus, this dissertation is essentially an empirical case study of pharmaceutical innovation in Ontario. Given that the average length of time from initial laboratory target discovery through regimented clinical trials to U.S. FDA approval is roughly 13 years (Collins, 2011), following a single pharmaceutical product from the laboratory bench to late-stage commercial applications is simply not feasible for this particular project. As such, I focus on the R&I efforts of actors at MaRS Innovations, the Ontario Institute for Cancer Research, JLABS @ Toronto, the Structural Genomics Consortium, and the University Health Network. I comparatively analyze the use of open and proprietary mediating devices by actors at these organizations and evaluate their differing impact on innovation efforts. These organizations were chosen because they employ a diverse range of proprietary-to-open arrangements and commercialization strategies, despite having similar mandates and operating in close (and in some cases overlapping) proximity. In focusing specifically on the role of mediating devices in research commercialization, I collected qualitative data by conducting semi-structured interviews. This data set offers a representative and nuanced explanation for the use of specific mediating devices in the larger context of corporate strategy, scientific competition, technology transfer, and academic and government policy. This chapter outlines the design and methodology of this research. I first outline research objectives and hypotheses, before discussing case study selection in detail and data collection and analysis.

3.1. Research Objectives

This dissertation addresses the following research questions:

1. *How do social actors in the pharmaceutical sector understand innovation? By extension, how can we theorize open and proprietary devices ?*

My aim here is to unpack the slippery concept of *innovation* and provide a conceptual outline of mediating devices. I argue they act as the linchpins that enable collaboration, commercialization, and knowledge transfer, and/or determine valuation of the products and processes of R&I. In analyzing the interview data collected, my goal is to shed light on what it means to innovate, how innovation is measured and valuated, the factors drives certain actors to invest in the development of innovative new biotechnologies, and the factors that accelerate or inhibit the commercialization of these innovations.

2. *Which proprietary and open devices are used in pharmaceutical R&I? For whom, and why?*

To answer this question, I evaluate the ways in which mediating devices such as NDAs, MTAs, reach-through license agreements, open licenses, and open libraries and databases are used by interview participants. More specifically, I examine the role of MTAs in the process of academic technology transfer, as well as their associated costs and impact on drug development. Further, I analyze the ways in which mediating devices affect collaboration agreements, particularly in the context of contracts and open databases and libraries. Finally, I examine the embeddedness of patents in Ontario's legal and regulatory architecture and how this impacts the commercialization of new pharmaceutical products in the province.

3. *How do different devices facilitate or hinder collaboration and knowledge translation in this sector? At what stage in the innovation process are they most effective, and why?*

Here I examine the ways in which the impact of open and proprietary mediating devices on pharmaceutical innovation are highly context dependent. More specifically, I evaluate the impact

of broad versus narrow patent claims and their impact on innovation. I argue that the efficacy of open and proprietary devices, both in terms of accelerating the translation of pharmaceutical research and encouraging collaboration, is dependent on: firstly, when they are employed in the innovation process (i.e. upstream versus downstream); and secondly, what they are applied to (i.e. tool compounds used to develop candidate drug products versus the products themselves).

4. *How can they be employed in the development of innovation strategies so as to streamline the process of drug development?*

Building off the argument that the efficacy of open and proprietary devices is context dependent, I conduct a case study of the open molecule JQ1 to answer this question. The purpose of this case study is to demonstrate that open and proprietary devices may be complimentary at particular stages of R&I, and, when used together, can accelerate advancements in the pharmaceutical sector.

3.2. Case Study Selection

This research analyzes and critiques the parameters of open and proprietary devices and their respective roles in Ontario's rapidly changing R&D landscape, specifically addressing the network of actors and institutes shaping Canada's pharmaceutical sector. I extend my focus to intermediary organizations established to facilitate the translation of basic research into marketable products, in addition to public research institutes, small- to medium-sized private pharmaceutical firms, and incubator labs in Toronto.

Specifically, I focus on MaRS Innovation (MI) and its affiliate firms and public research hospitals, the Ontario Institute for Cancer Research (OICR) and the Fight Against Cancer Innovation Trust (FACIT), Johnson & Johnson's incubator space JLABS @ Toronto and its affiliate firms, and the Structural Genomics Consortium (SGC). These organizations employ a variety of collaborative research arrangements and disclosure practices, ranging from the SGC

releasing the entirety of its research products into the public domain to the proprietary commercialization tools and non-disclosure agreements favoured by the MI technology transfer office. Given that the object of social inquiry is rarely an individual person or enterprise, case studies are optimal for testing hypotheses in situations that are both complex and involve a myriad of not highly isolated variables (Gomm, Hammersley, Foster, 2009: 23-24). As such, case studies such as this offer the opportunity to make general assertions about the role of open and proprietary mediating devices in pharmaceutical development broadly, and allow social scientists to predict trends in and/or outcomes of their use (ibid). The organizations outlined below provide an interesting and salient case study site: together, they represent the range of organizational structures in which pharmaceutical research currently occurs, where private firms work alongside and often in conjunction with public research institutes, and research parks composed of public and private organizations working symbiotically innovate and commercialize new drug candidates. Further, they are located in close proximity to one another, have similarly broad mandates (to accelerate the development of novel pharmaceuticals), and are all subject to the same provincial and federal laws and regulations.

3.2.1. MaRS Innovation, the OICR, and FACIT

As discussed in Chapter One, MaRS Innovation is a pan-provincial non-profit organization created in 2008 as a Centre of Excellence for Commercialization and Research by the Networks of Centres of Excellence (NCE). Created in 1989, the NCE program "supports large-scale academically led research networks that harness the creativity and inventiveness of Canadian health, natural, and social scientists and engineers" by engaging partners from academic institutions and public and private sector organizations (NCE, 2018). MI is an *intermediary organization* – defined by Kivimaa et al. (2019) as an organization "found to bridge between actors

involved in situations where direct interaction is difficult due to high transaction costs (e.g. locating a suitable partner to collaborate with, disincentives to collaborate) or communication problems resulting from…capacity to absorb or exchange knowledge" (1063). As such, the purpose of MI is to accelerate the translation of academic discoveries to marketable products and services by providing researcher groups with capital, industry networks, and laboratory space (MaRS Discovery District, 2016). As Canada's largest research cluster, MI works in conjunction with academia (specifically York University, University of Toronto, and Ryerson University) and public research institutes (such as University Health Network and Sunnybrook Research Institute), industry partners from a range of sectors (such as Northern Biologics), venture capitalists and angel investors, and government agencies. In partnership with six major pharmaceutical companies (Johnson & Johnson, GlaxoSmithKline, Pfizer, Merck, Baxter and LifeLabs), MI identifies and funds early-stage technologies via seed funds, in exchange for which partners "receive a first look at data from the project to facilitate further licensing discussions" (NCE, 2017b). The purpose of this approach is to avoid funding gaps between early- and market-stage development that traditionally slow the commercialization process (ibid). This ensures that emerging firms and startups are supported while developing technologies through to maturity, while at the same time reducing risk by sharing R&D costs with industry (ibid). By housing academics, banking and legal offices, and venture capital (VC), med-tech, and pharmaceutical firms in one building, MI further aims to facilitate non-traditional collaborations among residents and promote the cross-pollination of information and ideas (MaRS Discovery District, 2016).

The OICR is a non-profit translational research organization established in 2005 by the Government of Ontario, focusing primarily on "the prevention, early detection, diagnosis and treatment of cancer" (OICR, 2016). As "receptors" to translational pharmacology research, OICR and MI work in partnership, connecting research in fields like genomics and bioinformatics from

Ontario's universities and hospital-based research institutes (e.g. Toronto's University Health Network [UHN] hospitals) with private organizations to facilitate oncology innovation and commercialization. Both organizations work together to navigate proprietary systems of IP protection by providing in-house licensing of technologies in early stages of clinical development and by fostering relationships between the aforementioned public and private research institutes, investors, and commercial partners (ibid).

FACIT, a provincial business trust working in conjunction with MI and OICR (and under the auspices of MI), funds and licenses early stage research through its Intellectual Property Development and Commercialization (IPDC) fund (FACIT, 2016). The IPDC fund is designed "to support early-stage commercialization activities [including] proof-of concept (POC), validation, standard operating procedures, market analyses, IP protection and acquisition, expert guidance and management" (ibid). FACIT, OICR, and MaRS work together to navigate proprietary systems of IP protection by providing in-house licensing of technologies in early stages of clinical development and by fostering relationships between the previously discussed public and private research institutes, investors, and commercial partners.

3.2.2. JLABS @ Toronto

Opened in 2012, Johnson and Johnson's JLABS @ Toronto is an incubator space housed in the MaRS Tower. It is the first JLABS site operating outside the United States (JLABS @ Toronto, 2017). Working in collaboration with J&J Innovation, Janssen Inc., the Government of Ontario, and the University of Toronto, JLABS leases wet and dry laboratory space to its residents, the majority of which are small, early-stage firms focused on therapeutic or medical device technology development (ibid). In addition to lab space, residents have access to J&J's equipment and molecular libraries and platforms, and operational management services. JLABS, like MI, aims to

indirectly promote knowledge diffusion by providing open office and conference spaces that encourage interaction and collaboration among its residents. As an incubator, the purpose of JLABS is to catalyze innovation (JLABS @ Toronto, 2017). It is distinct from MI as it has no external partners. JLABS maintains a 'no-strings-attached' arrangement, whereby residents are not required to disclose IP as a condition of leasing space, and "there is no first look, no first right of refusal and no equity assigned to Johnson & Johnson or Janssen" (JLABS, 2017a). Its pseudo-open model makes JLABS an interesting comparative study, especially when discussed alongside the more traditional, proprietary innovation model embraced by MI and the more "radical" open model employed by the SGC outlined below.

3.2.3. The Structural Genomics Consortium

As a non-profit public-private consortium, the SGC undertakes basic scientific research "…of relevance to drug discovery. [Its] core mandate…is to determine 3D structures on a large scale and cost-effectively – targeting human proteins of biomedical importance and proteins from human parasites that represent potential drug targets" (SGC, 2017a). Operating out of the University of Oxford in the UK and the University of Toronto in the MaRS Tower, the SGC works in collaboration with a network of academic, industry, and government partners, namely AbbVie, Boehringer Ingelheim, the Canada Foundation for Innovation, the Canadian Institutes for Health Research, Genome Canada, GlaxoSmithKline (GSK), Janssen, Lilly Canada, the Novartis Research Foundation, the Ontario Ministry of Economic Development and Innovation, Pfizer, Takeda, and the Wellcome Trust (ibid). Research at the SGC is focused on determining the crystal structures of proteins that act as "targets" for drug therapies for various types of cancer, diabetes, and psychiatric disorders. They are thereby developing the *tools* that enable drug discovery and

design rather than the drugs themselves, a significant distinction that will be discussed in Chapter Five of this dissertation.

Of particular importance for this study is the fact that the SGC releases its crystal structures into the public domain with no strings (i.e. no proprietary IP rights) attached. More specifically, partnerships between the SGC and large for-profit private firms such as GSK, Pfizer, Janssen, and Lilly have been made with the understanding that no proprietary IP rights (i.e. patents, NDAs, etc.) or publication restrictions will be imposed on any of the structural data researchers produce. Crystal structures are deposited into the Protein Data Bank, a repository that can be freely accessed by researchers from public or private institutes around the world. The SGC maintains an open model under the assumption that "provid[ing] the public with this fundamental knowledge [and] allow[ing] commercial efforts and other academics to utilize the data freely and without any delay" will bring new drugs to market sooner and more cost-effectively (ibid).

These organizations were chosen because they represent employ a diverse range of proprietary-to-open arrangements and commercialization strategies. Each of these organizations – MI and the OICR, JLABS, and the SGC – and their affiliated firms has a unique approach to innovating and collaborating. Some, namely a number of affiliate firms of MI and JLABS, have embraced Chesbrough's (2003b) "open" model, in that they have extended R&I efforts beyond internal firm boundaries. Others, specifically the SGC, have successfully employed the open devices discussed Chapter Two. And finally, many (in fact, the majority) of affiliate firms of MI and JLABS have been reluctant to open their innovation and commercialization processes and have employed the proprietary devices outlined in the previous chapter. Each of these organizations has made use of what, to them, are the most advantageous and cost-effective tools for forming collaborative working relationships with outside firms and for navigating through what can potentially be a cost-prohibitive web of proprietary IP rights, legal architecture, and personnel

issues. As will be discussed in further detail in Chapter Five, however, open and proprietary devices play markedly differing roles for each group in terms of enabling collaboration, attracting investment in early-stage research, and bringing profit-generating innovations to market.

3.3. Data Collection

Data for this research was collected via secondary literature and policy analyses and semi-structured qualitative interviews. In light of the objectives outlined above, data collection and analysis was divided into three stages: the first stage involved a broad synthesis of the existing literature on intellectual property and techno-scientific innovation broadly, as discussed at length in Chapter Two. This work provided a theoretical foundation for this dissertation and informed both the questions asked of participants and the analysis of the data obtained. This literature was drawn from science and technology studies (STS), economics and the political economy of science, and innovation studies. It focused broadly on scientific interdisciplinarity and collaboration, academic capitalism and commercialization strategies, business and innovation models, intellectual property and open science, and mediating instruments and devices.

The second stage included an analysis and secondary literature review of existing provincial and federal policy regarding pharmaceutical innovation and drug pricing. This included the *Patent Act* and the associated *Notice of Compliance (*NOC) Regulations, the Patented Medicine Prices Review Board (PMPRB), the data protection provisions of Canada's *Food and Drug Regulations*, and the Ontario Formulary. Relevant international legal agreements, such as the *General Agreement on Tariffs and Trade* (GATT) and the agreement on *Trade-Related Aspects of Intellectual Property Rights* (TRIPS), are also outlined. As discussed, the objectives of this project is to shed light on the means by which pharmaceutical innovation in Ontario is enabled or constrained by different mediating devices, and to ultimately provide an outline for improving

innovation networks in the pharmaceutical sector. To do so requires first outlining the existing domestic and international legal and regulatory architecture. This material is discussed at length in Chapter Four of this dissertation.

3.3.1. Primary Data Collection

Data collection in the third stage incorporated qualitative interview data on pharmaceutical R&I, IP, and the use of mediating devices in Ontario and Canada respectively. This research was approved in October 2016 by York University's Ethics Review Board, the Human Participants Review Sub-Committee, and conformed to the standards of the Canadian Tri-Council Ethics Research Board. Prior to the start of in-person interviews, participants signed an informed consent form outlining the aims of this research, potential risks, and the confidential nature of their participation. Interviewees who participated via phone provided verbal consent.

Interviews were conducted with twenty-five participants with five additional follow-up interviews, for a total of thirty 45-90 minute interviews conducted either in-person or by phone, with interviewees selected from the public and private sectors. Specifically, interviewees were drawn from MI and several of its affiliate firms, the OICR, FACIT, JLABS and one of its affiliate firms, the SGC, the UHN technology transfer office, the Princess Margaret Cancer Research Centre, Sunnybrook Research Institute, two leading law firms in Toronto, and one large pharmaceutical firm in the Toronto area. Participants included academic bench scientists, executives in the public and private sector, venture capitalists, IP lawyers, IP directors, patent agents, tech transfer officers, and innovation managers from these organizations. Table 2 below summarizes the details of interview participants:

Table 2: Interview Participants

No. of Participants	Location
6	MaRS Innovation and affiliate firms
3	OICR/FACIT
3	JLABS
2	Structural Genomics Consortium
	UHN Hospitals
5	Toronto area universities
2	Private law firm
2	Private pharmaceutical firm
2	Private Venture Firm

All interviews were recorded audio-recorded using the application *Recorder* on an iPhone and subsequently transcribed. Hand-written notes were taken throughout each interview to record follow-up questions and general impressions that could not be captured via audio recording. All responses were completely anonymized in transcriptions of interview recordings and subsequently in the write-up of this dissertation. Interviews were semi-structured: all participants were asked the same initial questions concerning their experiences with open and proprietary mediating devices and research commercialization, and their personal views on open access science. However, interviews made room for follow-up questions and relevant tangential discussions related to the specific expertise and/or experiences of the interviewee (Wengraf, 2001).

The aim of these interviews was to assess the IP practices of participants and to understand their respective views on openness and open devices as they relate to innovation in drug development. Interview questions stemmed from the five central research questions outlined above and were informed by the theoretical works discussed in Chapter Two. Questions ranged from the specific (e.g. *have you ever had to delay, significantly change, or abandon a research project due to onerous MTA restrictions or reach-through provisions, overly complex licensing negotiations, or prohibitively high royalties?*), to more open-ended and opinion-based (e.g. *based on your experiences, would increased openness be a benefit or detriment to pharmaceutical R&I?*). In either case, participants were not asked to disclose any personal, sensitive or unpublished

data/information.

3.3.2. Limitations

The primary limitation potentially impacting the generalizability of the findings of this research stems from the number of interviews conducted. My initial goal was to conduct 50 interviews, however I ultimately conducted a total of 30, With that said, a saturation point was reached midway through qualitative data collection. In the context of data acquisition (versus analysis), Grady (1998) argues a saturation point is reached when "data tend to be redundant of data already collected. In interviews, when the researcher begins to hear the same comments again and again, data saturation is being reached… It is then time to stop collecting information and to start analysing what has been collected" (26). Urquhart (2013) defines saturation as "the point in coding when you find that no new codes occur in the data. There are mounting instances of the same codes, but no new ones" (194). For Given (2016), saturation occurs at the point in which "additional data do not lead to any new emergent themes" (135), while Boddy (2016) notes, "once saturation is, the results must be capable of some degree of generalization" (428). During qualitative data collection and analysis for this research, a saturation point was reached after roughly 15-18 interviews were conducted, as new data began to repeat what was expressed in previous data and no new thematic concepts emerged during the coding process. Given that this saturation point was reached relatively soon into the qualitative data collection process, the sample size of this data set does not significantly hinder my ability to answer the research questions outlined in section 3.1, and the empirical findings may be extrapolated to a broader population with confidence.

3.4. Data Analysis

Interviews were analyzed in light of particular ontological considerations (Blaikie, 2010): firstly, that the acts of interviewing and observing are interpretive processes, that interviewees are, of course, subject to particular biases and motivations, and as such a critical attitude must be adopted when interpreting data. Secondly, that there exists "an underlying domain of structures and mechanisms that may not be readily observed" (ibid: 93) but that influences the process of drug development as a whole (i.e. the market-oriented paradigm in which research and innovation occurs).

Following transcription, interview data were coded twice by hand and subsequently using NVivo software (Grbich, 2013; Saldaña, 2013). The coding process involved describing, classifying, and connecting (Blaikie, 2010). *Description*, in this case, simply involved identifying the context of action (e.g. the conditions precipitating the use of a specific device) and the intentions of the social actors involved (ibid). Bearing in mind the ultimate aims, objectives and outlined in section 3.1 and the theoretical concepts discussed in Chapter Two respectively, *classification* involved first identifying primary and secondary codes made up of recurring themes, theoretical concepts, key words, viewpoints, and strategies (Grbich, 2013). These codes essentially form the "bones" of this analysis (Appendix D). Primary codes were descriptive, and included innovation, research motivations, commercialization, funding of and investing in R&I, collaboration, business models, and open and proprietary mediating devices. Sub-codes were analytical, and included definitions, metrics, and strategies (of innovation), barriers to and facilitators (of collaboration, funding, commercialization), and so on. As noted by Saldaña (2013), the process of coding "is not just labelling, it is *linking*," and thus these "bones" later became a working skeleton when integrated with the theoretical framework discussed in Chapter Two. Classification also entailed an evaluation of the causal and intervening conditions behind the use

of each mediating device (Blaikie, 2010). Finally, *connection* involved an examination and assessment of regularities, variations, and singularities of the qualitative data (i.e. of definitions and metrics of innovation and the use of particular devices, employed by whom, and in what context) (ibid).

The aim of this research is to unpack the innovation process and the role played by open and proprietary mediating devices in the pharmaceutical sector. In this case, qualitative interviews offered a detailed account of the particularities of these devices – *why* some why some institutes or firms embrace openness and others do not, why some actors see open devices as facilitating innovation in theory but not in practice, why others are able to successfully form commercial partnerships on the basis of using open devices and others are not, and why the success of open devices is dependent on what is being produced and in what context. Interview data also offered a holistic, representative account of mediating devices in the larger context of corporate strategy, scientific competition, technology transfer, and academic and government policy, and imparts a more nuanced explanation for the variations in innovation strategies between industry and academia as well as the varying role and efficacy of open versus proprietary devices in each environment (Wengraf, 2001). Linking theoretical concepts to empirical indicators presents the opportunity for a thorough analysis of the innovation process, and ultimately will point to areas in which revisions can be made to general assumptions regarding innovation strategies in the pharmaceutical sector (ibid).

3.5. Conclusion

This chapter provides an overview of the methodological approach taken in this research. Through the analysis of the data obtained, this research endeavours to unpack the process of pharmaceutical innovation in Ontario and evaluate the devices that mediate the interactions of

actors within this process. This dissertation is essentially an empirical case study of pharmaceutical innovation in Ontario, focusing specifically on the R&I efforts occurring at MaRS Innovations, the Ontario Institute for Cancer Research, JLABS, the Structural Genomics Consortium, and the University Health Network. These organizations were chosen because they represent employ a diverse range of proprietary-to-open arrangements and commercialization strategies.

Data collection was organized in three stages: firstly, a theoretical foundation of secondary literature was drawn from science and technology studies (STS), economics and the political economy of science, and innovation studies, focusing broadly on scientific interdisciplinarity and collaboration, academic capitalism and commercialization strategies, business and innovation models, intellectual property and open science, and mediating instruments and devices. Secondly, provincial and federal policy regarding pharmaceutical development, IP, and drug pricing, as well as international legal agreements were assessed at length (Chapter Four). The final stage involved collecting qualitative interview data on pharmaceutical R&I, IP, and the use of mediating devices in Ontario and Canada respectively (Chapters Five and Six). Qualitative data were coded descriptively and analytically according to theoretical concepts found in the secondary literature discussed in chapter two as well as themes that repeatedly emerged in the data itself.. Overall, the methodological approach employed in this research is intended to offer a thorough evaluation of the role and use of open and proprietary mediating devices in pharmaceutical development, how they affect (and are affected by) funding sources and collaborative arrangements, and their net impact on research and innovation in this sector. As will be discussed in Chapter Eight, the results of this research are generalizable and may be extrapolated to evaluate the state of pharmaceutical development in Canada more broadly.

4. Global IP Policy

While this research is not focused on government or institutional policy specifically, it is necessary to briefly discuss the policy landscape of pharmaceutical research and development. Understanding the legal and political architecture in which scientific research and innovation is undertaken, and the entrenchment of patents and other proprietary IP tools and practices within this architecture in particular, may help to explain why establishing new innovation practices and open business models remains such a challenging feat for SMEs, large firms, and public research institutes. This chapter focuses on international and national IP policies and innovation strategies, paying particular attention to central role played by patents in trade agreements, policies, and regulations and the subsequent effect to innovation. I will first discuss the *Agreement on Trade-Related Aspects of Intellectual Property Rights* (TRIPS) (1994) and the limits it places on R&D in the Global North and South and on countries and firms seeking to establish more open commercialization practices. Secondly, I will examine IP legislation in the United States, focusing specifically on the *Bayh-Dole* and *Stevenson-Wydler Acts* (1980) and the Supreme Court ruling in *Diamond v. Chakrabarty* (1980), and the ways in which these legal and legislative cases have dramatically affected biopharmaceutical research. Finally, I will discuss Canada's existing federal IP guidelines, examining the Notice of Compliance Regulations, the Data exclusivity Rules, and their effects on generic pharmaceutical development in Canada.

4.1. International Intellectual Property Legislation and Policy

This section examines international IP legislation and policy, focusing on the World Trade Organization's (WTO) primary IP agreement and several landmark legal and legislative cases in the United States. Though the policy and legal cases discussed in this section do not *directly* affect

the R&I discussed in the following two chapters of this dissertation, they have had a dramatic and wide-reaching effect on how scientific research is conducted and who benefits from its products (Popp-Berman, 2014). Moreover, they have resulted in the fortification and proliferation of proprietary IP devices across all stages of scientific R&I, as well as in the expansion in the number of *things* that may be enclosed behind proprietary IP rights. As Stiglitz et al. (2017) note, international agreements such as TRIPS (1994) and legislative acts such as Bayh-Dole (1980) perpetuate the notion that the introduction and strengthening of private monopolies – created through stringent and strictly enforced patent regimes – is best way to rectify the market undersupplying knowledge and inadequately incentivizing scientific research. The direct consequence of this has been R&D focused less on innovating and instead directed at "extending, broadening, and leveraging the monopoly power extended through the patent" (ibid: 2). As will be discussed in this section, despite the fact that knowledge and information play an increasingly important role in the global economy, the rules governing who has access to/who can profit from these intangible assets currently remain heavily in favour of large private firms in select sectors and the dominant capitalist countries that make up the WTO.

4.1.1. TRIPS

The WTO, a multilateral legal and institutional system (or regime) for the administration and development of trade relations, is comprised of 153 member nations and is the successor to the General Agreement on Tariffs and Trade (GATT) (1947). Its mission is "to provide fair and stable conditions for the conduct of international trade with a view to encouraging trade and investment that raises living standards worldwide" (Taubman et al., 2012: 4). Through several rounds of comprehensive trade negotiations, member nations agreed to pursue an agenda of trade liberalization, thus forming the WTO at the completion of the Uruguay Round of GATT

negotiations in 1994. In the same year, the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) was created as part of the same Uruguay Round (Rhoten and Powell, 2007). This section focuses specifically on TRIPS and its role in standardizing and fortifying an international Americanized IP regime. As Mirowski (2011) notes, while TRIPS "at first might seem a highly technical and arcane set of legal provisions [the agreement] can now readily wreak havoc with the livelihood of large numbers of citizens of any [WTO member] country seeking to evade or otherwise get around [it]" (p. 186). TRIPS has profoundly transformed the way knowledge (particularly scientific knowledge) can be and is commercialized.

Agreed upon by over one hundred signatories, the purpose of TRIPS was to globalize a set of IP principles and harmonize IP regulation across WTO member nations. TRIPS establishes minimum substantive standards in the governance of "copyright and related rights as well as trademarks, industrial designs, patents (including protection of pharmaceutical product, plant varieties, and computer programs), and undisclosed information including trade secrets and test data" (Rhoten and Powell, 2007: 350). TRIPS is particularly broad in its IP coverage, extending from patents and copyrights to source code, trade secrets, and industrial design. The agreement considers knowledge as "something discrete and individualized: there is no recognition of possible communal aspects of knowledge," and by extension no explicit room for openness (Mirowski, 2011: 187).

TRIPS defines the subject matter eligible for protection, the scope of IP rights (IPRs) that are to be conferred, permissible exceptions to those rights, and the minimal duration of protection provided. Importantly, the agreement sets comprehensive standards for digital technology and biotechnology that have benefited the United States, the European Union, and Japan immensely. These standards mirror significant legal and legislative changes passed in the United States in the early 1980s, primarily *Diamond v. Chakrabarty* (1980) and the *Bayh-Dole Act* (1980). The U.S.

Supreme Court decision in *Diamond v. Chakrabarty* set precedent for genetically modified microorganisms to be patented (Mirowski, 2011). The same year, the passage of the *Bayh-Dole Act* affirmed the right of universities to patent government-funded research (ibid). As will be discussed in the ensuing section, both solidified patenting as an essential tool in the commercialization of new biotechnologies, created an opportunity for public research institutes to attract investments from private industry, and expanded the marketplace for scientific knowledge and its byproducts. Further, WTO members must also enforce copyright laws protecting computer programs as a literary work, and patent laws that allow microorganisms and other biological material to be patented (Drahos and Braithwaite, 2004: 1). More specifically, articles 27 through 34 relate to intellectual property generated through scientific R&D, establishing what is considered patentable material (e.g. genes, organisms, plant varieties, drugs, cell lines, and other biotechnological materials), and outlining penalties for noncompliance and infringement (Mirowski, 2011).

Tyfield (2008) argues that TRIPS was largely a product of the (American) university-industry (U-I) complex that emerged following the rapid growth of the biotech sector: although "the political agency behind TRIPS was big pharma, its capacity to take over the state's agenda for international trade diplomacy was built upon…a U-I complex in the life sciences" (p. 3). As discussed in Chapter Two, the usually stated purpose of IPRs is to facilitate economic, social, and cultural progress by encouraging creative work and technological innovation and rewarding ingenuity (Posner, 2002). Moreover, patents and IPRs offer a means of extracting economic value and appropriate financial returns from the products of research and therefore provide an incentive to finance applied R&D (Taubman et al., 2012: 3). Given the expensive nature of pharmaceutical development and its dependence on patenting, large pharmaceutical firms sought to establish a global market so as to recoup the costs of R&D via sales and establish cheaper means of production

in the Global South (ibid). Further, with the increasing number of U-I partnerships in the biotech sector from the 1980's onwards, it became equally as important for large pharmaceutical firms to lobby for patent reform on a global scale. Thus, large pharmaceutical firms also campaigned for the harmonization of international patent regulations in an effort to reduce profit losses stemming from local competition and weak patent regimes in developing countries, reverse engineering and imitations (Tyfield, 2008: 5). Regarding TRIPS specifically, the political leverage of the pharmaceutical sector resulted in the United States pursuing "a regime of strong, *global* patent rights that would cover *pharmaceuticals and biological materials* in particular" during international trade negotiations" (ibid: 12).

The international enforcement of IPRs and regulations through the enactment of TRIPS has primarily benefited the dominant capitalist countries that make up the WTO: namely, the United States, members of the European Union, and Japan. With respect to the Global South, the enforcement of TRIPS has not been particularly advantageous and has brought few gains, especially as it applies to pharmaceuticals (Barton, 2004). As Zeller (2008) notes, the integration of IPRs into WTO rules is a particularly important means of strengthening national competitiveness (of the Global North) and ensuring transnational corporations (such as Pfizer, Merck, etc.) profit significantly and principally from the agreement. With the ratification of TRIPS, "the dominant capitalist countries also obtained an arbitration mechanism with sanction possibilities" (ibid: 95), thus reinforcing the role of the Global North as the primary recipients of license fees and rent payments and widening the existing global technological divide (p. 109). The brunt of this divide (between the dominant capitalist nations of the WTO and their counterparts) is felt especially in the context of pharmaceuticals. Articles 51 through 60 of TRIPS "render importation of any 'pirated' generic pharmaceuticals illegal," even in the case of public health emergencies (Mirowski, 2011: 187). Further, countries in the Global South are prevented from

producing generic versions of essential medicines (e.g. patented antiretroviral and antimalarial drugs, treatments for tuberculosis and dengue fever, etc.), given the agreement's 20-year patent term stipulation (Rhoten and Powell, 2007). The costs of patented medicines are often exorbitant for patients in developing countries[1], and while WTO members have the right to override patents to produce generic versions during national emergencies and public health crises, these exemptions have become a contentious issue between pharmaceutical companies and countries in the Global South (Johnson, 2011: 1). Exemption disputes have largely revolved around what constitutes a national health emergency: for instance, chronic and non-communicable diseases have, until recently, been considered epidemics only in the Global South, and access to medicine for highly prevalent and debilitating diseases such as cancer and diabetes has remained prohibitively costly under TRIPS (ibid).

Today, the IP standards and regulations set forth by TRIPS continue to ensure the transfer and dissemination of new (bio)technologies by means of foreign direct investment (FDI), trade and licensing, and "define and structure the distinct rights and responsibilities in technology partnerships, such as research cooperation or technology sharing or transfer arrangements" (Drahos and Braithwaite, 2004: 1). By harmonizing international IP policy, TRIPS has created an international legal and regulatory architecture that ostensibly reduces barriers to trade, promotes technological innovation, and facilitates the transfer and dissemination of technology (in theory). Patents are a keystone of this architecture: having been lobbied for by a number of dominant private (American) corporations, patents were crucial in the growing commercial dominance of several key sectors in the global economy and ensured "unprecedented corporate control of the life sciences" (Williams, 2000: 69). Moreover, as Mirowski (2011) notes, the international fortification

[1] d4T, a patented antiretroviral sold by Bristol-Meyers Squib, cost roughly $1600 per patient annually versus the annual $55 per patient cost of the generic form – a mark-up of approximately 28-fold per patient (Rhoten and Powell, 2007: 360).

of IPRs through TRIPs has served to maintain and enforce a proprietary structure within pharmaceutical R&D, making it especially difficult for openness to penetrate this particular sector. Proprietary ownership (of knowledge, data, code and so forth) in the form of a patent constitutes the vast majority of monetary assets of most biotech companies and especially those operating on a global scale (ibid).

In the context of pharmaceutical development and commercialization, patents have become the standard tools by which products are brought to market and corporations profit from said products; they are therefore critically necessary for the advancement of R&D, particularly when capital investment is required. The standardization of international IP policy through TRIPS led directly to the reorientation of R&D itself. The weakening of antitrust laws and the strengthening of intellectual property practice coincided with the passage of TRIPS, resulting in the demise of in-house R&D and the growth of outsourcing corporate research in the early 1990s (Mirowski and Sent, 2008). The direct result of this was an unfettered corporate sector contracting research to external firms (such as research parks and academic start-ups) as a cost-reduction measure. By creating a standardized *global* IP regime, TRIPS established an international legal structure in which a small handful of corporate actors could maintain a monopoly in their respective sectors while outsourcing R&D efforts as a cost-saving measure. Prior to TRIPS, outsourcing R&D efforts – for example to India or China – would require adhering to the potentially weak IP standards of those countries (ibid). With its passage, TRIPS ensured that employing CROs outside the Global North (for example, in India – see Sunder Rajan, 2017) no longer meant large firms were constrained by weak IP standards (Mirowski and Sent, 2008). The lobbying efforts of pharmaceutical firms prior to TRIPS essentially resulted in the exportation of a US-style intellectual property regime around the world (benefiting the United States and the European Union predominantly) and ensured the primacy of patents within this legal architecture (Lexchin,

2016). As Stiglitz et al. (2017) note, these IP standards are designed not to maximize innovation and scientific progress, but rather to maximize the profits of large pharmaceutical firms (and others) and optimize their ability to sway trade negotiations.

While this dissertation and the case study at hand do not focus immediately on TRIPS or the sale of domestic pharmaceutical products across international borders, it is important to understand the broader policy background and legal context in which R&D takes place. TRIPS has essentially dictated the terms by which pharmaceutical products are developed and commercialized; it has extended the commercial market further upstream, and the requirement that WTO member nations adopt a US-style patenting regime has profoundly affected the way knowledge is commercialized and organized (Mirowski, 2011). As discussed in Chapter Two, pharmaceutical R&D is interdisciplinary by nature, and is a product of collaborative efforts both within and across institutional boundaries and international borders. The production of pharmaceutical products relies heavily on international supply chains (McKenna, 2018), and as such, research in this sector and the products it yields are subject to the conditions laid out in TRIPS. This, by extension, means protecting and commercializing research via proprietary devices is standard practice. Research (both corporate and academic) has thus been reoriented toward commercial priorities by "a small cabal of neoliberal economists and corporate representatives" (Mirowski, 2011: 186), making the implementation of open devices into this sphere particularly difficult. As will be discussed in Chapters Five and Six, while the participants of this study (e.g. researchers, investors, lawyers, IP agents, etc. in this sector) recognize the potential benefits of openness on pharmaceutical R&I, they also acknowledge the legal architecture established by TRIPS and the entrenchment of patents and other proprietary IP tools and practices within this architecture that makes establishing new innovation practices and open business models challenging.

4.2. Intellectual Property Policy in the United States

Following the birth of the biotech industry in the late 1970s, the gap between upstream, fundamental research and its commercial applications became progressively narrower (Rai and Eisenberg, 2003; Pisano, 2006). As universities began focusing on the commercial impact of science at this time, government funding for academic science stagnated in the 1970s and in-house corporate R&D declined precipitously, leading industry to rely on universities to conduct a significant portion of basic scientific research (Rosenberg and Nelson, 1996). University technology transfer offices opened as a means of liaising between academia and industry and transferring "university breakthroughs into the hands of the public" by way of patenting (Popp-Berman, 2012: 6; see also Geiger and Sá, 2008). Prior to the emergence and rapid growth of the biotech industry, the boundary between academia and industry was, for the most part, distinct: while university faculty served as advisors and consultants to industry, academic entrepreneurship was relatively limited – a result of a dearth of capital for early-stage industry developing academic inventions (ibid). However, a series of legal and legislative changes in the United States in the early 1980s helped in part to launch and sustain the practice of academic entrepreneurship in the biological sciences during this time and promoted the practice of intellectual property claims in fundamental R&D. This section will focus on three of these changes in particular – the Supreme Court case of *Diamond v. Chakrabarty* (1980), as well as the *Bayh-Dole* and *Stevenson-Wydler* Acts (1980), each of which helped to reshape the economic structure of scientific research and have ensured the primacy of patenting in today's drug discovery landscape.

With the growing entanglement of capitalism and science following the end of the Second World War, the scientific enterprise came to be seen as a potential economic engine (Weinberg, 1967). To ensure a means of return on public capital investment in scientific research, universities – the primary locus for scientific inquiry and knowledge production to this point – needed to

"harness the power of the market" (ibid: 95). This was made possible through the fortification of a national patent regime and the enactment of patent policies and research regulations founded on the bedrock principles of ownership and profiting from one's ownership (Kraemer, 2006). While the first piece of IP legislation in United States – the 1793 *Patent Act* – stipulated that nature, in any form, could not be patented, by 1930 the *Plant Patent Act* permitted the patenting of asexually reproduced plants (ibid). Following the loosening of recombinant DNA research regulations in 1977, the landmark Supreme Court case of *Diamond v. Chakrabarty* (1980) broadened the notion of patentability further by allowing microorganisms to be patented. The significance of *Diamond v. Chakrabarty* lies in the Court's distinction not between living and inanimate things, but rather "between products of nature, whether living or not, and human made inventions…[such as Chakrabarty's] microorganisms" (ibid: 83). The conclusion drawn was, essentially, that living things resulting from human ingenuity and research could be owned and turned into both private property and marketable commodities – a verdict that had far-reaching implications for biomedical R&D specifically, and for academic capitalism more broadly.

The same year, the United States Congress passed both the *Bayh-Dole Act* and the *Stevenson-Wydler Act*; the former affirming the right of universities to patent government-funded inventions, and the latter permitting federal laboratories to actively pursue technology transfer (Hacket, 2014). These acts of Congress, inherently market-oriented by nature, were "strongly motivated by concern with the economy, and by a belief that [science and technology] could be used to improve it" (Popp-Berman, 2014: 415). The purpose of these initiatives (particularly the *Bayh-Dole Act*) was to encourage public-private partnerships by making federally sponsored research more readily usable. More broadly, improving incentives for inventors was seen as a means of increasing techno-scientific productivity and improving American economic competitiveness. Granting ownership of exclusive patent rights allowed grantees (i.e. scientists, academic researchers, etc.) to license their

inventions to private firms – a move that was deemed "necessary to motivate private investors to pick up where government left off and transform new discoveries into commercial products" (Rai and Eisenberg, 2003: 290).

However, while the intent of both the *Bayh-Dole* and *Stevenson-Wydler Acts* was to accelerate techno-scientific innovation, facilitate technology transfer, and encourage public-private partnerships, neither piece of legislation drew a distinction "between downstream inventions that lead directly to commercial products and fundamental research discoveries that broadly enable further scientific investigation" (ibid). As discussed in section 2.4.3, Murray and Stern (2007) have illustrated the anti-commons effect associated with the granting of upstream patent rights, suggesting that intellectual property rights do, in fact, have a potentially negative impact on the diffusion of scientific knowledge. By extension, proprietary IP (particularly upstream) may impede innovation in the biological sciences by limiting avenues of inquiry, excluding certain groups from R&I, and creating bottlenecks through patent thickets (Heller and Eisenberg, 1998; Mirowski, 2011; Caulfield et al., 2011). Following the passage of *Bayh-Dole* and *Stevenson-Wydler*, public research institutes saw a flurry of new patent applications and an increase in MTA filings as private investment in public research institutions and public-private research collaborations grew (Mirowski, 2011). Granted broader patenting freedom with the Supreme Court ruling in *Diamond v. Chakrabarty,* universities in particular began to file patent claims on basic research discoveries, such as novel DNA sequences, cell lines, and protein structures, thereby extending the reach of proprietary tools into what was formerly the public domain (Rai and Eisenberg, 2003). Moreover, newly emerging university technology transfer offices sought to establish proprietary restrictions on research with commercial potential even when patents were not sought, specifically by requiring material transfer, reach-through or non-disclosure agreements that dictate or limit the use of research products and materials (Rai and Eisenberg, 2003; Rodriguez, 2005).

Some scholars have argued the passage of the *Bayh-Dole* and *Stevenson-Wydler Acts* has had a minimal impact (either positive or negative) on biomedical research and innovation activity, and further, that patents issued to universities following 1980 were, in fact, less significant and less general than those issued to applicants in academia prior to 1980 (Mowery and Ziedonis, 2002). Moreover, these scholars have argued that the increase in university patenting and technology transfer activity after 1980 was simply following along a natural trajectory, unaffected by the external legislative environment (Mowery et al., 2004). However, as Mirowski (2011) notes, *Bayh-Dole* and *Stevenson-Wydler*, as well as the *Chakrabarty* decision, were neither the sole nor the primary reasons behind the increasingly commercialized nature of academic science; rather, they encouraged the commercialization of research further upstream and "brought universities closer in line with IP law for corporations" by "…mandat[ing] the neoliberal restructuring of the university" (p. 149). These legal and legislative changes were, therefore, catalysts for what has been described as the creep of market-oriented neoliberal strategies into the academic sphere and ensured that universities played a more active role in reconfiguring research agendas toward more commercial interests (Lave et al., 2010).

Finally, the expansion in the number of *things* that could be patented (via the decision in *Chakrabarty*) and the consequent push to patent and commercialize academic research has led to an erosion of the norms traditionally associated with fundamental science: while the relevance of Merton's norms are debatable today, the impact of the fortification and proliferation of IPRs into academic science has extended beyond financial considerations and has enclosed what had previously been open. As Ziman (2012a) and others have argued repeatedly, the internal structure of science is a social formation, based on interdisciplinary knowledge flows and collaborative efforts. As will be discussed in ensuing chapters, patents (in addition to numerous other proprietary IP tools) constitute a barrier to these knowledge flows and collaborative endeavours. The ability to

make broad upstream patents claims, for instance, limits access to knowledge that extends far beyond the scope of the original invention, such as in the case of the OncoMouse patent which was "not limited to the mice actually modified, but claim[ed] all exploitation of the invention for all transgenic, nonhuman, mammalian onco-animals" (Radder, 2010: 247). Moreover, while the debate regarding whether scientific knowledge is a public good (see Callon, 1994) far exceeds the scope of this dissertation, conferring monopoly rights over upstream research and fundamental scientific knowledge prevents scientists from accessing the "communal stock" of scientific knowledge. As Jones (2009) notes, knowledge begets new knowledge, and R&I is therefore an aggregate process of producing new knowledge. Advancements in biotechnology or pharmaceutical sciences, then, require a collective pool of skills and expertise (Freeman et al., 2015; Raasch et al., 2013) – a process limited by the increasingly common practice of privatizing and commercializing academic research.

4.3. Intellectual Property Policy in Canada

The Canadian *Patent Act* (1985) governs pharmaceutical patents in Canada, and further outlines patentability criteria, establishes standards of patent enforcement, and provides a minimum period of market exclusivity for disclosures of inventions (Hore, 2004). The *Patent Act* originally conferred an eighteen-year period of exclusivity on new disclosures, though litigation on behalf of the United States through the World Trade Organization established Canada was in violation of TRIPS (WTO, 2001). Canada has since adopted a fixed twenty-year patent term. This section focuses primarily on Canada's Notice of Compliance Regulations and the Data Exclusivity Rules, both of which form the guiding federal principles of intellectual property disclosure and compliance and significantly favour the rights of brand-name drug manufacturers over generic competitors.

Prior to 1993, Canadian law established a "license of right" for 50 years on pharmaceutical products marketed in the country, whereby potential distributors of generic drug products "could apply for such a license and, if granted, could produce and market the patented medicine at competitive prices in return for a four percent royalty" (Reichman, 2009: 251). While Canada's use of the license of right was central to establishing a profitable environment for generic pharmaceutical development, by extension it deterred the growth of a robust research-based pharmaceutical sector (ibid). Given the less stringent regulatory and intellectual property market in the United States, brand-name firms have flourished outside of Canada, while their presence in Canada remains limited (namely because generic pharmaceutical development involves formulation research but no discovery, and thus is unaffected by lax IP laws). As Lexchin (2011) notes, efforts to expand the generic market poses a challenge to governments, whereby generics are needed to manage the cost of drugs, yet brand-name company investment often depends on the restriction of generic products.

In 1993, following pressure from the United States, Canada abandoned the license of right program and Canadian compulsory licensing was formally prohibited under the IP conditions laid out in the North American Free Trade Agreement (NAFTA) (ibid). Further, following the TRIPS negotiations in the early 1990s and a subsequent WTO court ruling on behalf of the United States against Canada, Canada's compulsory licensing system was deemed to be in noncompliance with the treaty (World Trade Organization, 2001). A latter provision of TRIPS stipulated "a WTO Member government cannot subject whole classes of pharmaceuticals – such as 'essential medicines' – to a pre-established compulsory licensing scheme. It must, instead, adopt a case-by-case approach and shape the compulsory license to meet the purpose for which each license was authorized" (Reichman, 2009: 252). This saw the consequent enactment of the *Notice of*

Compliance (NOC) Regulations and the establishment of a 20-year patent term for brand-name products.

The NOC Regulations stem from the *Patent Act*, enacted under Section 55.2, and have since been amended in 1998, 1999, 2006, and 2008 (Hore, 2004; Lexchin, 2011). Their purpose is to provide effective patent enforcement for new brand-name pharmaceutical medicines by tying the regulatory approval of generic products by Health Canada to the patent status of the original branded product (Lexchin, 2011). Following a successful review of a new drug submission to Health Canada, a Notice of Compliance is issued to the manufacturer. The process of new drug submission and approval in Canada is as follows:

1. When a sponsor decides that it would like to market a drug in Canada, it files a "New Drug Submission" with the Health Products and Food Branch (HPFB). This contains information and data about the drug's safety, effectiveness and quality. It includes the results of the preclinical and clinical studies, whether done in Canada or elsewhere, details regarding the production of the drug, packaging and labelling details, and information regarding therapeutic claims and side effects.
2. HPFB performs a thorough review of the submitted information, sometimes using external consultants and advisory committees.
3. HPFB evaluates the safety, efficacy and quality data to assess the potential benefits and risks of the drug.
4. HPFB reviews the information that the sponsor proposes to provide to health care practitioners and consumers about the drug (e.g. the label, product brochure).
5. If, at the completion of the review, the conclusion is that the benefits outweigh the risks and that the risks can be mitigated, the drug is issued a Notice of Compliance (NOC), as well as a Drug Identification Number (DIN) which permits the sponsor to market the drug in Canada and indicates the drug's official approval in Canada. (Health Canada, 2019b).

Essentially, through the NOC Regulations, the drug approval process is inherently linked to patent status as Health Canada is barred from permitting a generic market entry until the 20-year patent term of the branded medicine has expired. This will be discussed in detail in Chapter Six. Branded drug products that have received regulatory approval by Health Canada are also required to be listed on the Patent Register. In contrast to the United States and other jurisdictions where litigation

between patentees and generic producers is commonplace, generic producers seeking approval from Health Canada are required to address specific patents listed on the Register – by arguing the patent in question is either invalid or will not be infringed by the approval (ibid). This measure was intended to minimize wasteful post-approval litigation.[2] Following the 2006 revisions, the Patent Register required that a link be made explicit between patent subject matter and the underlying drug product – a means of minimizing abuse of the Register. Importantly, the NOC Regulations facilitate the ability of brand-name firms to prevent generic market entry by listing patents on the Register – should the patentee challenge a generic's application for approval, there is an automatic 24 month stay of regulatory approval placed on the generic (ibid).

Separate and distinct from patent protection are the Data Exclusivity Rules, enacted through the Canadian Food and Drug Act. Importantly, TRIPS specifies that WTO members should implement measures that protect intellectual property (e.g. pre-clinical, clinical, toxicological, or clinical trial data that support a branded new drug application) from unfair commercial use (Kendall and Hamill, 2016). Similar to other forms of proprietary IP protection, the Data Exclusivity Rules provide branded pharmaceutical manufacturers a limited period of protection in which to obtain regulatory/market approval for a given product. In Canada, where data exclusivity applies, generic manufacturers seeking to rely on a pharmaceutical patentee's data are prohibited from applying for a period of eight years following the approval of a branded drug product (ibid).

Both the NOC Regulations and the Data Exclusivity Rules have been widely criticized by generic manufacturers as having a significant delaying effect on generic market entry by allowing brand-name manufacturers to extend their market monopoly, in some cases for years after the

[2] Biologics – drug products that are synthesized from or manufactured in biological sources, such as viral and bacterial vaccines, radiopharmaceuticals, cell therapies, or gene therapies – are required to submit extensive evidence demonstrating safety and efficacy in addition to chemistry and manufacturing information beyond what is typically expected from patented new drug submissions (Health Canada, 2019a). They are then monitored by Health Canada according to their potential risk. Biologics are approved by the Biologics and Genetic Therapies Directorate of the Health Products and Food Branch of Health Canada (GaBI, 2014).

expiry of the patent in question (Hore, 2004). Notably, the NOC Regulations allow brand-name manufacturers to obtain automatic 24-month stays of approval by asserting a patent would be infringed by the generic product. Loopholes in the Regulations allow for brand-name manufacturers to obtain several continuous 24-month stays of approval, which has led to brand name patentees prolonging their market monopolies by engaging in lengthy litigations with generic manufacturers and significantly delaying generic market entry (often for years following the expiration of the original patent) (ibid). Additionally, the Data Exclusivity Rules grant a period of IP protection for eight years following approval of a branded product: during the first six years of this period, a generic manufacturer may not file for approval with Health Canada, and while they may file for approval during the final two years, it cannot be granted until the end of the eight years (Kendall and Hamill, 2016).

The purpose of this section is, again, to highlight the centrality of patents in Canada's pharmaceutical landscape, and to emphasize the privileged position given to proprietary forms of intellectual property. The legal and regulatory architecture of pharmaceutical development in Ontario will be discussed in more depth in Chapter Six. A recent report by Action Canada on the status of open innovation as a national innovation strategy found that among OECD countries, Canada has fallen significantly behind industrialized nations in establishing a robust, collaborative and open innovation S&T policy (see Gamache et al., 2016). Moreover, the report noted that while the current federal government has identified innovation as a priority by appointing a Minister of Innovation, Science and Economic Development and has recognized the importance of openness and collaboration in the context of scientific innovation specifically, the government has done little to encourage or foster working relationships between private firms, government, and public research institutes (ibid). Even excluding the consideration given to openness in the report mentioned above, pharmaceutical innovation – as measured by annual patent filing rates – has

fallen, according to the Canadian Intellectual Property Office's most recent Annual Report (CIPO, 2018). While in 2017, CIPO received 35,022 patent applications (an increase of 1% from 2016), the number of patent applications for pharmaceutical products has continued to drop since 2008 (ibid).

As discussed in Chapters One and Two, establishing increasingly open business models and creating collaborative networks of actors and institutions – actions that do not necessarily require firms to abandon contracts or other tools used to create market value – may offer a solution to the issues of bottlenecks and patent thickets associated with traditional proprietary and linear models of innovation. As it stands, however, Canada's established open innovation policy exists in name only, and is has failed to expand beyond policy discussions to practice (Gamache et al., 2016).

4.4. Conclusion

Patents form the backbone of the international legal and policy architecture that in large part determines the path of scientific innovation, particularly in the context of pharmaceuticals. Numerous national and international agencies have explicitly called for the adoption of full and open access to scientific data as an international norm associated with publicly funded research (International Declaration on Human Genetic Data, 2003; OECD, 2007), or have declared a commitment to making research data available to the widest possible audience as soon as possible to expedite the translation of research results downstream (NIH, 2003; CIHR, 2007; UK Medical Research Council, 2011). However, the fact remains that patents, MTAs, and other proprietary IP devices remain hallmark features of commercialization strategies across the globe. Though open innovation has become an increasingly appealing solution for a sustainable international IP regime (particularly as the economy of ideas, knowledge, and information continues to account for a growing share of output in both the Global North and South), the prevailing twenty-first century

IP regime continues to "[erect] more barriers to the use of knowledge, often casing the gap between social returns to innovation and the private returns to widen" (Stiglitz et al., 2017: 3). Even as private firms (such as GE, Samsung, and Johnson & Johnson) extend innovation efforts beyond traditional firm boundaries and university researchers continue building collaborative ties with industry, these relationships (and the process of commercialization itself) still hinge largely on NDAs, MTAs, and patents, and proprietary devices remain central to international IP policy (Caulfield et al., 2012). Moreover, patents and other proprietary devices continue to be used further upstream in the process of academic R&I, significantly impacting the dissemination of research results and hindering the commercialization process itself.

As will be discussed in the Chapters Five and Six, as firms and governments continually evaluate and update their business models and innovation strategies and policies, it is important to assess their efficacy in terms of accelerating the translation of pharmaceutical research and encouraging collaboration. Streamlining the innovation process will necessarily involve unpacking *when* open and proprietary devices are employed in the innovation process (e.g. upstream versus downstream) and *the context in which* they are employed (e.g. in a consortium versus a small- to medium-sized firm versus an academic lab). As Rai and Eisenberg (2003) note, the challenge to policymakers moving forward "lies in distinguishing discoveries that are better developed and disseminated through open access from discoveries that are better developed and disseminated under the protection of intellectual property rights" (291).

5. The Innovation Ecosystem in Ontario's Pharmaceutical Sector

This chapter addresses research question 1: *How do social actors in the pharmaceutical sector understand innovation? By extension, how can we theorize open and proprietary devices?* Specifically, it focuses on the concept of *innovation* itself – what does it mean to innovate? How do we measure and valuate innovation? What factors drives certain actors to invest in the development of innovative new biotechnologies? What factors accelerate or inhibit the commercialization of these innovations? *Innovation* is a particularly slippery concept, meaning different things and producing different end results to different actors within techno-economic networks. The ways in which innovation is measured also vary, and the metrics used to determine *innovativeness* at the firm- or country-level are inherently linked to the motivations behind R&I. By extension, these motivations are shaped largely by monetary considerations (i.e. public research funding, sponsored research agreements, etc.). Moreover, analyzing the concept of innovation and how it is measured sheds light on funding and investment decisions, largely by highlighting financial motivations that drive R&I. Unpacking these questions allows for a more nuanced understanding of the role played by open and proprietary mediating devices on innovation in the pharmaceutical sector. Understanding how the definition of *innovation* changes from the perspective of research scientists, executives, IP managers and so forth is critical in this particular study. As will be discussed in Chapter Six, what may hinder innovation for the research scientist who sees innovation as a process may conversely facilitate it for the CEO who sees innovation as a usable outcome. For example, a patent or MTA may inhibit collaboration and the aggregate process of knowledge production upstream but facilitate the market introduction of a new product downstream. This distinction is necessary for understanding the effect of mediating devices on innovation itself.

As previously discussed in Chapter Three, this research focuses on intermediary organizations established to facilitate the translation of basic research into marketable products, in addition to public research institutes, small- to medium-sized private pharmaceutical firms, and incubator labs in Toronto. Specifically, I focus on MaRS Innovations (MI) and its affiliate firms and public research hospitals, the Ontario Institute for Cancer Research (OICR) and the Fight Against Cancer Innovation Trust (FACIT), Johnson & Johnson's incubator space JLABS @ Toronto and its affiliate firms, and the Structural Genomics Consortium (SGC). These organizations employ a variety of collaborative research arrangements and disclosure practices, ranging from the entirely open model of the SGC to the more proprietary commercialization tools and non-disclosure agreements favoured by the MaRs Innovations technology transfer office. This chapter incorporates interview data collected from interviewees from both the public and private sectors. Specifically, interviewees were drawn from MI and several of its affiliate firms, the OICR, FACIT, JLABS and one of its affiliate firms, the SGC, the University Health Network technology transfer office, the Princess Margaret Cancer Research Centre, Sunnybrook Research Institute, two leading law firms in Toronto, and one large pharmaceutical firm in the Toronto area. Participants included academic bench scientists, executives in the public and private sector, venture capitalists, IP lawyers, IP directors, patent agents, tech transfer officers, and innovation managers from these organizations. These interviews have been anonymized and participants are identified by their title only.

This chapter begins by unpacking and analyzing the various framings of innovation encountered in both the literature and interviews conducted as part of this research. Here I endeavour to unpack the numerous and varying definitions provided in both the innovations studies literature and by interviewees, and evaluate how these definitions are shaped and change depending on the location of the actor within a particular techno-economic network. Following

that, I discuss the ways in which innovation is (mis)measured, focusing on the use of patent statistics and other macro-level means of quantifying innovativeness. Subsequently, I briefly discuss the drivers of pharmaceutical R&I in Toronto's pharmaceutical innovation ecosystem, assessing the relationship between the lack of public funding for research in Canada and the consequent profit-driven nature of research. Finally, I discuss at length the funding and commercialization of R&I in this sector. This section focuses on the role of mediating devices in attracting external investment as well as the ways in which these devices affect the commercialization of new technologies.

5.1. Defining Innovation

As discussed in Chapter Two, a major factor contributing to the disjointedness of innovation studies as a standalone field is the conflicting definitions of *innovation* offered by its scholars (Fagerberg and Verspagen, 2009). The term itself has become essentially a "hairball that sticks to everything," as a senior administrator of a large research hospital in Toronto noted (VP Research, 2017). The ambiguity of the term, its ubiquity and frequent use as a catchall meaning nothing and everything, pose significant problems for both policymakers attempting to guide the innovation process and firms seeking clarity of purpose. Collaboration may also be hindered by vague or discordant understandings of innovation, particularly in terms of clarifying mission orientation (Ziman, 2002) and differentiating between products and processes. Moreover, having a clear understanding of what innovation represents is necessary in assessing the *innovativeness* of a particular firm, research group, or collaborative arrangement. This section will unpack the varying definitions of innovation found in the innovation studies literature as well as those offered by interviewees.

In a broad review of the innovation studies literature, Quintane et al. (2011) have divided common definitions of innovation into two primary categories, wherein innovation is determined to be either a *process* or an *outcome*. Innovation as a process essentially involves bringing new modes of problem solving into practice (ibid). In the innovation studies literature, the notion of innovation as a process entails "the development and implementation of new ideas by people who over time engage in transactions with others within an institutional order" (Van de Ven, 1986: 590). It is "a highly uncertain process in which entrepreneurs, with financial support from investors, undertake a sequence of events over an extended period of time to transform a novel idea into an implemented reality" (Van de Ven and Polley, 1992: 92). Birkinshaw et al. (2008) define the process of innovation as "the invention and implementation of a management practice, process, structure, or technique that is new to the state of the art and is intended to further organizational goals" (p. 825).

Conversely, innovation as an outcome generally results in the development of an asset with some commercial value. It has been articulated as "an invention which has reached market introduction in the case of a new product, or first use in a production process, in the case of a process innovation" (Utterback, 1971: 77). Traditional definitions of innovation tend to vacillate between these two conceptualizations of innovation as either a *process* or an *outcome*, constituted by differing social processes that lead to the generation and implementation of an idea, or gauged by inherent features (e.g. novelty, technical versus administrative, incremental versus radical) (Quintane et al., 2011). As discussed below, the Quintane et al. (2011) propose a third definition of innovation as a knowledge-based conceptualization, arguing that innovation is essentially the production of new knowledge (ibid: 938).

One of the primary criticisms of innovation studies as a discipline, and the study of technological innovation more specifically, is the dominant (quantitative) framework of

neoclassical economics. Godin (2015) is particularly critical of Schumpterian innovation studies, arguing that the field has constructed a tradition of understanding innovation as the commercialization of technical inventions, focusing almost exclusively on firms, rather than examining innovation as a cultural force affecting social, political, and economic thought. Recall, Schumpeter (1942) argued that *innovation* extended beyond simply creating a new business to creating a new product or process or a new market for an existing product or process. Old or inferior products and services across markets and industries were subsequently replaced through "the "gale of creative destruction" (ibid). This understanding of innovation as a profit-building means to a technological end is evident in the interview data gathered in this research. One interviewee, the VP of Research and Innovation at a large research hospital in Toronto, defined innovation as "discovery to clinical impact through the medical marketplace" (VP Research, 2017). Similarly, another participant, the President and CEO of a small biologics firm, stated "innovation is basically taking an idea and turning it into a useful entity, a useful thing" (President and CEO, 2017). Likewise, the CEO of second small biologics firm argued innovation should be defined by its outcome, specifically as it relates to patent filings. He noted,

> In many ways innovation is not distinguishable from applied research, and I also would make the point that in many cases, maybe not every time, but in many cases, filing a patent application could be defined as the fruit of innovation… It's got to be useful, I mean, that's core of the definition of innovation. It has to be useful for a real world problem, and I don't think you can parse that from the definition of innovation, that is at its core. That you've innovated when you've created something that's useful to somebody… And the reason I think patenting links so well [to that definition of innovation] is that…it has to have utility, it has to have usefulness, it has to have industrial applicability. You can't patent something if it doesn't meet those criteria. And that's why I think the two are actually quite way more closely linked than people say. But you cannot remove the usefulness from either the patent process or the definition of innovation (CEO, 2017).

These definitions suggest that at the end of the innovation process there is necessarily something *usable*, whether that is a marketable product or a new technology. Understanding innovation as a

process leading to a product is logical in the context of private industry, where tangible deliverables are often a benchmark of productivity and growth.

However, moving beyond the fold of industry, the term becomes more abstract and fluid. In highlighting the link between the *processes* and *outcomes* of innovation, Quintaine et al. (2011) assert that both fall under the umbrella of knowledge production. Stemming from this, they define innovation simply as *new knowledge*, characterised by its duplicability, its demonstrated usefulness, and the novelty of its introduction (ibid). It is in the same way that Dosi (1988) defines innovation as a process of discovery and creation occurring via continuous change (e.g. progress along a technological trajectory) and radical change (e.g. with the emergence of a new technological paradigm). When asked, a senior research scientist working at a large incubator lab in Toronto stated:

> Innovation means something new, something out of nothing. It has something that's creating new knowledge, answering previously unanswered questions… To immediately skip to the end of the process and look for the marketability or the exploitability of the idea, I don't think, personally, that's what the word means. I'm willing to take a more broad definition that something can be innovative and have absolutely no application. Something can be completely academic and still be innovative. Who's to say that it has to have utility? (Senior Research Scientist, 2017).

Similarly, another research scientist working in the same incubator lab recalled a colleague discussing a biotech firm he had owned in the late 1990s. The company:

> …used to be very research intensive and decided to cut all of its in-house R&D, and instead said that they were going to focus more on innovation and less on research. And this is a discussion that he had had a number of times where he told me that he fundamentally thought that was the death of his company, because they stopped generating new knowledge and they thought that innovation was something that they could enlist, something that they could buy. And the point being that for a company that used to be known for its R&D, that was the nail in the coffin (Research Scientist, 2017).

Likewise, a research scientist and executive of one of Toronto's research hospitals defined innovation as:

> Taking what we know and organizing it to do something that we have never done before or never done in that way before… I think that it's a continuum, that you can't have innovation without discovery or insight; [innovation] is eventually downstream of all discovery (Research Scientist, 2017)

In arguing against the notion of innovation as necessarily resulting in a usable asset, the Director of Intellectual Property at a large non-profit organization highlighted the need for pharmaceutical innovations to be paradigm shifting, pointing out that:

> Much of what is considered innovative now, in terms of FDA approval, isn't really game changing… I think to be truly innovative, you [must] have a discovery that gets to the clinic that is actually game changing, it isn't this incremental extra month of life with no increase in quality of life, which is what a lot of these approved drugs are doing. So those who are making money from [the product] might see that as innovative, because they get some capture of market share. But to be truly innovative, you're doing something different and I think it should be game-changing (Director of Intellectual Property, 2017).

Further, they noted that innovation tends to happen incrementally, and conceptualizing innovation in biotech from an outcome- or product-based perspective ignores the incremental but impactful steps that lead to paradigm-shifting discoveries. Often, building upon each step is collaborative effort, they noted, "because science is difficult, biology is tricky, and we have to figure out all these other smaller pieces first, so those incremental pieces are actually what make [the end result] work, and those are going to be huge but they might not seem as big as that final product" (2017). Similarly, Obstfeld (2005) defines innovation as "a process of creating new social connections between people and resources they carry, so as to produce novel combinations" (p.100). These definitions suggest innovation stems from new ways of thinking and collaborating, rather than just producing. Here, if scientific R&I is an aggregate process of producing new knowledge (Jones, 2009), it is logical that innovation would involve a process of collaboration, and knowledge production and accumulation from the perspective of the research scientist working upstream.

The purpose of this section is not to define innovation as an immutable concept but rather to highlight the ambiguity of the term in practice. It is frequently used in distinct contexts, meant to

describe both tangible and intangible things. Distinguishing between definitions of the term – what it means, to whom, and why – is critical for understanding the effects of mediating devices on innovation itself.

5.2. Measuring the Value of Innovation

Given that the concept of innovation itself has proven to be ambiguous and context-dependent, by extension measuring and valuating innovation has also proven to be difficult. What qualitative and/or quantitative metrics indicate innovation has occurred or that an innovative process has had a positive effect on firm performance or maximized competitive advantage? If a novel pharmaceutical compound has been patented and becomes the knowledge base for a start-up company, but the start-up has not grown over a given period of time, is it less innovative than one that has? This section focuses on the valuation of R&I, focusing particularly on the role of IP tools in determining whether or not a new innovation holds (financial) value. A recurring point of discussion in both the innovation studies literature as well as the interview data collected here is the *mismeasurement* of innovation via patent statistics, and the conflation of patents and innovation. As will be discussed, the majority of interviewees cited innovation metrics that extended beyond the quantitative scope of patent statistics to a more complex process of worth attribution that incorporates labour, market growth, monetary inflow, and consumer base.

As discussed above, there is a tendency to understand innovation as the development of an asset with some commercial value. Stemming from this, patent counts at the firm, industry, or country level are often cited as a reliable measure of innovative output (Hall, 2013). Even in discussions of innovation as an intangible process, patents are used as proxy measures. As Griliches (1990) notes, considering the lack of consensus surrounding the concept of innovation, patent statistics "loom up as a mirage of wonderful plenitude and objectivity. They are available,

they are by definition related to inventiveness, and they are based on what appears to be an objective and only slowly changing standard" (p. 1661). The OECD cites patent statistics as a quantitative means of capturing a firm or country's contributions to innovation and growth, in addition to "innovation strategies and performance; enterprise dynamics, including the drivers of enterprise creation and of mergers and acquisitions; the determinants of productivity; financing innovative enterprises; the output of R&D activities and the returns to R&D investments; R&D depreciation; and the output of universities and public research organizations" (OECD, 2015: 87). Stemming from this, the Director of a Toronto-based international research consortium argued that patent statistics do not necessarily correlate with innovation at the firm- or country-level, and that connection presumes that a requirement to innovate is to be able to exclude others from using that innovation (Director, 2017). Heller and Eisenberg (1998) have also argued that patents may actually hinder innovation, while Lanjouw and Schankerman (2004) found that patent quality is inversely proportional to research productivity. Moreover, Pravitt (1988), highlights three sources of bias inherent in patent statistics: firstly, the differences across countries in the economic costs and benefits of patents, as well as the rigor of patent application reviews, size of market, and varying subject matter coverage; secondly, the differences among technologies and sectors in the importance of patents as protection against imitation; and finally, the differences among firms in their propensity to patent, particularly unimportant innovations.

Unsurprisingly, then, few interview participants listed patents as their primary metric of innovation, and several noted the common mismeasurement of innovation via biotech patents specifically. As one CEO of a small biologics firm pointed out, while patents do not necessarily indicate that a tangible innovative outcome has occurred, "in drug discovery, in the context of pharmacotherapy, they're not meant to... [Patents are] basically a signpost, a milestone toward achieving that goal. There's no direct link, nor is there meant to be a direct link, between a patent

and actually generating revenue" (CEO, 2017). The Director of Intellectual Property at a large non-profit organization highlighted the misleading nature of using patents to measure innovation, noting:

> We could file [for a patent] on everything we see and show a pretty nice number, but what is that translating into? …How many of those patents are turning into licensable products or company creation opportunities with some sustainability? What is the average value of each license transaction and have you followed those licenses to product development? So what – when you've followed five years out, how many of those licenses are becoming products? I can tell you we've had to terminate a couple licenses recently because they've just been sitting on shelves at companies (Director of Intellectual Property, 2017).

What, then, constitutes a suitable metric of innovation in the biotech sector? Most participants argued practical determinants of innovation would demonstrate long-term growth (of a start-up, for instance) and/or efficacy of a new technology or process. The Director of a tech transfer office at a university in Toronto argued:

> The best way to define [innovation] is by who's using the technology, like the end customers, how many of them are using it, how pervasive is the technology within that industry and obviously from a monetary perspective is it generating revenue, so are people willing to pay for it. If the innovation is being used by a lot of customers or a lot of end users and it's generating money, to me that's an impactful innovation right there. All the other numbers don't matter (Director, 2017).

Several participants also cited the number of start-up companies stemming from an innovative product or process as a more appropriate measure of innovation. A Business Development Director of a large incubator lab in Toronto emphasized the importance of focusing on longitudinal metrics:

> Start-ups should also be something of a weighted number, so you should be looking at the number of companies you create per annum and the number of people who are employed by those companies. You should be looking for a change over time, right? If you create a one- or two-person company and ten years later you still have a one- or two-person company, you've failed to innovate. That's absolutely the worst thing. It shows that you didn't have enough momentum to actually do anything. But if you start out this year and create a one- or two-person company and next year when you checked in again, you've got a ten-person company, and the next year a 50-person company then you did something significant (Director of Business Development, 2017).

Similarly, the Director of a technology transfer office at a large non-profit organization argued in favour of measuring innovation by:

> The number of start-up companies created around all this technology… And then we ideally want to take it one-step further, which is the companies that are created, are they selling [their] product, …does the technology get integrated into the receptor's business, are they making money, are they growing their business and are they hiring people (Director, 2017).

In terms of bringing innovative technologies or processes to the market or growing new businesses, innovation may also be measured monetarily or by the contribution of an innovation to an ecosystem (e.g. via either human or financial capital). The Director of Intellectual Property and Commercialization at a provincial business trust noted that money brought in from the private sector to support research commercialization was used as an important indicator that innovative R&D was occurring at its partner organization. They explained:

> The model has been that technologies here [in Toronto] get licensed off to U.S. multinationals, or start-up companies get going in Ontario and then they're sold and they move to the U.S. or occasionally Europe. One of the purposes of [this trust] actually is to try to help grow the local ecosystem for innovation in biotechnology. And in our group, one of the metrics we look at is how much cash comes in but also how many jobs are created at biotech and biomedical start-ups, there's several hundred right now that are directly attributable to our investment... When we deal with an investor like a venture capitalist or a potential partner like a farm company…they want to know you know, when did you apply for patent protection? We want to see your patent applications. We want to know about any public disclosures (Director of Intellectual Property and Commercialization, 2017).

These quotes suggest firstly that prior to measuring innovativeness, innovations are understood in the context of networks and ecosystems as a tangible *thing* – an innovative new technology that attracts investment from external stakeholders, or a technology around which a start-up is created, and jobs are grown. Secondly, they suggest that measuring innovativeness of a new product or process extends beyond the use of fundamental quantitative metrics (namely patent statistics) and involves a more complex process of worth attribution that incorporates labour, market growth, monetary inflow, consumer base and so on. Measuring the worth of innovativeness also means

examining the pervasiveness of a new technology (or process), its tendency to improve over time (lowering user costs, for instance), and its capacity to make it easier to invent new products and processes (Mazzucato, 2013).

As Chiapello (2015) notes, the process of worth attribution is increasingly financialized, and *value* is often qualified in terms of *returns on investment*. More specifically, Chiappetta and Birch (2018) note that unpacking how value is understood and managed, and by whom, is critical when attempting to conceptualize and measure innovation in the bio-economy. Evaluating non-proprietary innovations and demonstrating the concrete value of upstream research, such as in the case of the Structural Genomics Consortium, becomes especially difficult for researchers seeking external investment. How does the SGC convince investors of the value of its unpatented, publicly available research byproducts? While this will be addressed in Chapter Six, of relevance here is the question of whether open innovation (especially non-proprietary innovations) can be evaluated using the same criteria as patented innovations. Using the OECD's (2015) logic that patented innovations translate to greater technological and economic value, does open innovation generate less value by extension? Patents provide what is typically seen as an objective metric of inventiveness (Griliches, 1990). For investors or potential partners, then, research across all stages of the innovation process (including non-proprietary and intangible assets) is increasingly evaluated in terms of financialized or monetary reasoning (Birch et al., 2017). Here, Birch (2017) highlights the key role played by investors, business development managers, venture capitalists and others determining the value of new biotechnologies. As will be discussed in section 5.4. of this chapter, given that value is so frequently qualified in terms of returns on investment, mediating devices play a singularly critical role in constituting the value of R&I.

5.3. Drivers of Research and Innovation

Understanding the factors that determine how innovation is (e)valuated goes hand-in-hand with understanding the drivers of R&I. Stemming from that, unpacking the values that drive scientific innovation offers (in part) an explanatory basis for understanding the roles of different mediating devices employed in pharmaceutical development. This section seeks to briefly discuss the drivers behind R&I in Toronto's innovation ecosystem, focusing particularly on the profit motives behind industry engagement with academic endeavours.

Numerous governmental policy reports have cited a range of drivers for R&I, from increasing the communal stock of knowledge to developing novel biotechnologies for social and economic gains to creating competitive innovation hubs that attract capital. These reports tend to vaguely highlight the importance of innovation as a catalyst for "a thriving middle class and open[ing] the country to new economic, social and environmental possibilities" (Government of Canada, 2016). By extension, supporting R&I is generally seen as a means of engendering national economic growth. For example, the US National Science Foundation's (NSF) strategic plan for fiscal years 2018–2022 explicitly cites funding scientific R&I as a means of harnessing knowledge to enhance economic competitiveness (NSF, 2018). Likewise, the UK Research and Innovation Council unambiguously states that economic growth and competitive advantage is increasingly dependent on the production of new scientific knowledge (UKRI, 2018).

While Canada may have a robust research environment, its ability to transform ideas into novel marketable products and business models lags significantly behind its counterparts – to the extent that Canada ranks 22nd among the OECD's 34 member nations (Innovation Canada, 2018). Calls for strengthening Canada's basic and applied research capabilities by increasing funding for public research institutes also simultaneously stress the importance of promoting partnerships between these research institutes and industry as a means of attracting "…global talent, investors

and leading companies. These partnerships will strengthen value chains by connecting Canadian suppliers to large anchor firms, accelerating the commercialization of ideas and expanding market access" (ibid: 5). The emphasis on scientific R&D as a driver of economic growth is evident from this policy perspective.

From an industry perspective, prospective return on investment (ROI) is a primary motivator for investing in R&I and partnering with public research groups. Mediating devices play an important role here. Naturally, for organizations seeking to profit from R&I's downstream products, ownership of intellectual property is critical. This tends to affect how collaborative partnerships are formed and what types of research agreements are created (i.e. as consortia, traditional arrangements with strict NDAs, through the use of stringent MTAs, etc.), particularly in the context of public-private arrangements. A research scientist and senior administrator of a large research hospital in Toronto acknowledged, "we're coveting intellectual properties' currency in interacting with the private sector, because that's how the private sector makes money too" (Research Scientist, 2017). At the same time, interviewees working primarily in laboratory settings reiterated that profiting from R&I was not, in fact, a primary motivator for them. The same administrator also pointed out that "we do not do research with a view of commercializing it; we do research with a view to discovery, that's the driver. So, it's not money and commercialization. The motivation is not to make money, the motivation is to understand nature to help sick people" (Research Scientist, 2017).

Likewise, for the Chief Scientist of a Toronto-based international research consortium "the motivation [behind research] is not to gain IP for the sake of IP. That's not the major motivator of most academics. It's discovery: biological and biomedical inquiry, trying to make advances in science and human health" (Chief Scientist, 2017). While that consortium operates under a completely open business model, using only open IP tools and releasing all research biproducts

into the public domain, it is able to effectively partner with private industry as the fruits of that research facilitate new product development (and thus create an ROI for industry). The same scientist noted, "partner pharmaceutical companies don't make any money from [our research]. They just want to get the molecule out there for researchers to use down the line" (Chief Scientist, 2017).

From an industry perspective, ROI is an obvious motivator for helping to facilitate research at all stages of the innovation process, by providing seed funding, physical space, consulting and insight, and so on. As a tech transfer officer at a non-profit research institute in Toronto pointed out:

> If a researcher's motivation is really to impact patients worldwide, then to a great extent the best way of doing that, as long as they've developed something that's commercializable, is actually make it into a product. The only way to do that is to license it to either a start up company or an existing company and for them to then invest…more than what was done originally in the research side to turn it into a real product (Tech Transfer Officer, 2017).

Moreover, the President and CEO of a small biologics firm stated, "it's really for-profit entities that generate the vast majority of drugs and a lot of people don't understand that. And …there needs to be a profit motive there for entrepreneurs and industry to…spend the huge amount of money required to develop new drugs" (President and CEO, 2017). What can be inferred from this is that ROI remains a motivator for industry support of R&I of the innovation process, even further upstream where application value is less certain. Public/private partnerships, such as in the case of many of the collaborative partnerships between academic researchers and industry at MaRS Innovations or the OICR, are formed on a contingency basis where funding is provided with the understanding that industry will have an option or first right of refusal on the IP produced. By extension, the option to commercialize (and profit) from R&I remains the primary motivator for industry R&I (Lezuan and Montgomery, 2015). As the CEO of one of Toronto's largest non-profit research organizations noted, "We cannot expect any company driven by financial returns to be

overly altruistic" (CEO, 2017). As will be discussed in the following section, profit motive also explains (in part) the reluctance of industry to employ open devices in R&D where IP ownership is key to competitive advantage.

5.4. Funding and Commercializing Research and Innovation

As discussed at length in Chapter Two, scientific R&D has been affected significantly by the spread of neoliberal principles, and characterized by a growing entanglement of science and capitalism. This entanglement has resulted in R&D becoming progressively more commodified, commercialized, and privatized (Lave et al., 2010). Science has become inherently linked to national prosperity, and the value of research and its byproducts is qualified in terms of returns on investment (Chiapello, 2015). The extension of neoliberal values further upstream has coincided with a decrease of public funding for scientific research and a growing alignment of research agendas with commercial interests (Lave et al., 2010). This section focuses on the ways in which mediating devices affect funding and investment decisions, and by extension the commercial viability of R&I. As will be discussed, the ability to extract value from new innovations is a primary factor affecting funding decisions, and is affected largely by the mediating devices employed in contract negotiations, research agreements, and other financial transactions.

Stephan (2012) notes that while economic growth is fuelled by upstream research, this research is generally years away from leading to new products. Given its high level of risk and uncertainty and potentially low level of appropriability, as well as the high costs and time associated with commercializing upstream discoveries, attracting (private) funding for early-stage research is particularly difficult. Recall, it costs roughly USD$1-1.5 billion per NCE, from initial laboratory target discovery through clinical trials and including all other ancillary costs such as advertising and salaries (Collins, 2011). In terms of opportunity costs, diseases with large target

populations (such as diabetes or chronic hypertension) offer investors and manufacturers a greater opportunity to earn a higher return on their investment. Conversely, rare diseases with smaller target populations are extremely costly and have significantly longer ROI rates (Gassmann and Reepmeyer, 2005). As will be discussed, industry and private investors are thus less likely to provide risk capital for early stage sponsored research agreements, particularly in the case of R&D targeting rare diseases.

One way to attract private investment is to employ proprietary IP tools that guarantee the byproducts of research have a period of market exclusivity – in essence, "a legal owner empowered to demand payment for [their] use" (Ziman, 2002: 335). Moreover, in the current neoliberal research paradigm, even the results of fundamental research can be a commodity, the value of which "depends entirely on the context in which it is transferred from the vendor to the customer" (ibid). By ensuring exclusionary rights, impeding competitors, and monopolizing specific markets for a period of time, patents help to realize profits that will repay (and hopefully surpass) the high costs of drug development, marketing, and distribution (Scherer, 2002). In addition to patents, proprietary licensing structures such as material transfer agreements (MTA) or reach-through license agreements (RTLA) allow the licensee to seek rents from new research tools that are used to create products further downstream, often extending for periods well beyond patent terms and netting rents that far exceed the initial cost of development (Jones et al., 2007). Like patents, the use of MTAs and RTLAs guarantees an ROI particularly in cases where *tools* (versus *products*) are being developed, such as in the case of high throughput screening technologies, cell lines, and reagents (ibid).

Interview data suggests that an ROI was the primary motivator for investors, and those seeking sponsored research agreements articulated the importance of proprietary IP tools in securing that investment. The need to seek out these sponsored research agreements (and by

extension, to create proprietary barriers around new R&I) stems from the lack of public funding for translational R&I in Canada.[3] The President and CEO of a small biologics firm articulated this dilemma as such:

> I think there should be more taxpayer dollars available for for-profit entities that do that exclusivity. You know what do taxpayers want, they want cures for cancer. Well those don't come out of universities so what are you going to do? I think the [Canadian Institutes for Health Research] should be putting more money into small for-profit entities that do have exclusivity. But the reality is that if you actually look at applied research or innovation in this country, there's very little government money available for that – there's none actually which is a problem, and that's what I believe is one of the major problems we have in Canada and that's why there's so little innovation in this sector. It's because there's just no money to fund them. There's an imbalance between the amount of funding that goes to basic research versus innovation… The only way you're really going to stimulate innovation, at least in biotech and drug discovery, is…there needs to be more public dollars brought to there to get firms off the ground, and until then we need private funding (President and CEO, 2017).

Similarly, the VP of Research and Innovation at one of Toronto's research hospitals highlighted the detrimental effect of both the lack of public funding for R&I in Canada and the consequent reliance of researchers on private funds, stating:

> The public purse has to make a more material investment in early stage technologies than we currently are full stop, otherwise when we're brokering our licensing agreements or our start-ups to the private sector. And that money, once the asset has been sufficiently de-risked, will disappear from the Canadian landscape. And all of the monies invested in it until that point have been, I don't want to say wasted because at the end of the day [a new drug] ultimately will benefit humanity, but it sure won't benefit Canada's GDP (VP Research and Innovation, 2017).

In the case of these sponsored research agreements or collaborative public-private partnerships, the investor secures their ROI either from royalties from patents or other proprietary licensing structures (or both, in the case of products with stacked royalties), or from investors

[3] For reference, the Canadian Government's 2018 R&D budget allocated $9.8 billion *over five years* for scientific R&I (translating to roughly $1.96 billion per year) (Science and Economic Development Canada, 2018). It costs roughly $55 million annually to run technology transfer offices across the country with a return of $62 million, for a net revenue of $7 million on a $1.96 billion annual budget (De Baere and Maine, 2018).

obtaining equity in a start-up. The CEO of a small biologics start-up noted most of the relationships his firm had formed with larger industry players "[were] done on a contingency basis. So the idea is they give us money and they have an option or a first right refusal on any intellectual property that is created" (CEO, 2017). Profit motive also appears to be inherently linked to proprietary IP devices, namely in that they grant market exclusivity and by extension the ability to extract value (Lezuan and Montgomery, 2015). The Director of an industry liaison office at a university in Toronto noted potential industry partners are almost entirely profit driven:

> Their mandate is coming from a board of directors that's saying we need to compete so we can make as much money as possible. That proprietary IP allows them to create a barrier [between them and competitors]. So, the big companies on one side are saying we need to be competitive. The researchers on the other side are saying we just want to get this technology out into the real world. They're happy following the process of patenting or whatever it may be (Director, 2017).

Likewise, the Director of a technology transfer at one of Toronto's research hospitals stated explicitly that "all the industry money that is coming to the hospital through licenses or sponsored research agreements would likely disappear…if the companies that are providing that money don't have some level of proprietary right" (Director, 2017). In this context, proprietary IP offers the promise of competitive advantage that incentivizes investment and collaboration. Highlighting the lack of public funding for R&I in Canada and the consequent necessity of seeking private investment for new research ventures, the CEO of a small biologics start-up pointed out the increasing difficulty in distinguishing entrepreneurship from innovation. He argued the profit motive that currently drives a significant portion of R&I in Canada means there's an added commercial rationale to research. Moreover, they noted:

> It's become difficult to parse entrepreneurship from innovation. There's a reason that so few drugs come out of universities, and that's …90% 95%, whatever of drugs that are launched come from industry and not universities. And it's because you need to have that profit motive, you need to have entrepreneurship at the core of that work. But to the extent that this needs to be supported by investment, you can't get away

> from that profit now; you can't get away from the need to have the competitive advantage over other third parties (CEO, 2017).

The dearth of public funding for R&I in Canada has certainly made room for profit motives to become a primary driver of pharmaceutical development, despite public research institutes actively participating in the commercialization process. Sponsored research agreements have become imperative to moving upstream research towards commercialization, and by extension proprietary IP devices have become increasingly prevalent further upstream.

From the perspective of investors, profit motives are a given, and non-proprietary IP devices are a nonstarter in terms of incentivizing investment and collaboration. Confirming this, the CEO of one of Toronto's largest non-profit research organizations stated: "I can tell you beyond any doubt, no matter what people tell you – that they can take a idea and run with it all the way to the finish line, which is launching a product to the market – we will not invest unless it is well protected and we have a proprietary position on it" (CEO, 2017). Similarly, and perhaps more explicitly, the CEO of a medium-sized pharmaceutical firm headquartered in Toronto stated: "I don't really care that people think that it's stupid to be money-driven. That's the way the world works. You have money that drives decision-making and if we wanted to help people in Africa we need the money to do that. Good thoughts don't get you anywhere" (CEO, 2017). These quotes suggest not only that non-proprietary IP devices are a deterrent in terms of investing in R&D, but also confirm that, as per Abboud et al. (2013), the motivation to fund research for drugs with small target populations is low, as the financial incentives to do so are negligible.[4]

[4] Rare diseases present an interesting case here. As discussed in Chapter Two, small drug target populations make recouping the cost of development more difficult for firms (Abboud et al., 2013). A study by Sarpatwari et al. (2018) found that the upward trend in approvals for drugs targeting rare diseases in recent years has less to do with the market exclusivity granted by patents (aided in large part by the US Orphan Drug Act of 1983), and instead found that firms are incentivized to target rare diseases due in large part to the opportunity to charge higher prices for new products that tackle unmet patient needs. Moreover, firms were also found to be incentivized by tax credits for development costs (ibid).

While proprietary IP tools offer the opportunity for investors to earn royalties, acquiring an equity stake in a startup "may afford more latitude for risk taking and deferred exits" (Fernandez et al., 2012: 965). As investments in early stage technologies are difficult to valuate due to their "inherent, high level of both technical and market uncertainty," equity investments are a safer, timelier option for recouping ROI (Baldi et al., 2015: 226). More simply, taking an equity stake in a company provides a less risky path to earning their ROI than does the opportunity to earn royalties from a patent (for instance), as a large percentage of patented technologies do not make it to market (Pisano, 2006). The Director of Intellectual Property and Commercialization at a provincial business trust summarized this logic as such:

> If we're putting money into a researcher's lab at a university or hospital, …if it's a large amount of money, we usually ask for a small percentage royalty. If that IP ever goes on to become a product, a small amount comes back to us. That's a very long process, of course. More often, especially with the larger amounts of money, we're investing in start-up companies, so we're either taking equity and we own 20% of the company or 10% of the company with a bunch of other people, or we'll put in some debt which converts. So basically we loan you a million dollars, and when you get financed, that loan turns into shares. Or you can pay us back, but people don't like to pay back, they just convert to shares. That way, the end result is the same. We own a chunk of the company. And that works out well for us, because you don't have to wait until you get a product at the end. That product may raise some money, it may raise some more money, it will get diluted down, but at some point the company's going to be bought out or go public. Usually these days it's bought out. And the outside investor comes in with a premium, buys up all the shares, and you get a return on your investment. So if we were buying our shares at a dollar a share and then an investor offers $4 a share, everyone sells and everyone makes money. And then we take that money and put it into our next investment. Having a piece of start-ups works out much better. It's a much shorter timeline than getting a royalty… And as you know, a lot of drugs and devices never make it to market, so that royalty is always in jeopardy until the thing's actually on the market, whereas if you can get in and out of a start-up company in a few years, you can make money even if at the very end the product fails. You just don't want to be the last one holding the bag (Director of Intellectual Property and Commercialization, 2017).

This suggests that the option to take an equity stake in a startup as a means of maximizing ROI from new business transactions is another incentive for established firms to invest in R&I. Even in the context of this non-profit provincial trust, where funds are being funnelled directly into

university labs and academic spinoffs, investment decisions hinge largely on financial incentives. The same Director also noted mitigating risk was a central component of these considerations:

> I'm putting in all this money, I want to know what are the risks that I'm not going to get it back. One of the risks is that your invention, your technology, is going to get stolen, copied, somehow ripped off. And that's a real risk. So, we consider that along with all the other risks, like the risk of bad management, the risk of capital markets, debt crises, the risk of a technology failure, things just don't work out, government risk, the FDA comes up with new rules that cost a fortune – there's all these risks that we're looking at and trying to manage and reduce (Director of Intellectual Property and Commercialization, 2017).

This implies, as Fernandez et al. (2012) suggest, that funding decisions are often motivated less by the desire to accelerate breakthrough discoveries or foster a more innovative ecosystem, than they are by business cycles and windows for conducting initial public-equity offerings (see also Birch, 2016; Hopkins et al., 2013). This again raises questions previously discussed in this chapter regarding open mediating devices – how can they be employed as a means of facilitating innovation when external investment hinges so frequently on the opportunity to extract value from proprietary IP? How have consortiums such as the SGC been able to attract significant amounts of external private investment given its completely open business model and unpatented, publicly available research byproducts? Though proprietary devices may incentivize investment in R&I, do they truly facilitate innovation in the pharmaceutical sector? Understanding the motivations (and deterrents) behind R&I funding is necessary to understanding why particular mediating devices are used, by whom, and when.

Significantly, what this interview data shows is that factors affecting the use of mediating devices such as patents, MTAs, or open licenses, extend beyond a research group's immediate circumstances to the broader techno-economic network of which they are a part. More specifically, macro-level policy decisions regarding federal R&I budgets affect the mediating devices used in public-private research agreements and in academic tech transfer offices. Recall, Callon (1991)

defines the techno-economic network as "a coordinated set of heterogeneous actors…interact more or less successfully to develop, produce, distribute and diffuse methods for generating goods and services" (133). Miller (2007) notes that these networks extend beyond simply a heterogeneous group of actors: "a whole set of intermediaries circulates among them. These [intermediaries] give material content to the links uniting the actors. They may be written documents, technical artefacts, human beings, or money" (710). Techno-economic networks have grown to include technology transfer offices, funding agencies, policymakers, venture capitalists, and so forth (Popp-Berman, 2012), and have continued to increase in complexity given the interdisciplinary and data-accelerated nature of contemporary R&I in the biological sciences.

As discussed in Chapter Two, the concept of a *mediating instruments* has been discussed at length in the accounting and economic sociology literature, largely in the context of the broad range of financial and economic models (Morrison and Morgan, 1999), instruments, metrics, and mechanisms related to practices of calculation, valuation, budgeting, and computation (Miller, 1992; Miller and O'Leary, 1987). These instruments serve to mediate the interactions between science and economics, shaping the ways in which science is governed and regulated, as well as the means by which the products of R&I may be exchanged (Miller, 2007: 708; see also Power, 1994). Others have similarly defined *market devices* as "the material and discursive assemblages that intervene in the construction of markets," encompassing "analytical techniques to pricing models, …purchase settings to merchandising tools, …trading protocols to aggregate indicators" (Muniesa, Millo, and Callon, 2007: 2; see also Muniesa, 2007).

As previously outlined, I expand the concept of intermediaries to include various forms of open and proprietary mechanisms (Chiappetta and Birch, 2018). I theorize these mechanisms as *mediating devices*, building on the premise that particular open and proprietary devices enable public and private research groups, government regulators and policymakers, and investors to

interact, collaborate, and bring commercialize innovative research. The interview data discussed above suggest that certain mediating devices – particularly patents, MTAs and RTLAs, and open licenses – are the linchpins in these techno-economic networks that enable collaboration, commercialization, and knowledge transfer, *as well as the management of value in the development and commercialization of assets and products in the life sciences* (ibid: 67). They play a critical role in configuring the organization and governance of R&I as well as in the valuation of its byproducts, and further dictate the ways in which research results are circulated and disparate groups collaborate. Moreover, they attach value to the interactions between actors in this particular techno-economic network (e.g. by stipulating potential royalties) (Birch et al., 2017). The role of mediating devices is equally important in discussions of commercializing new technologies, particularly as academia excels at discovery but not development and public-private partnerships become increasingly important as research is translated (Stephan, 2012). This will be discussed further in Chapter Seven in the context of broad upstream patents and the use of open devices downstream.

This, then, leads to a discussion of the necessary and sufficient conditions required to commercialize new pharmaceutical research. Based on the interview data discussed above, external investment hinges on the ability to recoup the costs of development and marketing, which is in turn determined by the proprietary nature of the mediating devices used in sponsored research agreements or public-private partnerships. Reiterating the importance of proprietary devices in the commercialization process, the VP of Research and Innovation at one of Toronto's research hospitals stated:

> The most commonly used commercialization vehicle is licensing. So open [science] is nonsense, [R&D] becomes open as soon as we file the patent application, and in many cases we don't file patent applications so it remains trade secret. Our goal is actually to commercialize – I want to commercialize for the betterment of patients but oh by the way, I'm not shy about making money, because that feeds back…into

> the discovery engine. So, licensing agreements and material transfer agreements are currency (VP Research and Innovation, 2017).

Beyond emphasizing the necessity of proprietary devices, interview participants also highlighted the detrimental effect of open devices on the commercialization of new products. A tech transfer officer at a large non-profit institute in Toronto articulated the issues associated with open devices when translating new assets from the lab to the market. They stated:

> Intellectual property is like the first [check] that we need to see before we even think of commercialisation. So we work heavily based on intellectual property and intellectual property alone primarily because the state at which we vet technologies is so early that it's considered actually pre-pre-seed. If there's any Copyleft in [a negotiation], it really screws things up our ability to market the product or even to commercialise it, because now we have to offer it as Copyleft too. So, that's problematic when we incorporate third party Copyleft into our [transactions]. I can't go to [a large biotech firm], offer them a piece of software to incorporate if that software is based on Copyleft work, because that means it's going to contaminate their whole platform and now they no longer can sell their platform. They have to offer it for free, too. It's just not feasible commercially (Tech Transfer Officer, 2017).

What can be extrapolated from this is that proprietary devices are considered the best vehicle for commercializing new assets. Miller and O'Leary (2007) have previously highlighted the means by which certain mediating instruments "…link science and the economy through acting on capital budgeting decisions, and in doing so how they contribute to the process of making markets," where mediating instruments "refer to those practices that frame the capital spending decisions of individual firms and agencies, and that help to align them with investments made by other firms and agencies in the same or related industries" (p. 702). Stemming from this, I argue these mediating devices, as articulated above, similarly link science and the economy by constituting the ways in which knowledge and information are circulated and in which disparate groups collaborate. Moreover, by attaching value to the interactions between actors within techno-economic networks and regulating how value may be appropriated from the products of these interactions, these devices are fundamental to either accelerating or hindering innovation and the

commercialization of new technologies (Lezuan and Montgomery, 2015). As will be discussed further in the next chapter, distinguishing between the development and commercialization of *tools* versus *products* is critical to understanding in which contexts and at which points in the innovation process open devices may in fact be the best vehicles for developing new assets, in contrast to the proprietary devices discussed above.

5.5. Conclusion

This chapter focused on the concept of innovation – how it is defined, how it is measured, what motivates actors in Toronto's R&I ecosystem to innovate, and what factors affect its funding and commercialization. Section 5.1. endeavoured to evaluate the numerous and varying definitions provided in both the innovations studies literature and by interviewees, and evaluate how these definitions are shaped and change depending on the location of the actor within a particular techno-economic network. The purpose of this chapter was to highlight the ambiguity of the concept of *innovation*, and discuss the ways in which the definition of the term changes from the perspective of research scientists, executives, IP managers and so forth. As outlined by Quintane et al. (2011), understandings of innovation in both the innovation studies literature and amongst interview participants fell into three categories of processes, outcomes, and new knowledge.

Section 5.2. evaluated the ways in which innovation is (mis)measured, focusing on the use of patent statistics and other macro-level means of quantifying innovativeness. Interview data suggested that patent statistics are a misleading but easy quantitative metric of productivity, and further that measuring the innovativeness of a new product or process extends beyond the use of quantitative metrics (namely patent statistics) and involves a more complex process of technology pervasiveness and worth attribution that incorporates labour, market growth, monetary inflow, consumer base and so on.

Section 5.3. briefly discuss the drivers of pharmaceutical R&I in Toronto's innovation ecosystem, and in particular the relationship between the lack of public funding for research in Canada and the consequent profit-driven nature of research. What can be inferred from the interview data discussed is that ROI remains a motivator for industry support of R&I along the innovation spectrum, even further upstream where application value is less certain and commercial relevance is unclear. Public-private partnerships and research agreements are formed on a contingency basis where funding is provided with the understanding that industry will have an option or first right of refusal on the IP produced. Simply, the option to commercialize (and profit) from R&I remains the primary motivator for industry-funded R&I.

Finally, section 5.4. discussed at length the funding and commercialization of R&I in this sector, focusing specifically on the role of mediating devices in attracting external investment as well as the ways in which these devices affect the commercialization of new technologies. The data discussed in this section suggests that funding decisions are often motivated less by the desire to accelerate breakthrough discoveries or foster a more innovative ecosystem, than they are by business cycles and windows for conducting initial public-equity offerings. Moreover, what is clear from this data is that proprietary devices are the best vehicle for commercializing new assets, though as will be discussed they may hinder innovation in large collaborative arrangements. Additionally, factors affecting the use of mediating devices such as patents, MTAs, or open licenses, extend beyond a researcher group's immediate circumstances to the broader techno-economic network of which they are a part. More specifically, macro-level comprehensive policy decisions regarding federal R&I budgets affect the mediating devices used in public-private research agreements and in academic tech transfer offices.

The chapter will focus on the architecture of pharmaceutical R&I in Canada, specifically as it relates to the use of open and proprietary mediating devices. Further, it will discuss the role of

these mediating devices in shaping collaborative efforts within and between the intermediaries at hand.

6. Mediating Devices and the Architecture of Research and Innovation

A central feature of the techno-networks outlined by Callon (1993) are *intermediaries*, which referred to "anything passing between actors that defines the relationship between them" (Miller and O'Leary, 2007: 709-710). These intermediaries, referred to in this dissertation as *mediating devices*, form a central component of research and innovation in the pharmaceutical sector; I argue that they are inherently embedded in the architecture of R&I. Elsewhere, Miller and O'Leary (2007) have outlined the means by which certain devices "link science and the economy through acting on capital budgeting decisions, and in doing so how they contribute to the process of making markets" (p. 702). In this context, they are referring to "those practices that frame the capital spending decisions of individual firms and agencies, and that help to align them with investments made by other firms and agencies in the same or related industries" (ibid). Here, I argue that mediating devices similarly act on techno-economic networks by constituting the ways through which knowledge and information are circulated and in which disparate groups collaborate. More specifically, I argue that mediating devices configure the ways in which actors within these networks collaborate and transfer knowledge across institutional boundaries, for instance by subjecting collaborative agreements to lengthy and onerous legal conditions or by hindering knowledge transfer via significant administrative bottlenecks at university technology transfer offices (TTOs).

This chapter addresses research question 2: *Which proprietary and open devices are used in pharmaceutical R&I? For whom, and why?* Specifically, I focus on specific mediating devices in the context of the broader architecture of research and innovation. I first discuss material transfer agreements (MTAs) as they relate to academic TTOs, emphasizing the difficulties and costs associated with executing MTAs and the impact of these costs on pharmaceutical research and

innovation. Secondly, I discuss how mediating devices configure collaboration agreements, focusing specifically on the effects of proprietary contracts and open databases and libraries on research and innovation. Finally, I discuss patents and their role in the legal architecture of research and innovation, highlighting how they (re)configure the commercialization of new pharmaceutical products in Ontario and the implications this has for the use of open devices. The primary argument in this chapter is that mediating devices – primarily proprietary devices – are inherently embedded in the current architecture of research and innovation. The embeddedness of proprietary devices has resulted in an additional layer of in/tangible administrative costs and onerous legal negotiations being added to the R&I process that, more often than not, makes the use of open devices especially difficult and impedes innovation in this sector.

6.1. The Institutional Architecture of Academic Research and Innovation

As discussed in Chapter Five, mediating devices help actors attach value to their interactions within techno-economic networks and regulate how value may be appropriated from the products of these interactions. To illustrate, in this context, interactions may occur between potential investors and primary investigators of research labs (PIs), or between TTOs and research institutes (e.g. moving biological materials from on lab to another). At each point, mediating devices define the terms of the interactions between these actors, most notably by outlining property rights and ownership (Mirowski, 2011) stipulating the terms of collaborations through MTAs, NDAs, or other contractual arrangements, thereby helping to commercialize new technologies (Scherer, 2002), and acting as linchpins in the establishment of business models (Hope, 2008). These devices are fundamental to either accelerating or hindering innovation and the commercialization of new technologies. Here, I argue that (proprietary) mediating devices can hinder R&I by exhausting financial resources and creating administrative bottlenecks at universities.

This section focuses on mediating devices in the context of TTOs, and in particular on the ways in which proprietary devices executed by academic TTOs can create bottlenecks in the R&I process and drain capital from these institutes. Mediating devices are important here as they are the *things* that link labs, universities, industry, and government – in the form of contracts for research agreements, material transfer agreements, platforms in which shared research materials and data are housed, and so on. They facilitate collaboration between these entities, and they enable commercialization by allowing for the translation of research across institutional boundaries where it can be further developed. Academic TTOs are an interesting case in understanding the impact of mediating devices on R&I, particularly because they are the sites at which a large majority of research contracts, MTAs, and patent applications are executed and filed for research in the life sciences.

As outlined in Chapter Two, the passage of the *Bayh-Dole Act* in 1980 created a new marketplace for knowledge and its byproducts and (further) blurred the boundary between the university and industry (Mirowski, 2011). In determining that the market "[was] the best way of getting university breakthroughs into the hands of the public, and patents create the incentive that [made] that happen," universities began to develop technology transfer offices with the idea that patenting research was necessary to attract investment in research projects (Popp-Berman, 2012: 6). TTOs operated (and continue to operate) under the principle that "universities had a responsibility to patent to prevent publicly funded research from languishing unused… Simply creating knowledge and making it accessible was not enough. Universities needed to harness the power of the market" (ibid: 95). Through the fortification of patent rights in the ensuing years, and the enactment of patent policies and research regulations founded on the bedrock of ownership and profiting from one's ownership, universities were supposedly guaranteed a means of return on public capital investment in scientific research (Kraemer, 2006). The growth of university TTOs

following the passage of *Bayh-Dole* also helped to spur academic entrepreneurship across OECD countries, with patents "represent[ing] only one mechanism by which academic research results [were] transferred to the market place. Other mechanisms include[d] licensing, the generation of academic spin-offs, collaborative research, contract research and consulting," as well as joint publishing and networking with industry practitioners (Grimaldi et al., 2011: 1047). In effect, universities became *vendors* of science, as much as they were sites of knowledge production (Geiger and Sá, 2008).

Today, university TTOs in Canada and the United States focus primarily on drafting research agreements, promoting community engagement and research communication, facilitating external partnerships (e.g. between university labs and industry partners), nurturing early-stage and proof-of-concept discoveries and facilitating the transfer of these ideas into marketable products, and licensing/commercializing intellectual property (see Massachusetts Institute of Technology, 2019b; University of Toronto, 2019; York University, 2019). MIT's Technology Licensing Office defines technology transfer simply as "the movement of knowledge and discoveries to the general public," occurring via "the formal licensing of technology to third parties" (Massachusetts Institute of Technology, 2019b). Grants to third party licensees may include established companies or new startups, while license requirements generally stipulate terms "that require the licensee to meet certain performance requirements and make financial payments" to the home institute where the TTO is located (ibid, 2019a).

Figure 1 below illustrates the technology transfer process from the initial submission and disclosure of a new technology through the patenting/protection phase and finally the commercialization of a marketable product.

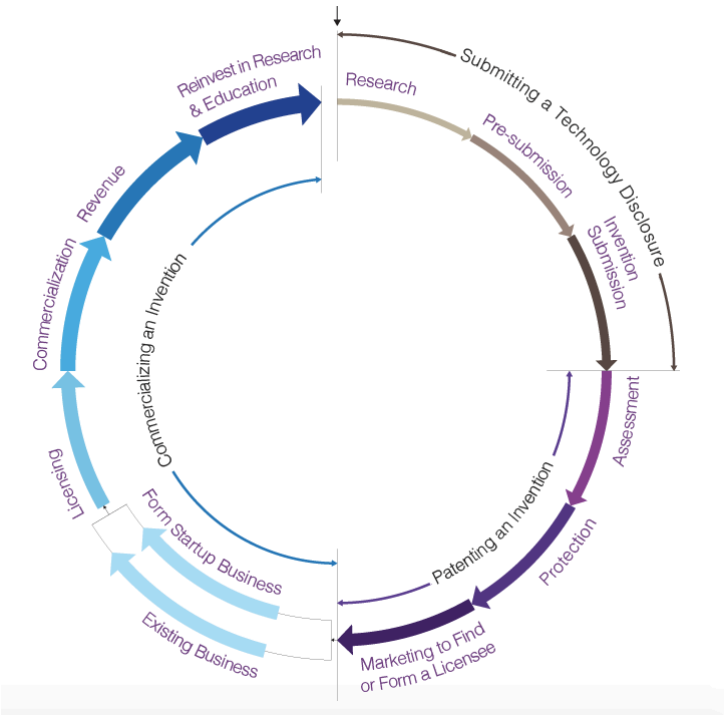

Figure 1.: The standard academic tech transfer process (source: Massachusetts Institute of Technology, 2019b)

During the patenting and protection stage, both financial and non-financial terms of the license are established: financial terms typically include annual fees, royalties, and equity shares (if a startup, rather than a product, is established), while non-financial terms generally include (non)exclusivity of the license or contract, and due diligence requirements of the licensee (ibid, 2019c). During this stage, the TTO also drafts and negotiates other proprietary devices beyond patents, including non-disclosure agreements (NDAs), MTAs, reach-through license agreements (RTLAs), and option agreements. In the context of university TTOs, NDAs are used "to protect the confidentiality of an invention during evaluation by potential licensees," as well as proprietary information used in research (ibid). Likewise, option agreements grant a third party the right to "evaluate the technology and its market potential for a limited time before licensing," providing them with a non-commercial, internal-use license for a fee while they assume responsibility for the payment of patent costs during the option period (ibid).

According to a 2017 survey by the Association of University Technology Managers, start-up formation in Canada increased 11% between 2016 and 2017, and 95% between 2012 and 2017 (AUTM, 2017a). Further, in an increase of 62% since 2016, 907 start-ups were reported to be still operational at the time of the survey (ibid.) As the report notes, what can be inferred from these statistics is that "the role the technology transfer office (TTO) plays within an entrepreneurship ecosystem is growing and impactful. Recognizing that most university start-ups are formed around patented technology, this prolonged growth and increased survival rate reflect research showing that start-ups with patents are 35 times more likely to be successful" (ibid: 3).

Mirowski (2011) argues that the introduction of MTAs (and their associated RTLAs and NDAs) from the mid-1980s onwards demonstrates the beginning of universities resorting "to contracts over research tools to control research happening in other universities" (p. 155). These devices are legally protected contracts facilitating the exchange of materials (e.g. cell lines or sequenced proteins) for safekeeping (e.g. in gene- or biobanks), for research or commercial use (Rodriguez, 2005). They may apply to "anything from materials that are simply under the control of the originator but have no formal intellectual property rights attached to them to proprietary materials protected by patents and trade secrets" (Bubela et al., 2015: 2). They transfer *possession* of the material in question, not *ownership*, meaning that the original party can still assert ownership rights (ibid).

MTAs vary in their complexity, with some TTOs or organizations (such as the NIH's Uniform Biological Material Transfer Agreement [UBMTA]) offering a boilereplate contract with simple conditions (i.e. that an organization will not make any proprietary claims on byproducts of the material in question (Rodriguez, 2005). Others stipulate more complex legal conditions, such as limitations on publications and asset distributions, and controls on the development and use of material derivatives (ibid). These legal conditions may actually expand the rights of the institution

(e.g. the university at which a researcher is employed), particularly in the case of RTLAs. Unlike patents, MTAs include the material in question *and its associated data* as the subject matter of the license in question. As a result, Bubela et al. (2015) note "the terms of an MTA may…extend rights beyond the patented invention if they 'reach through' the patent to lay claim (e.g. for royalties) on anything developed using the invention or that incorporates the invention" (pp. 2-3). Examples of this include new inventions that use a previously patented amino acid sequence, a patented nucleotide, or developed using a patented reagent (ibid.).

In his critique of RTLAs, Mirowski (2011) describes their use as "ransoming the future of [ones] research to someone whose only contribution was the provision of a single material accessory input into the process" (p. 155). Posner (2012) also emphasizes the capacity of contracts such as MTAs and RTLAs to limit the ability of the receiving party to freely conduct research, stating "if the only people who have access to your property happen to be the people with whom you have a contract, you can regulate their access by means of contract and forget about property law" (p. 6).[5] As discussed throughout previous chapters, these types of mediating devices operate in the spaces between actors within techno-economic networks. Not only do they directly dictate ownership (or lack thereof) of the byproducts of research, but they also indirectly impact innovation by necessitating onerous legal or administrative work, such as in the case of MTAs executed by academic TTOs. Consequently, beyond simply placing research materials within legal confines, these devices outline the working relationships of academic researchers and their industry (or other academic) partners, in effect dictating the terms of collaboration.

[5] The difference between contract versus property law is an interesting tangent here. In the case of MTAs and RTLAs, there is a fundamental shift in the ways in which ownership and the control of property are exercised. With the use of a contract, IP is licensed rather than owned. In these cases, value comes from the contractual costs imposed on the licensee (see Birch and Muniesa, forthcoming).

MTAs and RTLAs can prove prohibitively costly, in terms of the actual associated financial costs for all parties involved but also in the time and resources required for university TTOs to execute them. As Lave et al. (2010) point out, as academic capitalism has expanded and university research has become increasingly commercialized, a growing number of research tools (even the most basic and commercially irrelevant) have become encumbered by these proprietary devices. Moreover, Mirowski (2011) notes the disparity between the operating costs associated with executing MTAs versus the profits that academic TTOs make from them. Aside from the transactional costs associated with these particular devices, the institutional costs associated with MTAs can hinder innovation given the time and experience required to execute them. As the Director of a large research consortium in Toronto noted:

> A material transfer agreement on average, if things go well, takes a month to execute. The University of Toronto alone executes a thousand per year, with the majority delayed. That is about equivalent to 100 person years [to execute]. In the biotech/pharma sector one fulltime [employee] equivalent – if you were running a company and you hire someone, you say how much money do I have to hire that person? It's about $200 to $250,000 [annually]. That's a fully loaded, fulltime equivalent and includes the [rent] of that person, the healthcare costs, the consumables, the HR team that, you know, all in. So, if you take 100 person year delays, times $200,000 per year per person is what it costs. So, trying to equate the delay into an economic terms like lost opportunity costs or something, comes out to about $20,000,000 in the hole at the University of Toronto just based on their policy of executing [these devices]. Now does this sort of MTA process slow down innovation? Well, it does and to me, and it slows it down by about $20,000,000 a year (Director, 2017).

A Technology Transfer Officer at one of Toronto's large research institutes similarly highlighted the negative effect executing MTAs and other contracts had on innovation broadly, stating:

> Yes, it's a hindrance in that the researcher can't transfer [materials] until the MTA is done. The problem is the legal departments and the TTOs that represent these researchers, they're inundated with other work so an MTA that you think should take a day actually takes six months because we're dealing with bureaucratic processes on both ends…So in my opinion, the MTA itself is not the issue, it's the amount of time that the legal department in every single institution takes in reviewing these documents. And again, when you look at it from the perspective of a legal department within an institution, there are a handful of them, like lawyers or contract agreement

> reviewers and they have thousands of agreements to go over (Technology Transfer Officer, 2017).

Likewise, the Direct of Intellectual Property at a large non-profit organization in Toronto emphasized the detrimental impact of limited human capital on the execution of these proprietary devices, and its subsequent impact on innovation, stating:

> Well [these devices] slow stuff down, I wouldn't say they stifle. [Using these devices] definitely slows down innovation because you're saying I won't send you the materials until you sign this document and then our legal [team] looks at it and then their legal [team] there looks at it says 'Oh you have to change this clause' or 'We don't like this' and then come back and so that to me is the biggest hold up. So academic legal council needs to change how they operate because it's crazy slow… The issue is people as a limited resource (Director of Intellectual Property, 2017).

Importantly, these costs are not just institutional in nature – they can mount up on a national scale and affect the budgeting of universities (see Deering and Sá, 2017). As discussed in the previous chapter, for example, the Canadian Government's 2018 R&D budget allocated $9.8 billion *over five years* for scientific R&I (translating to roughly $1.96 billion per year) (Science and Economic Development Canada, 2018). It costs roughly $55 million annually to run technology transfer offices across the country with a return of $62 million, for a net revenue of $7 million on a $1.96 billion annual budget (De Baere and Maine, 2018). In a study conducted of roughly 2,100 biomedical science researchers and faculty members act American universities (Blumenthal, 1997), 19.8% of respondents reported "delaying publications of research results for greater than six months in order to prepare and file patent applications, to provide time for patent prosecution, to protect their intellectual property rights, or to resolve contentious intellectual property ownership issues" (Mgbeoji and Allen, 2003: 87). Moreover, the study found that these publication delays correlated with research groups collaborating with private firms attempting to commercialize university research, particularly given the involvement of university TTOs. The study concluded that "withholding results was not a common practice among life science researchers, but was much more

prevalent among faculty research groups pursuing university technology transfer opportunities and corporate partnerships" (ibid).

Clearly there is a significant cost associated with executing MTAs and filing patent claims. Devices such as MTAs "give material content to the links uniting the actors" and in turn determine "the multiplicity of possible interactions that can arise" between actors within techno-economic networks (Miller and O'Leary, 2007: 710). The above quotes suggest that mediating devices such as MTAs *themselves* may not necessarily inhibit innovation (or at least not to the same degree as suggested by Edwards et al., 2017). Rather, their embeddedness in this institutional research and innovation architecture and broader techno-economic network – and by extension, the in/tangible administrative costs that arise in executing several thousand MTAs between several thousand research institutes annually – can have a particularly detrimental effect on both collaboration and knowledge translation. Undeniably, research materials are generally costly to produce, and supplying them freely to third parties may be financially impractical. However while MTAs do enable the distribution of research tools, the onerous legal negotiations and delays that are associated with their execution may in fact discourage the use of the materials that come under their purview (see Walsh et al., 2003, 2005; Murray and Stern, 2007).

6.2. Mediating Devices and Organizational Collaboration

Extending from the discussion above, the question of how mediating devices impact collaborative arrangements is raised. If, as argued, mediating devices are situated within complex techno-economic networks between actors, determining at what point in the R&I process actors within these networks interact, it is important to unpack how both proprietary and open mediating devices configure these interactions – in other words, whether they help or hinder collaboration. This section focuses on proprietary contracts and open access data libraries and screening

platforms, and their respective impact on collaborative research arrangements. In doing so, I discuss the impact that open and proprietary devices have on collaboration efforts in the pharmaceutical sector, and evaluate whether they facilitate or hinder innovation in the sector.

6.2.1. Contracts and Collaborative Arrangements

In the pharmaceutical sciences, R&I generally occurs in the form of public-private partnerships, sponsored research agreements, physical and virtual networks, and research consortia (OECD, 2011). What these formats have in common is the constant exchange of knowledge and information between groups of scientists, lawyers, tech transfer officers, investors, and so on (ibid). As the STS literature has emphasized throughout the field's existence, knowledge is collectively constituted, meaning that collaboration is an intrinsic aspect of the R&I process, though what varies is the degree of openness inherent in these collaborations (ibid.). The degree of openness in these collaborative efforts is necessarily determined by the mediating devices used in these collaborations: whether negotiations are open or closed to external actors, whether the research in question and its byproducts will be enclosed behind proprietary barriers (e.g. NDAs, patents) or released into the public domain. These devices can have a fairly innocuous effect on collaborative arrangements: many contracts can act simply as a means of outlining the relationship between two or more actors. Lezuan and Montgomery (2015) argue that it is the initial proprietary IP that attracts others into a partnership, and ultimately, proprietary IP devices are the tangible assets that structure the process of relaying research between collaborators. As a tech transfer officer at a large provincial non-profit organization stated:

> The MTA and NDA frame the relationship [between research partners]. Service agreements and sponsored research agreements also have an additional benefit where they create a relationship and clearly outline who is responsible for what, so there's no confusion or legal issues on the back end (Tech Transfer Officer, 2017).

They also outlined the "instinct" to add a layer of exclusivity when outlining these relationships in contractual agreements (particularly in the life sciences), noting "we [want a degree of exclusivity] one, to make sure they don't steal our idea, but two, because I want to talk to them before partnering. I want to know if it makes sense for us to invest our resources in this relationship without losing any IP or trade secrets I bring in" (ibid). At the same time, however, the same tech transfer officer noted:

> I've been on the other side, too, where somebody's saying sign this NDA and there is something there that formalizes the relationship to a degree and it's a hindrance because you can't talk as freely as you otherwise would. And now you got to get some other third party involved to sign an agreement. And agreements take a lot of time to review and approve, so it slows down a lot of things (ibid).

While the instinct or predisposition to add a layer of exclusivity to research agreements is useful in outlining the responsibilities and expectations of all parties involved, it configures collaboration in particular ways. Even in cases such as large research consortia where proprietary devices are not used, open research agreements similarly act as a means of clarifying and outlining the relationship between two or more parties (see Hayden, 2010). The Director of one such consortium in Toronto noted the ease with which the standard collaborative contract they employed had expedited the collaboration process:

> The more we got into it the more we realized how powerful our open agreement was. Because when we met with collaborators and said, "we're not going to file a patent, we're keeping this one open" – it was like a three second collaboration deal and off we go. And so, our transparent policy of openness allowed us to collaborate with a bang and get more science done per dollar invested in us. But in our current organization we have such a transparent agreement that we can decide literally in seconds whether [a partnership] is going to be feasible. So, if a company comes to us and says would you like to collaborate and what we would like out of it is to get X, Y, and Z and if we find anything we'd like to patent it, we just say no. We're the ones who don't do the deal because our principle is that we will never enter into a collaboration where the expressed intent is to file a patent on research and our agreement makes that clear (Director, 2017).

In contrast, as discussed in Section 6.1, these proprietary devices can also act to create bottlenecks and generally slow down efforts to innovate through collaborative efforts. By adding a proprietary

dimension to research partnerships, some interviewees argued the inclusion of a patent requirement or NDA in a research agreement diverted focus away from the actual research being conducted and towards profits. The Managing of Operations of a large incubator lab in Toronto noted as much, stating:

> I feel like people don't even have a good opportunity to get collaborative and start working. If you start thinking about patents or who can and can't discuss what right out of the gate, don't even waste your time… I strongly discourage people from worrying about patents on Day 1 because I think you will discover things along the way that you have absolutely no idea that you're even looking for yet. But if you start worrying about the patent as the first step, you're probably going to be stymying your own efforts because you'll pigeonhole yourself too soon. This extends to partnerships, when the concern becomes about the patent and the profit, and not the innovation (Managing of Operations, 2017).

As suggested above, focusing primarily on IP often results in one looking for IP-relevant findings. Likewise, the CEO of a small biologics firm and scientific advisor to a large VC firm in Toronto outlined the particularly unfavourable effects of proprietary mediating devices on collaborative arrangements:

> At the micro level, [proprietary devices] certainly create a barrier, right. If I want to collaborate with someone, we've got to put in place a contract, we've got to spell out intellectual property rights and who owns what and fair royalties and things like that, going back and forth – we have to do that and that takes time and it takes money and you have get lawyers to outline those contracts, and all that just means that none of the research is getting done (CEO, 2017).

Similarly, the Director of Fund Operations of a large provincial research trust also highlighted the negative impact of proprietary devices on collaborative agreements, stating:

> I've come across a few contracts that say, basically, we co-own whatever you create, or you're giving us an exclusive license to commercialize this. And, our opinion is that's simply trying to profit off of our work, not help us do the work. Because we're not a contract research organization. So, if you give us money, it's an academic relationship, we're not a lab for hire. So, you don't get to own inventions that we create (Director of Fund Operations, 2017).

What these quotes suggest is that in theory, proprietary mediating devices do not necessarily create a barrier to innovation or inhibit collaboration, particularly as seen in the context of research

consortia like the SGC where openness is laid out explicitly at the front end of a collaborative negotiation. Rather, proprietary devices such as patents, MTAs, and NDAs tend to configure collaborative relationships as transactional relationships where the primary focus is on are ownership and profit.

6.2.2. Open Databases and Collaboration

As discussed in previous chapters, the shift in focus of research from objects (e.g. the gene, the protein) to systems (e.g. the genome, the proteome) in the late 1980's resulted in scientific R&I becoming largely data-accelerated, interdisciplinary, and increasingly dependent on databases, libraries, and screening platforms. Researchers rely heavily on databases to interrogate nucleotide sequences of interest, compare protein sequences, and search for sequence data in particular disease contexts (Birch et al., 2018). For example, gene therapy in cancer research has become increasingly reliant on research commons for the development of sequence data (i.e. gene, protein, or other transcript sequences). In the case of structural genomics, high-throughput technologies employed to determine the three-dimensional structure of proteins used in drug targeting and discovery are expensive to run and maintain, with the average cost of deciphering a protein structure estimated to be roughly US$300,000 (Chandonia and Brenner, 2006; Sá and Tamtik, 2011). As Stephan (2015) notes, while some of the equipment used in contemporary R&D, "…although expensive, [is] still affordable at the lab or institutional level. Some, however, such as nuclear magnetic resonance (NMR), [carry] sufficiently large price tags *to encourage, if not demand, collaboration across institutions*" (339, emphasis added). Traditionally, drug discovery also involves substantial preclinical optimization (e.g. detailed studies of drug potency, safety, pharmacokinetics), "which significantly increases the resources, time, and risk associated with developing new medicines" (Janes et al., 2018: 10750). As such, discovering new therapeutic drug

targets and new clinically relevant compounds is "a Mount Everestonian size task" in terms of both the breadth of data that must be evaluated and the financial resources needed to conduct such evaluations (Roy et al., 2010: 764).

The challenge and resource-burden of accessing data that would otherwise be prohibitively costly to duplicate is mitigated by the availability of open devices such as open screening libraries and platforms (Janes et al., 2018). Open devices allow researchers to leverage "prior investments in medicinal chemistry, pharmacology, and toxicology, which helps to focus, or even eliminate, resource intensive chemistry and profiling" efforts (ibid: 10750). Moreover, as Lezuan and Montgomerey (2015) note,

> Where the traditional profit incentive is seen as inoperative or too uncertain to warrant risky expenditures on research, the key is to create new communities of sharing, to trigger processes of reciprocal exchange that will reactivate the circulation of resources. Actors with the relevant expertise and capabilities—academic institutions, governments, philanthropic organizations and, critically, pharmaceutical companies—must join forces and launch new collaborative ventures (p. 5).

As discussed in Chapter Two, openness enables heterogenous collaboration by establishing ease of engagement, while open science initiatives "tend to involve collaborative projects that pool the work of many participants and make advances available to a broad community," ensuring that research results are non-proprietary (Feldman and Nelson, 2008: 25). The CEO of a small biotech firm, and faculty member of a large research hospital in Toronto highlighted the research opportunities afforded by open drug screening platforms, stating:

> That [open screening library] was a huge, huge benefit to us because it meant that we didn't have to go and assemble our own library of compounds as our initial screening tool. We had our own hundred thousand compound library in-house but you didn't even go to that big screen until you put it through the first openly licensed one in order to just see if anything stuck. We started all of our screenings with that library of pharmaceutically active compounds, …and we used those as our jumping-off points to start any drug discovery process because as much as we have an in-house compound library, and as much as we had hundreds of thousands of compounds in the library, starting with a broad set of data presents, obviously, a much greater computational challenge to try and crunch that, analyse all that, and the existing

> technology is such that you can't just start with a really, really big screening set and try to go looking for something. It's just an intractable problem (CEO, 2017).

Similarly, the Manager of a large incubator lab in Toronto underlined the potential usefulness of open repositories of data, particularly for researchers undertaking upstream drug discovery projects:

> But I'm wondering if you're right, that if we could make more freely available the consolidation of all these companies' data to anyone doing drug development, and we say we've all pooled our resources and this is the cherry-picked, best starting point, screening set. Something like that might be really, really cool, really cost and time effective. It would be really advantageous to say, you've got your best probability of success if you start by at least screening this compound library (Manager, 2017).

Highlighting the efficiency of having some degree of openness in the R&I process, the same Manager also stated:

> If you look at not just the individual players here, but if you think about all these companies existing in the same sector, and if you think about just the loss of productivity of everybody, in theory, starting the same or similar project at once and they're all starting from scratch, think of just the loss of potential of people screening the same dead ends and the same bad ideas but not telling each other that they're doing it. I'm thinking about it, not about individual companies, but just about the productivity of the sector on the whole. There must be so much lost in terms of resources, so much lost utility, of everybody doing the same bad ideas and following the same bad leads at the same time until they all weed out those early bad ideas and start getting on with something that actually looks promising (ibid).

As Janes et al. (2018) have noted, the use and availability of open databases of chemical compounds and drug targets dramatically reduces the time and resources required to translate upstream research through trials and into clinical setting. Having "more eyes" going over data sets and research results necessarily leads to products with low or no commercial potential being weeded out of the R&D process sooner (ibid). Further, collaboration is facilitated by the ease of access to research materials. While this differs from the collaborative arrangements seen in proprietary contract research agreements (where the results of R&I remain confidential between the participating parties), contributing data and research materials (i.e. sequence data or crystal

structures) to open databases is nonetheless a collaborative effort. Examples of these multidisciplinary, international efforts include the Structural Genomics Consortium (SGC), the Repurposing, Focused Rescue, and Accelerated Medchem (ReFRAME) Initiative, the Human Genome Project, and the International HapMap Project, all of which receive public and private funding. In each example, "participation extends beyond a single lab, institution, or research contract, commercial barriers to entry are low, and participation is not limited by proprietary restrictions" (Birch et al., 2018: 602).

By mediating between non-proximal actors within a broader network, open devices such as screening platforms or data libraries have effectively changed the spatial pattern of collaborations, creating commons-like research networks and allowing more disparate, heterogeneous teams of researchers to work together (Hoekman et al., 2019; Feldman and Nelson, 2008). The database or library, acting as an (open) mediating device, serves as an intermediary between actors within these broader networks. For example, the SGC releases its data into the Protein Data Bank, where it may be freely accessed by anyone with the requisite software (SGC, 2017a). In doing so, the SGC creates a cost-efficient way to ensure as many research groups as possible can coordinate R&I efforts and create new pharmaceutical products without having to duplicate prohibitively costly research. This is facilitated by the openness inherent in the devices employed by the SGC. ReFRAME is another example of a successful open access library facilitating collaboration by reducing barriers to entry, wherein a library of "roughly 12,000 high-value compounds composed of purchased or resynthesized FDA-approved drugs (38%), as well as investigational new drugs currently or previously in any phase of clinical development (59%), including 522 non-commercially available compounds" (Janes et al., 2018: 10753). Like the SGC, compounds included in ReFRAME are available to collaborators "around the world via a simple material transfer agreement, which contains a commitment to global access" (ibid). As per Hoekman et al.

(2010), the use of these open devices has effectively altered the proximal dimensions of collaborative arrangements, as the reduction of cost barriers has broadened who may participate in the drug discovery process.

As discussed above, mediating devices serve to configure the relationships between actors within techno-economic networks; these devices, operating at the nexus between disparate actors, can entail onerous legal and administrative deliberations in the collaborative research process. Conversely, open devices, such as open research agreements with no limitations on publication or disclosure beyond the requirement that collaborators not exercise intellectual property rights in a way that would preclude access to research results, are a means of increasing transparency in business practices (Gitter, 2013) and expediting R&I as a result. Moreover, as noted by several interviewees above, the inclusion of proprietary devices in collaboration negotiations adds a financial and bureaucratic burden to the process of outlining research agreements. Openness in this context may grant research groups (particularly those coming from academia) who "may not have the financial capacity to navigate the maze of patent rights and licensing" more flexibility in terms of their ability to collaborate (Feldman and Nelson, 2008: 25). As will be discussed in Chapter Seven, however, while openness lowers barriers to entry (see Hope, 2008), the current "rules of the game" are such that to be able to bring new drugs to market and to profit in this particular sector, protecting one's intellectual property and maintaining some degree of ownership is crucial.

6.3. Patents and the Legal Architecture of Research and Innovation: A Case Study of Patenting in Ontario

As discussed in Chapter Four, the *Patent Act* (1985) governs pharmaceutical patents in Canada, outlining patentability criteria, establishing standards of patent enforcement, and providing a minimum period of market exclusivity for disclosures of inventions (Hore, 2004). The *Patent Act* originally conferred an 18-year period of exclusivity on new disclosures, though

following litigation on behalf of the United States through the World Trade Organization Canada has since adopted a fixed 20-year patent term (WTO, 2001). This section briefly outlines the legal mechanisms that embed proprietary mediating devices into the architecture of research and innovation and end up making open devices untenable options for firms commercializing new pharmaceutical products.

In 1996, the Government of Ontario mandated pharmaceutical manufacturers with products approved for sale by a federal regulator (Health Canada) to apply to the Ontario Formulary, a document listing pharmaceutical products for which reimbursement is provided by the Ontario Health Insurance Plan (OHIP) or the Ontario Drug Benefit Program for seniors (PausJenssen et al., 2003). The Formulary acts as a guide to physicians and pharmacists for which drug products are covered through provincial health insurance, which products may be interchangeable (e.g. in the context of brand name versus generic products), and, importantly, sets the provincial standard for the price of drug products (Government of Ontario, 2019). Manufacturers seeking to list their products on the provincial formulary are required to provide a comprehensive economic analysis outlining the cost effectiveness of the product, while "Formulary committees, once primarily focused on the clinical efficacy and safety of products, now consider economic issues when reviewing products for inclusion" (PausJenssen et al., 2003: 286).

The significance of proprietary mediating devices (particularly patents) as they relate to the Formulary was raised in a discussion with a senior partner of a major Toronto-based legal firm representing a large global pharmaceutical firm. Specifically, they noted that after the price of a patented drug is agreed upon and listed on the Formulary, ensuing (generic) market entries are priced accordingly. They stated:

> The reason I tell you that is that if [a large pharmaceutical firm] gets a licensed product on the Formulary, the second entry into the market will be at a lower price and the third entry will be at an even lower price. Where the license is a percentage of revenue, you don't want multiple players because that's going to decrease the costs,

> decrease the revenues and therefore decrease the royalties back. That's a reason why open licenses don't work… Legally, you can always command a higher fee for someone who has exclusivity. If the licensee has the monopoly, they can go to the pharmacies or the hospitals and say, "Look we're the only guys you can get the product from, our price is controlled but here it is." You can't do that without the proprietary license. So from my perspective as the lawyer and from the licensors perspective, without the proprietary license the revenue and the marketplace is lowered, driven down in part by generic competition and also the Formulary (Partner, 2017).

Essentially, this system ensures that the market is constructed on the basis of patent first, followed by a generic entry, thereby reducing costs but (at the same time) giving the monopoly price to the first (patented) mover. This suggests that not only are these proprietary devices embedded within the regulatory and oversight architecture of R&I, but they also configure the price of new drugs and the places these drugs are sold. They are not just *features* of this architecture; they are essential components of it – hence, competition within Ontario's drug market hinges on the tiered pricing system of the Formulary, in which the price of the patented drug determines the pricing of subsequent market entries.

Stemming from this, in highlighting the embeddedness of proprietary devices such as patents in the legal architecture of R&I, the CEO of a small biologics firm and Entrepreneur-in-Residence of a large global biotech investment firm noted,

> There's this whole onerous legal architecture that's all built to ensure that the dollars that investors put into our company are used to generate new intellectual property and that intellectual property is wholly owned or licensed, so it's a big deal for us. Any open license or open source would derail that investment for us (CEO, 2017).

In the above quotes, open devices are explicitly described as *things* that inhibit the competitiveness of new drugs on the market. Schumpeter (1942) argued competition had a negative impact on innovation, stating that the uncertainty inherent in competitive markets diminished any potential return on investment (ROI) and by extension minimized incentives to invest in R&D and innovate. Conversely, Arrow (1962) argued competition was the catalyst for innovation, and this debate has remained prominent in both economics and innovation studies over the last five decades (see also

Dixit and Stiglitz, 1977; Nelson and Winter, 1978, 1982; Romer, 1990). Vives (2008) highlighted more complex factors affecting the relationship between competition and innovation; specifically market size, entry costs, and product substitutability, where increases in product substitutability (e.g. access to generic drugs) encourages R&D, and larger market size may prompt investment in R&D. More recently, Negassi et al. (2019) found that there is a positive correlation between high competition and innovation in both the public and private sector. While this quote obviously does not demonstrate one way or another the quantitative effect of open devices on innovation, it does highlight the notion that the use of open devices is difficult even to conceive of given the entrenchment of their proprietary counterparts within the legal and regulatory architecture of Canada's pharmaceutical market.

Significantly, as discussed previously in Chapter Five, what this interview data shows is that factors affecting the use of mediating devices such as patents or open licenses, extend beyond a research group or firm's immediate circumstances to the broader techno-economic network of which they are a part (Callon, 1991). Callon's (1991) discussion of the relationship between science and capitalism makes the argument that political economy and technoscience cannot be divorced, particularly given the ways in which the former informs and shapes the latter. Miller and O'Leary (2007) also argue that certain devices – in this case, proprietary devices like patents – "link science and the economy through acting on capital budgeting decisions" (p. 702), and in doing so contribute to the process of making markets. In terms of broader policy implications, it is evident that macro-level regulatory requirements affect the mediating devices used in the commercialization of pharmaceutical products, and conversely, the use of these devices affects the market in which pharmaceutical products are circulated. Moreover, this data highlights the difficulties inherent in attempting to introduce a degree of openness into a system built on proprietary ownership and exclusion.

6.4. Conclusion

This chapter focused on specific mediating devices as they relate to the legal, administrative, and regulatory architecture of research and innovation processes. First, I discussed material transfer agreements as they relate to academic TTOs, noting in particular the difficulties and costs associated with executing MTAs and the impact of this on public pharmaceutical research and innovation. Second, I unpacked the impact of mediating devices on collaboration agreements, focusing specifically on the effect of proprietary versus open contracts on research and innovation. Finally, I discussed patents and their role in the legal architecture of research and innovation, outlining the impact they have on commercializing new pharmaceutical products in Ontario and the impact this has on the use of open devices.

These discussions suggest that mediating devices – primarily proprietary devices – are embedded in the broader architecture of research and innovation. The embeddedness of proprietary devices has resulted in an additional layer of in/tangible administrative costs and onerous legal negotiations being added to the R&I process that, more often than not, impedes this process. This is evident in the case of academic TTOs, where executing MTAs and RTLAs can prove prohibitively costly in terms of both financial costs and the time/resources required, in addition to the disparity between operating costs and profits. In the case of collaboration agreements, proprietary devices have the effect of reconstructing collaborative relationships into transactional relationships where the primary priorities are ownership and profit, rather than research and innovation. Finally, as the case study on patenting in Ontario suggests, the deeply rooted nature of patents in Ontario's legal and regulatory framework for commercializing new pharmaceutical products has perpetuated a system built on proprietary ownership and exclusion, and all but ensured that attempts to introduce a degree of openness into this system would be difficult to imagine and implement.

7. Evaluating Open and Proprietary Mediating Devices

The impact of open and proprietary devices on technoscientific innovation has been debated at length in the STS and innovation studies literature. As discussed in previous chapters, however, labeling open and proprietary mediating devices as strictly either facilitators or hinderers of innovation is reductive. For instance, some scholars have argued proprietary devices impede innovation in the biological sciences by limiting avenues of inquiry, obstructing collaboration and excluding certain groups from R&I, and creating bottlenecks through patent thickets (Heller and Eisenberg, 1998; Mirowski, 2011; Caulfield et al., 2011). Mirowski and Sent (2002) and Radder (2010) have also been critical of the ways in which proprietary, commercialized R&I is inherently self-limiting. In the legal context, Posner (2002, 2003) has been particularly critical of the ways in which expansive proprietary property rights limit the production of intellectual property itself. Other scholars, such as Lezuan and Montgomery (2015), are critical of the ways in which proprietary devices are described in the literature as a means of enclosing knowledge and information and entangling partners in long-term collaborations, arguing they are necessary for outlining collaborative research relationships and provide incentives for investing in research. They write:

> Rather than a tool to protect a market monopoly and exclude others from the use of a particular innovation, [proprietary] IPRs are…an attractor to bind diverse interests to a shared mission and give material reality to the new drug development enterprise. In other words, instead of demarcating public and private domains, property [devices] are used to increase the porosity of that boundary, allowing heterogeneous actors to come together around projects where that distinction is temporarily suspended (p. 7).

In this chapter, I address research question 3: *How do different devices facilitate or hinder collaboration and knowledge translation in this sector? At what stage in the innovation process are they most effective, and why*; and research question 4: *How can they be employed in the*

development of innovation strategies so as to streamline the process of drug development? In doing so, I first examine the impact of broad versus narrow patent claims and their impact on innovation. More often than not, the implementation of proprietary devices too early in the R&I process, particularly in the case of broad upstream patent claims involving tool compounds, results in bottlenecks that slow down or stop knowledge translation entirely. Conversely, the use of open devices downstream in the commercialization process of new drug candidates is likely to derail private investment. Following this, I conduct a case study of the open molecule JQ1, a tool compound used in the development of therapeutic products for certain types of cancer. The purpose of this case study is to highlight the importance of distinguishing between research *tools* versus marketable *products* when attempting to understand the overall impact of open and proprietary mediating devices on pharmaceutical innovation. I argue that the impact of these devices, in terms of both accelerating the translation of pharmaceutical research and encouraging collaboration, is dependent on two factors: firstly, when they are employed in the innovation process (i.e. upstream versus downstream); and secondly, what they are applied to (i.e. tool compounds used to develop candidate drug products versus the products themselves). As will be discussed, this is significant given the dichotomous and incompatible image of open and proprietary devices that is presented in the STS and innovation studies literature outlined above.

7.1. Broad Versus Narrow Patent Claims

Just as examining *when* these devices are employed in the innovation process is critical for understanding their net effect on innovation, so too is unpacking the scope of the research/knowledge/data enclosed by them. In the case of proprietary devices, specifically patents, the STS literature tends to present them as a dichotomy; as being either obstructions to innovation or catalysts of it (see Heller and Eisenberg 1998; Mirowski, 2011; Lezaun and Montgomery, 2015).

This section focuses specifically on the scope of patent claims and the subsequent effect on pharmaceutical innovation.

What does it mean to make a broad versus narrow claim? Typically, broad patent claims are made upstream and are speculative in nature (Canadian Biotechnology Advisory Committee, 2005). For example, a broad patent claim might be made on a molecule with potential commercial application for multiple diseases, while conversely, a narrow claim would be made further downstream after the molecule has been modified and refined so as to be directly applicable to one disease. For instance, patenting gene segments that are relevant drug targets for several disparate diseases would fall under the umbrella of a broad patent claim. In this example, researchers seeking to understand either the expression of the gene in question on a certain type of tumour or the impact of a chemical compound aimed at that genetic segment would be required to pay for access to that gene segment (Abbott, 2001). Stemming from this, the practice of "evergreening" involves obtaining multiple patents covering different features of the same product (Canadian Biotechnology Advisory Committee, 2005).

As Posner (2002) notes, the central principle of patent law is that market exclusivity is conferred upon the inventor on the basis of the patent application itself, in which novelty and utility are explicitly outlined. Moreover, the majority of intellectual property – "even of a distinctly innovative sort" – builds heavily on existing IP; thus, if the patent system is operating as it should, other inventors or researchers should be able to build upon the existing patent to create new/better products (ibid: 12). Where issues arise, however, is when patent claims are speculative in nature and lack demonstrable utility, as in the case of scaffold compounds for instance. In biochemistry, scaffold compounds are core structures made up of smaller molecules; they are not drugs, though many structural analogs that make it through to market contain the same core scaffold compound (Dimova et al., 2018). Broad patent claims on scaffold compounds are becoming increasingly

common, and essentially mean that any products with specific clinical designations derived from the scaffold core are limited by proprietary IPRs (in other words, the approximate skeleton of a drug with no direct clinical use has been enclosed behind a proprietary barrier) (Lowe, 2018). Mgbeoji and Allen (2003) describe these broad, upstream patents as *speculative patents*, where the patent seeks to claim potential future technologies yet invented, and argue that they create bottlenecks in the drug development process by delaying the translation of knowledge.

While the majority of interviewees did not fall strongly on either side of patents-as-obstructions-to-innovation debate, one particularly interesting and recurring point of note concerned the scope and location (i.e. upstream versus downstream) of patent claims. The overwhelming majority of interviewees, even those staunchly in favour of employing proprietary devices in R&I, commented on the detrimental "bottleneck" effect resulting from broad, upstream patent claims. For example, the Chief Scientist of a large research consortium argued that the proprietary boundary (i.e. the demarcation point at which open, fundamental research becomes enclosed behind proprietary devices such as patents) should be moved further downstream as a means of facilitating collaboration and accelerating innovation:

> I think the whole field should move the proprietary boundary further along the drug discovery pipeline to free up the exchange of ideas and reagents earlier in the [innovation] process. I think that would speed up biomedical research and development greatly. I do think that, instead of protecting everything from the very, very beginning, that moving that bar further down the drug discovery pipeline would make things go faster from the beginning (Chief Scientist, 2017).

Additionally, the Director of Intellectual Property of a large non-profit organization in Ontario argued that patent claims should cover *only* specific drug applications, rather than all possible applications of a given compound:

> I never understood this urgency to have these big broad [patent] claims; I mean really I think that's overstepping what the patent system was supposed to do. I think there's absolutely no reason why within some reasonable degree of scope, you couldn't go after a more narrow claim that more specifically captures what you're pursuing clinically and yet, excludes sort of the immediately obvious variations right, that

> somebody could try and enter onto the market too soon. But there's no reason why we need [these broad claims] – we're going to get further faster if the basics are shared (Director of Intellectual Property, 2017).

Likewise, the Venture Development Manager of the same non-profit organization made a similar case for requiring patent claims to fall within the scope of a specific drug application, stating:

> What is the problem with having a more narrow [patent] scope on a molecule? You know, still within some reasonable scope limitation, one that's going to work and be protective enough to get [the drug] to the clinic and get your ROI. You'll have some investors who say that's not good enough, someone could come along and maybe they're going to tweak this part [of the molecule] over here and they could get around you. My response is, it's better to be more narrow because you've selectively found out that you need to make these changes to make [the molecule] work, it has to cross the blood brain barrier, it has to accumulate at a certain concentration and it has to work specifically through that receptor and not the five others that look just like it. That's what we want; we don't want the broad claim because nobody's going to develop a clinical product outside of that selection (Venture Development Manager, 2017).

These quotes imply that while the *use* of proprietary devices such as patents does not necessarily impede pharmaceutical innovation, their location in the innovation process does. The use of proprietary devices upstream delays the translation of research data by increasing transaction costs required to access critical fundamental knowledge and data, thereby creating bottlenecks around the movement of knowledge downstream or across institutional boundaries. By extension, this may limit the ability of researchers to pursue tangential avenues of inquiry that involve the patented subject matter (e.g. a patented scaffold compound) (Mgbeoji and Allen, 2003). Empirical evidence from Lerner (1994) has suggested that "a one standard deviation increase in average patent scope is associated with a 21% increase in the firm's value" (p. 319). More simply, the marginal value of broad patent claims is increased when there are many substitutes of the same product in the same class (i.e. in the same class of drugs). This explains the push by private firms for research partners (particularly those at public research institutes) to file broader patent claims. The Director of the Industry Liaison Office at a large university in Toronto noted as much, stating:

> Let's say you have a very general compound that has applicability in cancer, HIV, multiple sclerosis. There might be three different pharmaceutical companies that have an interest in each of those applications or in one of those applications. With that initial compound, that individual can say well, I can do a deal with each three of these organizations, I can make money from them and I have the ability of streamlining the development of this technology down the road. It becomes a situation where the robustness of that filing versus its value in the commercial landscape or in the real world is really what the value that the company's looking for – what you filed a patent application for originally has a really broad claim, and [large pharmaceutical] firms love that. Is it great for everyone else [doing similar research]? Maybe not. But firms love that because they can now make money off all three applications instead of just one, so you need to try to claim as broadly as possible (Director, 2017).

The Director of Intellectual Property of a large non-profit organization in Ontario expressed frustration at this outlook on upstream research:

> Having worked in the patent world, I've felt for a while the claims being issued are way too broad and I do think that's what can have a negative impact on innovation. That said, they don't preclude you from doing the research, they just preclude you from commercializing. Instead of saying: I have a drug for this sub-population of Alzheimer's that also treats this population of ALS, this sub-population of MS, how about saying I have a drug for Alzheimer's, you know? The claim needs to be of the drug that targets receptor X for treating disease Y, not just a molecule that might bond with X if we tweak it here and there. I think the point at which the biology and the animal models show some selective advantage over a small class of compounds, I think at that point, the minute somebody has devised a class of compounds that work for a specific clinical indication that is within some reasonable scope, then I think [the IP] has to be proprietary. But not before then (Director of Intellectual Property, 2017).

Historically, there are of course many examples of patented drugs or technologies built on earlier patents and unpatented work. For instance, Merges and Nelson (1990) cite Genentech's patent claim (U.S. Patent 4704362) on specific recombinant proteins, a breakthrough stemming from both patented and unpatented upstream research. However, in biomedical R&D, while broad upstream patent claims may in fact be "good for business," the proliferation of these overlapping claims and licenses nonetheless impedes pharmaceutical innovation by slowing the movement of research downstream (Eisenberg, 1996). The effective result of this is an obstacle to access fundamental knowledge and info required to develop clinical products.

As discussed in Chapter Four, to receive a patent in Canada the application must demonstrate

novelty and utility as well as non-obviousness, as per s. 2 and s. 28.3 respectively of the Canadian Patent Act (Canadian Biotechnology Advisory Committee, 2005). Under the Patent Act, genetic or biological material with known utility are also considered patentable subject matter (ibid). However, stemming from the discussion above, section 53(1) of the Canadian Patent Act stipulates that a patent is void "if the specification and drawing contains more or less than is necessary for obtaining the end for which they purport to be made" (Mgbeoji and Allen, 2003: 84). This is particularly relevant in the context of broad versus narrow patent claims. Recently, the Canadian Intellectual Property Office's (CIPO) Commissioner of Patents (2011) rejected Geron Corporations application to patent a purified telomerase molecule, stating the claim did not "adequately distinguish the invention from the prior art since the telomerase protein was previously known" (p. 6). Moreover, the claim was rejected on the basis of the comprehensive application value of the telomerase protein itself (CIPO, 2011).

Demonstrably, given recent legal decisions, the CIPO recognizes the harm these broad claims may potentially have on innovation further downstream. In terms of policy implications, this is significant. Given the ongoing reduction of public funding for scientific R&I and its reorientation in universities towards public/private partnerships, research agendas have been reconfigured and reshaped in accord with the commercial or social interests of the groups subsidizing it (Lave et al., 2010). With decreasing public funding of science, the onus has fallen on public research institutions to forge partnerships with private industry to ensure that research generates innovative socio-economic gains (such as much-needed novel pharmaceutical products). As universities pursue commercially oriented research agendas designed to develop and market commercial products, and consequently file for broad upstream patent claims, fundamental scientific knowledge will be limited. Upstream research enclosed behind these proprietary devices "will not provide broad-based contributions to science, and like- wise innovations with maximum

benefit to society will be limited" (Mgbeoji and Allen, 2003: 89). Rejecting these unnecessarily broad upstream patent claims is essentially an acknowledgement by the CIPO that commercially oriented research "generally produce the innovative impact within the scientific community as research designed at characterizing basic biochemical and genetic processes" (ibid). The purpose of this section is to demonstrate the significance of *when* proprietary mediating devices are employed, and how this affects pharmaceutical innovation. I argue innovation is negatively affected when proprietary devices are applied to upstream pharmaceutical research not predicated on a direct clinical application. This is specifically due to the high transaction costs required to access critical fundamental knowledge and data that arise for researchers downstream.

7.2. JQ1: A Case Study on Openness

Given the pitfalls of employing proprietary devices discussed above, the question of whether openness offers a panacea to these problems arises. Would maximized openness and the increased use of open devices truly transform the process of drug discovery and development, as argued by bench scientists and STS scholars alike (see Edwards et al., 2017; Hope, 2008)? Longitudinal studies following and comparing open and proprietary drug compounds as they move from the lab through clinical trials and finally to the market are unavailable, given both the time necessary to develop new drug products as well as the relative newness of the open science movement (and particularly its recent foray into the pharmaceutical sector). Most long-term evaluations of the impact of proprietary devices on pharmaceutical innovation tend to focus on citation metrics as a means of evaluating impact. For instance, a quantitative assessment of patent-paper pairs by Murray and Stern (2007) examined the bibliometric citation rate for scientific publications before and after formal IP rights associated with the publication were granted. The study found an anti-commons effect that becomes more pronounced over time, notably for researchers with public

sector affiliations, suggesting intellectual property rights do, in fact, have an impact on the diffusion of scientific knowledge (ibid; see also Williams, 2011).

This section is a case study of JQ1, an open access molecule argued to have expedited drug development by virtue of its openness (Arshad et al., 2016). The case in question involves a thorough discussion with an Adjunct Professor at a large teaching hospital in Toronto who is also the CEO of a small biologics firm (hereby referred to as AP). Our discussion focused specifically on their experience using proprietary analogs and their critique of JQ1 molecule.

Arshad et al discuss the impact of JQ1's availability in an open compound library at length in a 2016 opinion piece. The article begins by describing the current state of drug discovery as being costly and inefficient, noting that it takes roughly 10-15 years to move a drug candidate from target discovery through to market at a cost of roughly $1.8 billion per new molecular entity (NME), despite increasing R&D budgets across North America and Europe (ibid: 322). Stemming from this, the authors argue that the traditional, proprietary model of drug development is unsustainable and suggest increased openness – in terms of increased use of open devices and increased methodological transparency/decreased barriers to access – as a viable alternative (ibid). The authors then argue that by making JQ1 freely available in an open library, they have expedited the process of moving the molecule from the lab to the clinic, stating that JQ1 is currently in Phase I and II clinical trials in the United States (ibid). The authors also conduct a bibliometric study and patent citation analysis to compare the use of JQ1 versus its proprietary counterparts in later research. They argue that the initial open availability of JQ1 positively impacted the number of patents filed for compounds involving the same scaffold compound (ibid: 327).

To begin, JQ1 is an inhibitor of the family of *bromodomain* proteins (including BRD2, BRD3, and BRD4), a group of proteins known to be highly relevant drug targets in both human

cancer and multiple sclerosis (Qu et al., 2018). As AP noted in our discussion and their critique of Arshad et al.'s (2016) discussion of the molecule:

> [Arshad et al.] refer to JQ1 as a drug candidate throughout this paper, and clearly, they've never been involved in drug discovery, because a drug candidate has a very specific meaning. And a drug candidate is a compound that is essentially ready to go into humans or barring that, but you could also define something as going into regimented, pre-clinical talks as a drug candidate. So generally, when you're in the drug discovery business, you start out with a *hit*, which is just a compound that hits your targets with some predefined level of potency. And then the next step is to engage in medicinal chemistry, and work on that. And so, in our case, it took us over two years to transition from a hit to a drug candidate. And between having that hit and having a drug candidate, we synthesized more than 1,500 iterations [of the initial molecule]. So, there's a very big difference between a drug candidate and a hit, and throughout this paper they refer to JQ1 as a drug candidate. It's not, and this is very important, it's not semantics (AP, 2017).

As Filippakopoulos et al. (2010) also highlight, JQ1 is not a *product* intended for use in a clinical setting. It is a *tool*, much like the crystal structures sequenced by the SGC, used to develop pharmaceutical products. This is due in large part to its short half-life, as AP further points out:

> Now, [Arshad et al.] also are a little bit vague in this paper about where JQ1 came from, and I've been familiar with JQ1 for a long time. JQ1 came out of an academic lab, it's not from [a large pharmaceutical firm] as they somewhat allude to. It came out of an academic lab in the US, and they were looking for inhibitors bromodomain, and they identified JQ1. So JQ1, tying all this together, is more a hit and less a candidate; it's never been optimized for pharmacodynamics, pharmacokinetics, any of the things that a drug discovery firm will do. Indeed, one of the major limitations of JQ1 is its very short half-life. So, you put it into an animal, you put it into a human, and it's metabolized in about half an hour, this is very short. Too short to be a legitimate product (AP, 2017).

Stemming from this, a review of *clinicaltrials.gov,* a site maintained by the US National Library of Medicine listing all publicly and privately funded clinical trials occurring in the United States, shows no current or cancelled trials of JQ1 (National Institutes of Health, 2019). As this relates to Arshad et al.'s (2016) argument that the open availability of JQ1 has expedited its progress from the lab to the clinic, AP argued:

> I think, pivotal to the argument being made in this paper, part of the argument is that essentially by using an open innovation model and an open platform, they have expedited the progress of JQ1 from hit or to the clinic, and then they make this

> statement that it is currently in Phase I and II clinical trials, which is false. There's no clinical development of JQ1 going on right now, there's absolutely none (AP, 2017).

To assess the impact of the molecule's open availability, Arshad et al. (2016) compare JQ1 to three drug candidates: Selumetinib, a drug product developed and approved by AstraZeneca for the treatment of lung and thyroid cancer, and PRI 724 and MK 1775, two similar (but proprietary) first-in-class molecules also used in the treatment of cancer (ibid: 323-324). The authors use two metrics to compare the R&D stages of translation for each molecule, namely bibliometric citation rates and patent citation rates (ibid). The authors argue JQ1 has had a greater number of citations compared to its proprietary counterparts; therefore, suggesting open availability can increase the "dissemination and awareness of a drug candidate's discovery" and "may lead to wider, more multidisciplinary community acknowledgement of drug candidate discovery" (ibid: 325). Moreover, Arshad et al. (2016) conducted an assessment of the number of downstream inventions involving bromodomains (targeted by JQ1) versus those involving the targets of its proprietary counterparts. The authors concluded that, due to the higher number of inventions involving bromodomains, the open availability of JQ1 positively impacted downstream innovation (ibid: 327-328). However, as AP (2017) reiterated, the comparison is not necessarily accurate, given the difference in hit compound versus legitimate drug candidate. In their critique of this analysis, AP noted:

> It's really not a fair comparison, comparing a hit with legitimate drug candidates. [JQ1] is something that's really not eligible going to humans. So, to make the argument that you've expedited the process to clinical development is just not reality… So [Arshad et al.] talk about the publication and citation data. They say okay, we'll compare the day the first reference in PubMed[6] to these other three candidates, and they use that date as *T0* to do various calculations of citations. Well, in our business, and for companies, we typically don't publish anything until the patent is issued, until all the work is done. So, there's a considerable lag in the industry that you don't see in academia. Remember JQ1 came out of a university. In academia, you're trying to publish as soon as you bloody well can. In industry there are certain hurdles that you need to clear before you're going to be in a position to publish. In many cases you

[6] A scholarly database maintained by the NIH

> won't see a publication on a compound or a target from a pharmaceutical company until even ten years after the initial work was done. So, to compare those as both being *T0* is kind of a little bit misleading. I think a bigger and more specific kind of problem with all this was around one of the key arguments – that by using an open innovation model you increase the number of citations. The problem is if you look at the original paper JQ1 was published in, and published in *Nature*, which is arguably the best scientific journal in the world, it has the highest impact factor of any basic research journal. Its impact factor is about 40 if not a little bit higher, so the average number of citations per paper is 40. And you compare that for example to MK 1775, that was published in *Current Drug Targets*, which has an impact factor of 3.5. So, that is an average 3.5 citations per article. So naturally, you're going to have a lot more citations for something that was published in *Nature* compared to something that's published in *Current Drug Targets* that nobody reads. So this is meaningless. I mean all of this could be accounted for by one, publications in *Nature*, the others are all in inferior journals. Even *PNAS*, which is where the Selumetinib was published, it's only got an impact factor of 9. Again, you're comparing that to 40 or 42 for *Nature*, big difference (AP, 2017).

Regarding the comparison of patent metrics, AP noted as much:

> [Arshad et al.] are looking at patent families, and they're searching a database to see how many related patent families cited the various targets [of JQ1, Selumetinib, PRI 724 and MK 1775]. They talk about bromodomain, WNT pathway, and checkpoint kinase, so three categories of targets [for JQ1, PRI 724 and MK 1775 respectively]. But let's actually look at the search they ran. In the case of PRI 724, WNT pathway is not the specific therapeutic target of this molecule. So anything that cites its specific target is not included. But then you at JQ1 and they cite not only BRD-4, which is extensively the main target of JQ1, but they also cite BRD-1, BRD-2, BRD-3, BRD-5, 6, 7, 8, 9. So, you're talking about apples and oranges, you've got one little irrelevant target space, compared to all of the BRDs, which of course is hot area research right now. It's a completely inappropriate comparison. And the same holds true [for MK 1775], where they're not necessarily looking at its primary target (AP, 2017).

AP made a final, salient point regarding the arguments made by Arshad et al. (2016), namely that the patent metrics discussed clearly demonstrate the ability of open availability to spark innovation. As they point out, JQ1 was maybe one factor but by no means *the* factor in the proliferation of inventions involving bromodomains. Moreover, JQ1 was published shortly after the sequence of bromodomain crystals became available, raising the question of whether or not that availability is actually what sparked downstream innovations. They noted:

> Now the key point that [Arshad et al.] make is that the initial open access availability of JQ1 positively impacted the number of patents filed regarding inventions involving bromodomains, that's a statement they make, and that seems to be a pretty key learning

> in this article. But the interesting thing is that 2010 [when JQ1 was published] was just after the time you started to see [bromodomain] crystals being sequenced. Here you had JQ1 published, but you also started to have, right before that, the emergence of the actual BRD crystals, many of which came from the SGC. So, to say that it was JQ1 that stimulated that work in bromodomains, again, I don't think the evidence supports that, I don't think there's any link whatsoever. And I think JQ1 had very little to do with the increase in the number of patents involving bromodomains, it's really more about the huge availability of the crystals. So, you know, their argument is flawed in my view, from beginning to end. The way they actually generate all their data in the first place makes their argument questionable (AP, 2017).

While AP's refutation of the arguments put forth by Arshad et al. (2016) do not necessarily negate all evidence supporting the positive impact of open devices on pharmaceutical innovation, what is important to note here is the following: first and most importantly, JQ1 is not a drug candidate, it is a tool compound (Qu et al., 2018). Stemming from this, comparing bibliometric and patent citation data of upstream tool compounds to downstream pharmaceutical products approved for clinical use is misleading. As discussed in the previous section, the use of open devices such as open libraries or databases, particularly as it relates to fundamental science, will facilitate innovation as the knowledge/data in question tends to be used more prevalently downstream (Gitter, 2013; Harnad et al., 2008; Murray and Stern, 2007). As AP (2017) noted, the general argument of Arshad et al. (2016) is not incorrect per se, but rather is problematic. While the open availability of JQ1 positively affected innovation downstream, the same could not be said for Selumetinib, PRI 724 and MK 1775 because these molecules *already exist downstream* (AstraZeneca, 2019; National Cancer Institute, 2018; National Institutes of Health, 2018). They have already passed the rigor of target discovery, pre-clinical and clinical trials, and FDA approval – they are products with designated clinical use. Again, this is not to negate the argument of Arshad et al. (2016) that open devices facilitate innovation, but rather to point out the flaws in the comparison their argument is based upon. As will be elaborated upon in the final section of this chapter, the key take away from this case study, then, is that parsing the difference between *tools*

and *products* is critical the understanding impact of proprietary devices such as patents on pharmaceutical innovation.

7.3. Operating Within the Rules of the Game

As evidenced in the discussion above, open devices such as open libraries and platforms may be critical in the development and dissemination of research tools, while patents or other proprietary devices can be used to expedite the development of drug candidates through to the clinic, all within the same R&I paradigm. What, then, does this mean in a more applied context? Are patents and other proprietary devices truly a "necessary evil" of pharmaceutical innovation? When asked if open devices were a feasible alternative (to proprietary devices) for pharmaceutical R&I in Canada, the CEO of a small biologics firm and Entrepreneur-in-Residence of a large global biotech venture firm said as much:

> For now we have to operate within the rules of the game, as they are set. So the rules of the game basically say you've got to protect your intellectual property with patents, those patents fundamentally generate a huge amount of value for not only our company but they also make up the vast majority of the monetary value of the assets of most of the companies in our investor portfolio. What we do for a living is we take intellectual property usually in the form of at least some basic patent filings and we try to make those as valuable as possible by generating a whole bunch of additional proprietary data that shows how awesome these now patent-protected chemical entities of molecules are. So for us to operate these businesses and for us to play within the rules of that game, the patenting and the protection of intellectual property is almost the be-all-and-end-all of how we generate monetary value (Entrepreneur-in-Residence, 2017).

This raises a new question: If the existing IP framework was different, and market exclusivity was a non-issue for pharmaceutical firms developing new drug products, would the current "rules of the game" change? The same Entrepreneur-in-Residence addressed this as well:

> So what if the rules of the game were fundamentally different? I've always thought that the whole social contract around patents is a little bit weird right, this idea that you know, we're going to incentivise inventors to disclose their inventions by giving them a 20 year monopoly on the use of those inventions. I think if we really look at it and study it the way that you're studying it, I think the jury is still out on whether it's actually enhanced or impeded innovation. If I look at just our industry, the downside of patents

> and having to protect innovations is that we don't share information, we don't share data with colleagues, collaborators, competitors, you name it, any kind of partners or stakeholders that we have, we don't share that data very freely because we're so concerned about protecting it and keeping it under patent protection because that's what generates monetary value. If the rules of the game were changed to say that every piece of data ever done in a human clinical trial needs to be shared publicly, that would be hugely valuable I think to the overall field of medicine, the overall field of pharmaceutical discovery (ibid).

How would this paradigm shift affect innovation? They added:

> And I think it would probably – and this is just a bit of a thought experiment – something radical like that would probably increase the pace of innovation in pharmaceutical discovery and certainly the pace of adoption of new discoveries and new pharmaceutical compounds. It would be incredibly difficult for a biotech company like ours to attract investor dollars unless we had really solid patented states when investors come look at our company and do IP diligence. In our industry it's basically the case that if you take 100 different patents or 100 different molecules that are under different intellectual property protection, 99 of them are going to be worth zero dollars and one is going to be worth a billion dollars and if you have any intellectual property leakage around that one that's going to be worth so much, that billion dollars gets cut in half or it gets cut by an order of magnitude. So the value of that proprietary set of patents and data around an individual molecule, the value can just be so vast, literally billions of dollars that we're all fighting tooth and nail to keep all our data and our results and our intellectual property in this silo (ibid).

This suggests as much: research scientists, executives, and investors alike understand the value of openness and open devices in terms of facilitating the translation of knowledge, and they acknowledge the potential obstructions to innovation posed by proprietary devices. In terms of policy implications, as Rai and Eisenberg (2003) note, the challenge to policymakers moving forward "lies in distinguishing discoveries that are better developed and disseminated through open access from discoveries that are better developed and disseminated under the protection of intellectual property rights" (291). What can be gleaned from this dissertation is that basic, upstream research (the majority of which tends to be *tools*) is likely better developed and disseminated through open proprietary devices. Similarly, the development of *products* downstream will likely benefit most from the application of proprietary devices.

Privatization holds both risks and rewards: while patenting may offer incentives for researchers to undertake risky research projects, too many owners holding property rights in previous discoveries, the stacking of multiple licenses (e.g. patents and RTLAs), or the deployment of proprietary devices too soon upstream may present barriers to future research (Cohen, 2004; Birch et al., 2018). Paradoxically, limiting the use of proprietary devices may, in fact, be necessary to facilitating the production of IP and ensuring its widespread use (Heller and Eisenberg, 1998). Hope (2008) notes, "the challenge, then, of modelling open source licensing in bio-technology is to create new licenses that can accommodate the complexity and variety of biotechnology transfer agreements, yet remain faithful to the underlying logic of open source" (p. 144-145). The argument being made here, though, is that perhaps openness/the use of open devices is not feasible for all stages of drug development. As the above quote indicates, the rules of the game at the moment are such that to be able to develop a product that reaches the market, and subsequently recoup the associated costs, proprietary devices are necessary. This does not necessarily mean that changes to this paradigm are not needed – currently, pharmaceutical R&D is prohibitively expensive and unsustainably slow, and this model has not been significantly adjusted or improved by any stretch (Collins, 2011; Gassman and Reepmeyer, 2005). However, one of the principal problems of IP management in the pharmaceutical sciences that needs to be taken into account when discussing potential policy solutions is the heterogeneity of the IP in question. Unlike in the development of computer software, where open devices may be easily applied, "this technological heterogeneity [in the pharmaceutical sciences] gives rise to heterogeneous patterns of ownership.... Each technology is thus covered – often incompletely – by a patchwork of different protections" (Hope, 2008: 144). Software tools used in biotechnology and bioinformatics for instance are easily adaptable to the more open IP environment for information technology. For the bulk of drug

discovery, though, where developers are seeking to recoup the costs of product development, it simply isn't feasible to argue for increased openness (Mgbeoji and Allen, 2013).

The Director of Intellectual Property at a large non-profit organization in Ontario pointed out that one of the primary issues perpetuating this unsustainable system of drug development is the lack of public funding in Canada that forces researchers to partner with industry, whereby the use of proprietary protections is mandated. They noted:

> That's the quid pro quo: we need the money, so we have to follow the rules to be successful in the current model. But the current model sucks. The current model of drug development is you claim broadly, take [the drug] to market and then realize it really only works in 10% of the population. We're kind of stuck in this vicious cycle. I don't think you can reasonably expect to do everything in a closed box the way pharma's done for years and they've learned that, right, they've all hit these patent cliffs. All their big products are coming off patent, clinical trials are hard, most of them failed depending on the clinical indication, so now what? Well, now they're going around trying to partner with academics. From a university perspective that's great cause they take 40% overhead on research grants. For the professor it's good, it gets her name on some patents. Maybe it ends up being a big licensing deal, maybe it doesn't, and maybe it just goes nowhere. I don't know how anything changes unless you have [federal] granting agencies that want to step up and say we want to keep it all in Canada and be able to license and commercialize as we want, we don't want industry dictating the terms to us. And we're at a disadvantage because these agencies just don't have the money for us to do the R&D. There has to be a change of thinking for [a paradigm shift] to happen. [Private firms] have to have some evidence that open innovation is beneficial to them, because they're in business to make money, they're responsible to their shareholders, and they need to act in their own best corporate interests, right? They wouldn't be doing that if they threw everything into the open (Director of Intellectual Property, 2017).

This suggests that even the practitioners of drug development see the need for a system in which open and proprietary devices are used together in different ways. Clearly, as AP noted, neither open nor proprietary devices on their own are sufficient for expediting pharmaceutical innovation. AP also noted as much, stating:

> Would we be able to develop new products without an intellectual property framework? The answer's no. You have to remember that universities seldom develop drug products. You know maybe back in like the twenties with insulin and drugs like that, but that's far from the norm. It's really for-profit entities that generate the vast majority of drugs and a lot of people don't understand that. And I think there needs to be a profit motive there for entrepreneurs and industry to see what it takes to spend the huge amount of money required to develop new drugs. I mean having access to a crystal is absolutely

> critical, right. And I think you know SGC has contributed a third of the crystals in the Protein Data Bank or something, so I think that's a really good model. So I think that really works. But when it comes to the core IP of a product that is monetized, I do think that that needs to be protected, I do think it needs to be proprietary and that's necessary first and foremost to be able to secure the capital necessary to move these things forward, venture capital in particular. It's very, very difficult to raise venture capital as it is, the risks are so high, you need so much money, there needs to be a profit motive. [Investors] want the world and they want things protected from end to end, you know. And so trying to convince them that there should be less exclusivity I think it's going to be a tough sell, that's not the real world of entrepreneurship and biotech (AP, 2017).

Acknowledging the unavoidable costs associated with drug development, AP concluded the interview by stating:

> I think that knowing the economic realities of how expensive it is to develop these products; [proprietary devices are] an essential tool when used correctly for the right property at the right time. I suggest then that in the early days, openness is needed so as to get things initially started. But to use the intellectual property tools and the experts like the IP lawyers and patent agents to develop that product so that someone would be willing to invest in it, to take it the rest of the way. The economic reality is that you won't be able to get these technologies translated out into the world unless you develop something like a company that could actually mobilize that. Because a patent to be licensed is only a piece of paper until somebody actually goes and does something with it. So you need that [proprietary device] in place to secure investment in something that will be accompanied that could then translate that into the world (ibid).

As the quotes above indicate, patents appear to be the only viable (though perhaps not sustainable) means of achieving a return on investment in the development of a new drug product.

7.4. Distinguishing Between Tools Versus Products

The previous section outlined in detail the importance of first distinguishing between *the types of things* that open and proprietary devices are applied to, before making blanket statements regarding their efficacy and impact on innovation. This section discusses this in further detail, unpacking the importance of differentiating between tools and products and why this matters in the context of mediating devices and pharmaceutical innovation.

In the case of JQ1 above, Arshad et al. (2016) make the claim that open devices (in particular open libraries and platforms) positively impact pharmaceutical innovation by increasing the

"dissemination and awareness of a drug candidate's discovery" and facilitating "wider, more multidisciplinary community acknowledgement of drug candidate discovery" (p. 325). Beyond a brief technical description of its applications, the article contains no detailed discussion of the *type* of molecule JQ1 is and in fact erroneously categorizes it as a drug candidate. Similarly, though scholars of STS, innovation studies, and economics of science have discussed the impact of open and proprietary devices at length, I have yet to find any discussion of their differential impact on pharmaceutical tools versus products. Among others, Heller and Eisenberg (1998), Mirowski and Sent (2002), Mirowski (2011), Caulfield et al. (2011), and Lezuan and Montgomery (2015) have discussed upstream versus downstream property rights and the impact of broad patent claims versus narrow patent claims (as outlined in section 7.1. of this chapter). However, there is no comparative analysis of the *kinds of things* that are subject to broad patent claims or impacted by the use of open/proprietary devices. Perhaps it is generally assumed by these scholars that the reader understands that if a broad patent claim is made it will enclose a *tool* rather than a product, or if a proprietary device is employed downstream it will be applied to a *product*. While this may be the case, it is nonetheless critical to explicitly distinguish between tools and compounds in discussions of open and proprietary devices. This is especially relevant in the context of the SGC, an entirely open consortium that has successfully partnered long-term with a number of large, for-profit global pharmaceutical firms (SGC, 2017b). How does the SGC maintain these partnerships given its open business model and the open devices embedded in their day-to-day operations? The answer, as AP noted in our discussion, lies in the differentiation between tools and products:

> There are tools and then there's the product itself. I think that that parsing is absolutely critical. Again, I've seen no evidence that having an open access compound, molecule, candidate, hit – I've seen no evidence that that facilitates bringing drugs to market faster. I think there's likely unlimited evidence that having tools like the SGC creates is massively beneficial, and indeed, we have made use of their open access crystals on multiple occasions and that's facilitated our efforts without any doubt about it, 100%. So, it's the tools versus the product itself, that's what makes the difference. [The SGC's] partners don't care if [the crystal structures] are openly available, because

> having the tools means they'll get to the drug faster and they're betting they're the only ones who can make that drug, even if everyone else has the tools to do it. But when it comes to the core IP that forms the basis of the product that is monetized, I that that needs to be protected. Firms want it protected. It needs to be proprietary and that's necessary first and foremost to be able to secure the capital necessary to move [pharmaceutical products] forward, especially for venture capital in particular. It's very, very difficult to raise venture capital as it is, these [firms] want the world and they want things protected from end to end. And so trying to convince them that there should be less exclusivity around the product, I think it's going to be an impossible sell. Around the tool? Sure (AP, 2017).

Similarly, the Director of Fund Operations of a research trust at a large non-profit organization in Ontario highlighted why the SGC's open model works, stating:

> We partnered with [the SGC] and used several of their crystals and that worked fine. But that was early [in the R&I process], we actually called [their compound] a tool compound. But that compound was not a drug, it actually didn't bind to the protein, and it didn't have the other properties you would want to see in a drug, such as low toxicity and high solubility, it didn't pass through the intestine. All the good properties you'd want in a drug. So what our chemistry team did is start from that point [where the work of the SGC ended] and then developed a program to create a drug from that starting compound. So the SGC took [the research] up to a certain point, and then our chemists took it a proprietary way further, to try to bring a drug to market. And we have filed for patent protection on the compounds we've created from there (Director of Fund Operations, 2017).

Again, what this suggests is that open devices are suitable in the context of tools with little direct commercial pressure. From this quote one can extrapolate that the open availability of tools does in fact facilitate innovation due in large part to the reasons discussed in section 7.1. (i.e. lower transaction costs, fewer barriers to entry, etc.). As Megbeoji and Allen (2003) reiterate, one of the critical underlying principles in the enforcement of intellectual property regimes "is the significant potential for economic gain. A significant portion of biomedical research is private, and the primary impetus for continued private research and innovation is capital earnings" (p. 89). Extending from this, it is also logical that open devices should be used up to the point at which a product is devised for a specific clinical use within a reasonable scope, whereby proprietary devices may be introduced with as little detrimental effect on innovation as tenable. This is due in part to the fact that there is little profitability potential with tool compounds beyond fees from

MTAs and patents (i.e. they will not be sold on a mass scale as a drug product would) – there are few reasons for industry to enclose them behind proprietary barriers. Along this line, the Director of Intellectual Property of a large non-profit organization in Ontario stated:

> I believe in the idea that tools and scaffold compounds should be open, with some basic understanding that fundamental science that should be free to everybody, there's no reason why those shouldn't be. So you find a tool compound that works in a [drug] screen or you develop a tool compound because you've sequenced the crystal structure – it's 99.9% likely that [tool compound] is not going to be what you take to market because it's not going to have all the pharmacokinetic data [a marketable drug would], and we're going to have to figure out all the liability issues, the bioavailability, all of those other usual developments are going to have to happen – but I don't know why the starting materials shouldn't be free for everybody. And I'd like to believe pharma – big pharma – is getting close to that because they realise they have all these libraries of scaffold compounds that have been sitting on shelves and research programs that have been discontinued for various reasons, that have been kept all in their proprietary warehouse, but what if there's potential for second life for some of those, right? So by making them open and having people with the scientific and biological knowledge be able to go at them, that would be really interesting, that would really help the state of [drug development]. I think that [making proprietary claims on those compounds] is ridiculous because those thousands of structures aren't clinically relevant. They're not going to make money. But at the end of the day, you need some exclusionary rights on what you're going to bring to market – and I think they should be pretty narrow (Director of Intellectual Property, 2017).

Likewise, the PI of a bioinformatics lab at a large university in Toronto also argued in favour of keeping tools openly available through the use of open devices, stating:

> I think open access, open source, open innovation all benefit basic research, we need [open devices] to make new biological discoveries. And then eventually those [discoveries] get translated into commercial products. So, I think the question always comes down to, what is the value of basic research, and you know, my lab isn't directly going to be making money from what we produce. Maybe there is no obvious [monetary] value but maybe the biological discoveries we make and the tools that we produce are useful and will get turned into products down the road (PI, 2017).

What this again highlights is the importance of keeping research tools openly available, and demonstrates the net positive impact open mediating devices can have on pharmaceutical innovation *when applied to tools rather than products.* Moreover, this also indicates that the use of proprietary devices does not necessarily have a negative impact on pharmaceutical innovation, but that their impact is likely determined by their application to either tools or products.

7.5. Conclusion

In this chapter, I have argued that the impact of open and proprietary devices on pharmaceutical innovation, in terms of both accelerating the translation of pharmaceutical research and encouraging collaboration, is largely dependent on: firstly, when they are employed in the innovation process (i.e. upstream versus downstream); and secondly, the context in which they are employed (e.g. in a consortium versus a small- to medium-sized firm versus an academic lab). More often than not, the implementation of proprietary devices too early in the R&I process, particularly in the case of broad upstream patent claims, results in bottlenecks that slow down or stop knowledge translation entirely. Conversely, the use of open devices downstream in the commercialization process of new drug candidates is likely to derail private investment. I have also argued that parsing the difference between research *tools* versus marketable *products* is crucial in understanding the net impact of open and proprietary mediating devices on pharmaceutical innovation. This is significant, particularly given the dichotomous and incompatible framing of open and proprietary devices that is presented in the STS and innovation studies literature discussed above. As demonstrated, open devices such as open libraries and platforms may be critical in the development and dissemination of research tools, while patents or other proprietary devices can be used to expedite the development of drug candidates through to the clinic, all within the same R&I paradigm. As such, I argue that in contrast to the discussions presented in the literature discussed, these devices may be complimentary at particular stages of R&I, and, when used together, can accelerate advancements in the pharmaceutical sector. The broader policy implications of this argument will be discussed in Chapter Eight.

8. Conclusions

The challenge, presented in Chapter One of this dissertation, is clear: how can open and proprietary devices be used *together* as a means of furthering advancements in pharmaceutical research and accelerating the development of novel drug candidates? This chapter will summarize the research questions answered in the previous three empirical chapters. Thus far, I have argued that the dichotomous and incompatible framing of open and proprietary devices that is presented in the STS and innovation studies literature is often reductive. Labeling open and proprietary mediating devices as strictly either facilitators or hinderers of innovation is an oversimplification, and a more nuanced approach is critical for forming sound policy decisions. This chapter begins with an overview of what has been discussed so far, followed by a summary of the key findings. It concludes with a discussion of policy recommendations and avenues of future inquiry.

8.1. Summary

This research focused broadly on pharmaceutical R&D and the development of novel clinical products in this sector. As discussed in Chapter One, drug development is notoriously expensive, slow, and precarious. As Collins (2011) and others (see DiMasi et al., 2016) note, pharmaceutical R&D averages 13 years and roughly $1.5 billion per new chemical entity (NCE) from initial laboratory target discovery through regimented clinical trials to U.S. Food and Drug Administration (FDA) approval. These figures are continuing to rise. However, while basic research often produces promising results upstream, research outputs lag far behind associated costs (particularly for universities) and the number of new medicines has not increased proportionately with investments made in basic pharmaceutical R&I. Downstream, attrition rates in late stage clinical trials are especially high and contribute to the risk and unpredictability

associated with investing in pharmaceutical R&I (Gassman and Reepmeyer, 2005).

The issue at stake in this dissertation stems from the fact that commercialization threatens to enclose crucial knowledge and information and restrict its access behind proprietary IP protection, slowing drug development even further. This has wide-ranging implications, as the need for novel diagnostic and therapeutic drugs able to combat increasingly insidious and prevalent diseases has grown in recent years. Moreover, because pharmaceutical R&D often relies heavily upon collaboration and access to diverse knowledge, the enclosure of knowledge behind proprietary barriers threatens to impede pharmaceutical innovation by raising transaction costs and barriers to entry (Feldman and Nelson, 2008). Bottlenecks in the development process arise when broad proprietary IP rights are applied upstream in the research process, as even the most commercially irrelevant research is often now encumbered by MTAs and broad patent claims (Scherer, 2002).

Openness and the increased use of open devices such as open databases and screening platforms has offered a potential solution to navigating through complex networks of proprietary IP licenses and patents, primarily by releasing project data into the public domain and ensuring broad user access (Gitter, 2013). Though science initiatives offer low entry costs and increased methodological transparency, there is significant debate within the science and technology studies (STS) and innovation studies literature concerning open and proprietary IP devices. In many cases, open and proprietary devices are often presented as dichotomous and incompatible. This work, however, built on the argument that open and proprietary devices may be complimentary depending on where they are employed in the R&I process.

Chapter Two offered an overview of the existing body of literature relating to the broader, theoretical concerns with scientific knowledge and its production, research commercialization and academic capitalism, innovation studies and innovation models, intellectual property, and open science. Here, I outlined the concept of mediating devices as the analytical approach used

throughout this dissertation. While the works discussed form a crucial component of the theoretical skeleton of this research, I argue there is nonetheless a significant gap in this literature that has yet to be addressed: despite much discussion of their significance as *tools* of commercialization, scholars in STS and innovation studies have yet to analyze how proprietary *and* open devices vary in terms of their efficacy when they are employed at different stages in the R&I process.

Chapter Three provided an overview of the methodological approach taken in this research. Specifically, I discussed data collection and analysis methods employed in this work. As this work was essentially an empirical case study of pharmaceutical innovation in Ontario, this chapter also outlined the reason for focusing specifically on the R&I efforts occurring at MaRS Innovations, the Ontario Institute for Cancer Research, JLABS, the Structural Genomics Consortium, and the University Health Network. As I discussed, these organizations were chosen because they employ a diverse range of proprietary-to-open arrangements and commercialization strategies.

Chapter Four outlined the integral role of proprietary devices in the international legal and policy architecture that in large part determines the path of scientific innovation, particularly in the context of pharmaceuticals. This chapter focused specifically on the TRIPS Treaty, its impact on Canadian IP policy, and both US and Canadian IP policy and law respectively. The purpose of this chapter was to highlight the fact that proprietary devices such as patents, MTAs, and other proprietary IP mechanisms remain hallmark features of commercialization strategies across the globe, and to note the challenge of introducing open devices into R&I processes as a result of this embeddedness.

Chapter Five focused on the concept of *innovation* itself and endeavoured to unpack it by highlighting its contextual basis and discussing how it is measured and how funding sources play a role in this. In analyzing the concept of innovation and how it is measured, the purpose of this

chapter was to shed light on the impact of funding and investment decisions on drug development and highlight financial motivations that drive R&I.

Chapter Six evaluated specific mediating devices in the context of the broader architecture of research and innovation. I discussed the institutional architecture of R&I at universities, as well as the ways in which mediating devices shape collaborative agreements and are embedded within the provincial legal and regulatory architecture of pharmaceutical innovation. The primary argument in this chapter is that mediating devices – particularly proprietary devices – are inherently embedded in the current architecture of research and innovation. Further, that this embeddedness has resulted in an additional layer of in/tangible administrative costs and onerous legal negotiations being added to the R&I process that, more often than not, makes the use of open devices especially difficult and impedes innovation in this sector.

Finally, Chapter Seven examined two specific cases of proprietary and open devices in action. I first discussed the impact of broad versus narrow patent claims and their impact on innovation, highlighting the negative effects of implementing proprietary devices too early in the R&I process and open devices too far downstream in the commercialization process of new drug candidates. Following this, I conducted a case study of the open molecule JQ1 as a means of highlighting the importance of distinguishing between research *tools* versus marketable *products* when attempting to understand the net impact of open and proprietary mediating devices on pharmaceutical innovation. The overall argument of this chapter is that a more nuanced unpacking of open and proprietary mediating devices is necessary for improving the costs and translation times associated with pharmaceutical innovation in Canada, and for ensuring broader societal needs for novel and efficacious therapies are met more efficiently.

8.2. Key Findings

In terms of contributions to knowledge, this dissertation endeavoured to fill gaps in the existing STS, innovation studies, and political economy of science literature relating to intellectual property and open innovation. In Chapter One I introduced the concept of mediating devices, arguing these devices are the linchpins that enable collaboration, commercialization, and knowledge transfer, and/or determine valuation of the products and processes of R&I. A primary purpose of this dissertation was to situate and evaluate these devices within the broader context of corporate strategy, technology transfer, public policy, and academic capitalism. Further, I argued that unpacking mediating devices in this context may help to the refine and streamline institutional innovation strategies, and may help to rapidly and cost-effectively translate innovative research findings from the lab to the clinic, particularly by highlighting which devices work for whom, and when. Ultimately, by examining the context in which pharmaceutical innovations develop as well as the devices that enable innovations to be rapidly and cost-effectively diffused to clinical settings, Canada will be better situated to address salient health policy issues (e.g. how to foster a sustainable and efficient environment for pharmaceutical R&D) and to answering the demand for novel diagnostic and therapeutic drugs.

Moreover, in addressing research question 2 (*Which proprietary and open devices are used in pharmaceutical R&I? For whom, and why?*), I evaluated the ways in which open and proprietary devices shape collaboration agreements and (re)configure the commercialization of new pharmaceutical products in Ontario. Here I argued that mediating devices – particularly proprietary devices – are inherently embedded in the architecture of Canadian research and innovation, making the application of open devices particularly difficult.

In answering research question 3 (*How do different devices facilitate or hinder collaboration and knowledge translation in this sector? At what stage in the innovation process are they most*

effective, and why?), I argued that the efficacy of open and proprietary devices, both in terms of accelerating the translation of pharmaceutical research and encouraging collaboration, is dependent on: firstly, when they are employed in the innovation process (i.e. upstream versus downstream); and secondly, what they are applied to (i.e. tool compounds used to develop candidate drug products versus the products themselves). From this, I argued that the role of open versus proprietary devices in facilitating or hindering innovation is dependent on several variables: namely, collaborative arrangements and the nature of the IP in question (e.g. a tool used in the development of drug candidates versus a pharmaceutical product itself). The context-dependent nature of these devices is a nuance little discussed or analyzed in the STS literature.

Finally, in answering research question 4 (*How can these devices be employed in the development of innovation strategies so as to streamline the process of drug development?*), I argued that, contrary to the dichotomous and incompatible framings of open and proprietary devices that is presented in the STS and innovation studies literature (discussed at length in Chapter Two), these devices may be complimentary at particular stages of the R&I process, and, when used together, can accelerate advancements in the pharmaceutical sector.

8.3. Applications and Recommendations for Future Research

What does a successful innovation policy model look like then? Knowledge production by consortium, as in the case of the SGC, is not the only alternative as suggested by the OECD (2011: 37). One solution might be for Canadian federal granting agencies (such as NSERC and CIHR) to mandate the open availability of research designated basic or fundamental. Already NSERC (2018a) requires the open publication of funded research projects – this could be extended to include a requirement that research products be shared in open access libraries or screening platforms. In terms of downstream product development, it will be difficult for federal granting agencies to dictate

when proprietary devices may be employed given the increasingly reduced amount of funding available to public research institutes. This will need to be addressed in federal and provincial budgets; as discussed in Chapter Seven, the realities of pharmaceutical development in Canada are such that public funding for R&I continues to decrease, and thus the current "rules of the game" require researchers and firms to adhere to the traditional proprietary commercialization model in order to profit from their innovations.

The Canadian government should also continue to foster and support Canadian Centre's of Excellence, focusing particularly on sites of open innovation and translational science. As it stands, the Government of Canada currently funds a number of Centres of Excellence (outlined in detail in Chapter Three), including MaRS Innovation, the SGC, the Center for Drug Research and Development, the Quebec Consortium for Drug Discovery (CQDM), and the Institute for Research in Immunology and Cancer among others (Industry Canada, 2016). The purpose of these centres is to promote collaborative and externalized R&D between public research institutes and private firms to commercialize discoveries and fill public funding gaps (ibid). Industry partners include AstraZeneca, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Johnson&Johnson, Merck, Novartis, Pfizer, Sanofi, and Takeda (ibid). While these centres operate under varying models (i.e. some are incubators, some, like the SGC, are entirely open), it would be beneficial for the Canadian government to develop a more cogent, uniform policy on openness and open data sharing that would be applicable to these centres. As demonstrated in the case of the CQDM's open innovation business model, the centre is still able to leverage funding from major private firms for pre-competitive research, while industry collaborators such as Pfizer, Merck, and AstraZeneca benefit from their open partnership by gaining early access to data given their constant interactions with research partners (Nasto, 2015). Demonstrably, these types of open models are broadly applicable,

particularly as it relates to upstream/pre-competitive research, and compatible with public/private partnerships that are so prevalent in Canada's current pharmaceutical R&I landscape.

One potential solution to be explored is the use of an open science financial trust. As outlined by Edwards et al. (2017), in an open science trust, "reagents are treated as a public-good resource governed by principles that promote the public interest, in this case, open science. [An] open science trust agreement codifies these public-good principles. Under its terms, a recipient of research reagents becomes a 'trustee' of the reagents. Trustees are bound by principles that specifically prohibit filing any patent claims that would restrict use of the reagents by others" (1). Generally, within this model, any profits generated from products developed go back into the trust to fund the next venture (ibid).

Stemming from this, trust-based initiatives such as M4K Pharma – the science and business successor of the SGC – offer an opportunity to evaluate whether making the tools/products distinction is relevant in the development of new drug candidates, and may potentially lead to a paradigm shift towards open drug development. M4K is a newly founded pharmaceutical firm in Toronto whose aim is to develop treatments for rare pediatric diseases with small target populations, starting specifically with diffuse intrinsic pontine glioma (DIPG) as its first initiative – a rare form of pediatric brain cancer with a five-year survival rate of <1% (M4K Pharma, 2019). In employing the business model of the SGC, M4K will not use any proprietary devices such as patents or MTAs, and the results of its research (i.e. the drug prototype) will be released entirely into the public domain and collaborators (such as CROs, academic partners, and other firms) will also be encouraged to openly publish research and data (ibid). M4K retains Investigational New Drug (IND) data as a means of maintaining international market exclusivity while avoiding filing for proprietary licenses. Interestingly, however, unlike the SGC, M4K Pharma is developing *products* to be tested in clinical trials and approved for sale and clinical use, rather than simply *tools*. Unlike in traditional modes of

pharmaceutical development, where funding sources typically include VC, equity markets, and internal cash flow, M4K will rely solely on public grants, and foundational and philanthropic donations to fund its R&D (ibid). Moreover, M4K is wholly owned by the Agora Open Science Trust, a trust created to hold the economic interests of M4K's financial contributors "whose sole beneficiary is open science and the public good" (ibid). Any profits from M4K's inaugural DIPG project will be used to launch subsequent initiatives. While it is too soon to make any definitive statements regarding the success of the M4K model, this will be an interesting case against which the tools versus products hypothesis can be tested in real time.

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