KNOWLEDGE TRANSLATION IN ACTION: CANCER BIOLOGY AND SYSTEMS PHARMACOLOGY AT THE NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCE

by

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Abstract

The need for novel diagnostic and therapeutic drugs with the potential to combat increasingly prevalent or particularly insidious diseases has grown in recent years. Concurrently, the issue of translating scientific knowledge from "bench to bedside" has become increasingly salient. In 2011, the U.S. National Institutes of Health created the National Center for Advancing Translational Science in an effort to remedy the recalcitrant gaps between fundamental laboratory research and late-stage clinical trial, thereby dramatically reducing the amount of time and expense needed to develop efficacious pharmaceutical prototypes for a range of emerging, re-emerging, and chronic diseases. However, the realities of pharmaceutical development are incongruous with the expectations of the lay public that even the most fundamental scientific research yield results with immediate social and commercial value. Traditional linear models of progress overlook both the epistemic nature of scientific innovation and the significance of the socio-economic supply and demand factors driving research endeavours.

The aim of this dissertation is to underline the epistemic and socio-economic characteristics of translational science – specifically in the context of research targeting novel oncology therapeutics and diagnostics – through the lens of Science and Technology Studies. In focusing on research in cancer biology funded by the National Center for Advancing Translational Science, this thesis highlights the significance of Mode 2 or "post-academic" science, and by extension the roles of interdisciplinarity and applicability, and the commodification of scientific knowledge, that arise in the process of translating scientific knowledge.

Preface

This thesis is original, unpublished, independent work by the author, Margaret Elizabeth Chiappetta.

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List of Abbreviations

Abbreviation	Meaning	Page
BTK	Bruton's tyrosine kinase	45
CSF3R	Colony stimulating factor-3 receptor	45
DBCL	Diffuse large B-cell lymphoma	45
ELISA	Enzyme-linked immunosorbent assay	39
FDA	Food and Drug Administration	1
NCATS	National Center for Advancing Translational Science	4
NIH	National Institutes of Health	4
PCR	Polymerase chain reaction	39
R&D	Research and development	5
Src	Sarcoma	46

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Dedication

For M.F.M. – my greatest influence and inspiration.

1. Introduction

"Technology is science in application: science in action is research."[1]

The need for novel diagnostic and therapeutic drugs with the potential to combat increasingly prevalent or particularly insidious diseases has grown in recent years; however meeting these needs has been hindered by bottlenecks in the development process stemming from issues of funding to failures of interdisciplinary communication. While research in the basic biomedical sciences frequently produces promising results for pharmacologists, oncologists, physicians, and patients alike, the rate at which knowledge moves from initial laboratory target discovery to clinical trial to U.S. Food and Drug Administration (FDA) approval of a candidate product for use in clinical and public health practice is unsustainable and notoriously slow, averaging 13 years and roughly $1.5 billion per novel drug.[2] The issue of knowledge translation from "bench to bedside" has thus become increasingly salient: hence the emergence of *translational science* as a discipline seeking to remedy the recalcitrant gaps between fundamental laboratory research and late-stage clinical trial. The aim of this dissertation is to highlight the epistemic and socio-economic characteristics of translational science – specifically in the context of research targeting novel oncologic therapeutics and diagnostics – through the lens of science and technology studies (STS).

The nature of the biological sciences is such that knowledge *may* often move across disciplinary boundaries with ease given its seemingly unified nature, though whether this movement occurs depends on a variety of factors, namely the *need* to put fundamental

[1] John Ziman, *Real Science: What It Is, and What It Means* (Cambridge: Cambridge University Press, 2002): 14.
[2] Francis S. Collins, "Reengineering Translational Science: The Time Is Right," *Science Translational Medicine* 3, no. 90 (6 July 2011): 1.

research results to a particular use. Indeed there is an expectation (on behalf of the lay public, public funding institutions, government groups, and so on) that even the most fundamental scientific research yield results with immediate social and commercial value. While not so explicitly expressed, knowledge is expected to fluidly move between disciplinary boundaries and ultimately be transformed into a marketable commodity from which economic and social benefits may be appropriated (in the form of profit, drug therapy, and so on). However, the realities of pharmaceutical development are incongruous with the expectations of the lay public that fundamental scientific research yield socially and commercially valuable outcomes. Traditional linear models of progress, wherein knowledge moves sequentially from the laboratory bench straight to the development of a candidate product, overlook both the epistemic nature of scientific innovation and the significance of the socio-economic supply and demand factors driving research endeavours. The rocketing costs of the continual proliferation of emerging, re-emerging, and chronic diseases negatively impacting public health are both social and economic in nature; for example, the quality of life for those with untreatable health issues continues to decline while the cost-per-patient burden to the national healthcare system increases concurrently.

On the other hand, the biomedical research community has approached the need to move knowledge across disciplinary boundaries from a more pragmatic standpoint, defining translational science as "part of a unidirectional continuum in which research findings are moved from the researcher's bench to the patient's bedside and community."[3] Diffusing knowledge from "bench to bedside" is understood to be a

[3] Doris McGartland Rubio, et al., "Defining Translational Research: Implications for Training," *Academic Medicine* 85, no. 3 (March 2010): 472.

multidisciplinary endeavour that involves feedback and exchange between research groups and institutions. However, this traditional definition says very little about either the context in which knowledge is produced, the means of moving research findings along the basic/applied spectrum, or the factors driving research.

It is at this juncture, between the esoteric or overly technical description of translational science given by the scientific community and the unrealistic expectations regarding the nature of scientific progress (specifically, of drug development) held by society at large, in which the opportunity to examine the ways in which the epistemic enterprise of *science* is affected by society, politics, and economics (and vice versa) presents itself. The aim of this dissertation is to underline the epistemic and socio-economic characteristics of translational science – specifically in the context of research targeting novel oncology therapeutics and diagnostics – through the lens of Science and Technology Studies. In focusing primarily on the concept of *Mode 2* or "post-academic" science, I aim to highlight the roles of interdisciplinarity and applicability, and the notion of science as a public good, that arise in the process of translating scientific knowledge from "bench to bedside." As will be discussed, interdisciplinarity and applicability branch directly from the practice of Mode 2/post-academic science, while in the context of translational science, the knowledge that is produced and applied as a result may be considered a public good.

While the creation and extension of scientific knowledge has long been a topic of study for sociologists and philosophers of science, translational science is a relatively new field, and the impatience (of funding agencies, the lay public, etc.) regarding the rate of diffusion of knowledge from the laboratory bench through to the hypothetical

medicine cabinet raises several questions for scholars of STS: What does it mean to translate scientific knowledge? Moreover, what role do socio-economic considerations play in research endeavours proposing hypothetical "products" with applicatory potential (such as novel pharmaceutical targets or prototypes)? Finally, is research funded by the National Center for Advancing Translational Science *translational* according to this definition?

I aim to answer these questions by highlighting the socio-economic and epistemic factors that characterize translational science as a discipline, as well as its principle fields of genomics, proteomics, and metabolomics, all of which exemplify the rapid growth potential and commercial salience that drive this particular form of science in action. Further, I argue for the categorization of scientific knowledge as a public good, which necessarily highlights the role played by socio-economic considerations in expediting translational science *in service of the nation*. I will endeavour to apply the concepts of interdisciplinarity, applicability, and commodification to translational science in action in the context of research directed towards the development of novel oncologic therapeutics and diagnostics. Specifically, I will look at research funded by the National Center for Advancing Translational Science (NCATS), a research body of the U.S. National Institutes of Health (NIH) whose overarching mission is to translate research findings from basic to clinical settings. Under the auspices of this centre, the time and expense needed to develop efficacious treatment strategies is, in theory, reduced following the introduction of innovative translational techniques, with NCATS-funded researchers focusing on new or prospective drug targets or compounds previously overlooked or abandoned by private pharmaceutical initiatives. Moreover, NCATS is aimed in part at

providing an environment in which similarly aligned research groups may carry out projects in conjunction with one another, while simultaneously facilitating the collaboration of public and private research. It therefore provides a particularly interesting setting for studying the interdisciplinary dynamics of translational research, and the commodification of research results.

I argue that the translation of scientific knowledge entails a transformation of fundamental research results produced by means of interdisciplinary collaboration to a *nearly* commercial, non-rivalrous, and non-excludable state with *potential* applicatory value. Moreover, translational science involves a synthesis of socio-economic and epistemic considerations in terms of how and why knowledge is produced, particularly in terms of what motivates public and private actors throughout this process, and involves the collaboration of actors and institutions from across the research and development (R&D) spectrum.

2. Knowledge Production, Commodification, and Translation in the Biological Sciences

2.1. Knowledge Production and Interdisciplinarity in the Biological Sciences

The social nature of *science* is a topic that has been thoroughly discussed by sociologists, historians, and philosophers of science alike. That being said, before discussing translational science, either in the abstract or concrete, it is necessary to first address the question of how contemporary scientific knowledge is produced. Given that the process of translating scientific knowledge requires the field-specific expertise of multidisciplinary teams of researchers, it therefore serves to discuss the nature of scientific knowledge production itself and the interdisciplinarity inherent in applying it to a specific context.

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."[4] Employing basic research results to specific applications is *necessarily* an interdisciplinary endeavour: providing solutions for *real-world* problems (e.g. to provide a therapy for a particular disease) requires the application of knowledge by multiple disciplines. In this particular case, applying knowledge requires an interdisciplinary group of actors to interpret and make use of information produced through laboratory bench work as well as to understand the factors driving the need for these applications. Research in the biological sciences is therefore continuously affected by social and

[4] Gaston Heimeriks, "Interdisciplinarity in Biotechnology, Genomics and Nanotechnology," *Science and Public Policy* 40 (2013): 98.

economic supply and demand factors, and projects that may be categorized as "basic" are also often assessed for their potential applicability. As will be discussed, translation and innovation occur within interdisciplinary contexts and involve a range of actors and methodologies from outside the laboratory. This section will examine particularly important concepts within STS, and, specifically, will detail the current state of "post-academic science" as well as the commodification of scientific knowledge.

2.1.1. The "New Production of Knowledge"

The notion that scientific knowledge production is a social endeavour is no longer especially novel. As numerous scholars of STS have noted, the image of the lone scientist in noble pursuit of an abstract truth is archaic and misleading, and despite the current intellectual delineation of various scientific disciplines, knowledge is often produced through interdisciplinary collaboration and frequently moves with rapidity between and across disciplinary boundaries.[5] To that end, it is necessary to first define what is meant by *research* within the sciences and distinguish between the two primary modes of scientific knowledge production, and to further define and discuss what is referred to as the "new production of knowledge," so as to accurately depict the current epistemic state of scientific research.

Standard definitions of what constitutes *scientific research* generally bring to bear inaccurate portrayals of research as an active attempt to understand natural phenomena without consideration for particular application. Following the growth of what is now referred to as *Big Science* during the Second World War, Vannevar Bush, then head of the United States Office of Scientific Research and Development, argued that scientific

[5] John Ziman, *Real Science: What It Is, and What It Means*.

innovation occurred in a linear fashion, in which basic research could only proceed successfully if it were undertaken by scientists seeking to understand the fundamental laws of nature, free from the pressure of commercial necessity.[6] While Bush's unrelenting insistence that basic science advances without the pressure to produce immediate, tangible results no longer holds true given the growth of university-industry-government relations in recent decades, definitions of basic research often emphasize the technical nature of laboratory bench work while failing to acknowledge the role of actors across the R&D spectrum. Gaston Heimeriks, for example, defines scientific research as "relat[ing] to everyday activities of researchers in their local context of work: gathering data, using equipment and infrastructures, data analysis, and writing up results."[7] However, as Steven Shapin, Peter Galison, and numerous other scholars of the history and sociology of science have emphasized, (fundamental) research extends beyond the technical work occurring within the laboratory, and knowledge production frequently results from a complex ebb and flow of information across disciplinary boundaries.[8] Research often begins with particular socio-economic supply and demand factors in mind (in terms of funding), and, as will be discussed, translational research specifically is driven only partially by a desire to understand natural phenomena (in contrast to the normative understanding of *fundamental* science).

In 1942, Robert K. Merton's work on what he famously described as the *normative structure of science* argued that well-founded scientific research follows a distinct set of

[6] Vannevar Bush, *Science: The Endless Frontier* (Washington: United States Government Printing Office, 1945).
[7] Gaston Heimeriks, "Interdisciplinarity in Biotechnology, Genomics and Nanotechnology": 99.
[8] See Peter Galison, *How Experiments End (*Chicago: University of Chicago Press, 1987); Steven Shapin, *The Scientific Life: A Moral History of a Late Modern Vocation* (Chicago: University of Chicago Press, 2010); and Partha Dasgupta and Paul A. David, "Towards a New Economics of Science," *Research Policy* 23, no. 5 (1994): 487-521.

criterion appropriately summed up by the acronym CUDOS.[9] If scientific knowledge were to be accepted as legitimate and incorporated into the "communal stock," it had to be communal in its availability, universally evaluated on the basis of impersonal criteria, disinterested in nature, original, and assessed with organized scepticism.[10] Essentially, the norms laid out by Merton provide a framework for guiding "good" science, and differentiate scientific research from all other fields of inquiry. Though the Mertonian norms of scientific research are somewhat outdated (particularly in terms of their implicit characterization of scientific research as an exercise outside of social, political, and economic influence), they nevertheless provide a basis for distinguishing between systems of knowledge production and highlight the significance of making research results communally available (i.e. of publication).

Traditionally, Mertonian norms are used to describe a particular system of knowledge production referred to as *Mode 1*, introduced by Gibbons et al. Any discussion of scientific knowledge production in academic, industrial, or political contexts that fails to acknowledge the now fundamental concept of *Mode 1* versus *Mode 2* systems of knowledge production and dissemination falls short of adequately explaining current research practices – namely, applicability and interdisciplinarity – in the sciences.[11] The underlying intricacies of Mode 1/Mode 2 systems of knowledge production are elaborate to say the least, suffice it to say for the moment that both modes refer to a complex set of methods, values, theories, and communities in which scientific

[9] The acronym CUDOS stands for the Mertonian norms of communalism, universalism, disinterestedness, originality, and organized skepticism.
[10] Robert K. Merton, *The Sociology of Science: Theoretical and Empirical Investigations* (Chicago: University of Chicago Press, 1973).
[11] See Michael Gibbons et al., *The New Production of Knowledge: The Dynamics of Science and Research in Contemporary Societies* (London: Sage Publications, 1994).

research occurs and knowledge is subsequently produced and circulated.[12] Knowledge produced under the conditions of Mode 1 is customarily a discipline-based product of problems set and solved by a distinct, homogenous group of practitioners, and generally adheres to Mertonian norms. It is, essentially, the production of knowledge occurring in the absence of a particular practical objective, with the term being used interchangeably with *pure* science.

In contrast, Mode 2 knowledge is produced *in the context of a specific application* and is motivated by real-world concerns. It is in this context that the concepts of interdisciplinarity and applicability come together: insofar as research is applicable, it is produced by interdisciplinary teams. As Gibbons et al. note, Mode 2 inquiry is guided by "…the integration of skills in a framework of action," and solutions to Mode 2 problems are comprised of both theoretical and empirical components.[13] Of importance is the understanding that *application* is not synonymous with *product development*, but rather, the process of *applying* knowledge involves an attempt to solve problems that incorporate expertise and knowledge bases beyond the scope of a single discipline – that are interdisciplinary by nature. For example, take the hypothetical case of treating drug-resistant cancer. Solving this particular problem (i.e. treating this disease) requires the application of knowledge from relevant fields of expertise to address a broad array of questions for a holistic solution: for instance, to what degree does the expression of specific gene sequences play a role in the severity of this disease? Are there particularly aggravating epigenetic factors? Which compounds are most efficacious in mitigating the effects of this disease, and in what dosages? What are the costs associated with pre-

[12] Ibid.
[13] Ibid: 5.

clinical and clinical testing, as well as product marketing? What social and economic considerations must be taken into account in developing a candidate product for clinical use? Should treatment be administered if the consequent side effects are too severe? Answers to these questions are not supplied *solely* by pharmacologists or *solely* by molecular geneticists, but rather they draw upon the *application* of knowledge and expertise from multiple disciplines, from biochemistry to applied mathematics to biomedical ethicists. Epistemic contributions from these disciplines (e.g. answers to specific questions such as these) are combined as part of a dynamic, holistic solution to a broader question. Answering this broader question is, essentially, Mode 2 knowledge production: a means of *applying* the knowledge of *interdisciplinary* groups in a larger collaborative process to design research projects, coordinate methodologies, interpret data, and ultimately solve a specific *real-world* problem.[14]

Though Mode 1 knowledge does not "collapse" into Mode 2 with the slightest suggestion of a specific use, both modes interact with their counterpart. As we see in the case of translational science, theories are often developed with a particular means of employment in mind and, conversely, applications are based on theoretical knowledge. For example, laboratory research examining the inhibition of particular enzymes in vitro may have no immediate practical application yet is undertaken with the aim of shedding light on potential therapeutic avenues; moreover, the refinement of doses and dosage regimens of a particular enzyme inhibitor is based on a pharmacokinetic and toxicological knowledge base. Each mode compliments its counterpart.

[14] See Gibbons et al., *The New Production of Knowledge*; Henry Etzkowitz and Loet Leydesdorff, "The Dynamics of Innovation: From National Systems and 'Mode 2' to a Triple Helix of University-Industry-Government Relations," *Research Policy* 29 (2000); and Gaston Heimeriks "Interdisciplinarity in Biotechnology, Genomics and Nanotechnology," *Science and Public Policy* 40 (2013).

In sum, the differentiation between these two primary modes of knowledge production lies primarily in the context in which research projects are undertaken: Mode 1 knowledge is produced to illuminate the nature of particular phenomena, while Mode 2 knowledge is produced in the context of application. As numerous sociologists of science have noted, it has become increasingly difficult to conduct and justify funding for research that falls solely within the confines of a single discipline. Knowledge production, particularly in the biological sciences, "…has been coupled more directly than before to political, economic, and social problems," and thus the "market" for scientific knowledge has broadened significantly.[15] The purpose of highlighting this "new production of knowledge" is to emphasize the relationship between the consideration given to contextual application at the outset of research projects and the consequent interdisciplinarity of practice and varying epistemic roles of actors involved in the research process. The diffusion of research results and information across disciplinary boundaries to "real world" applications that occurs in Mode 2 research results from this relationship. As will be discussed in ensuing sections, the emphasis on the utility and applicability of knowledge produced under the conditions of Mode 2 is demonstrated by the allocation of public and private funding primarily towards research with manifest potential to address widespread social and economic problems.

2.1.2. "Post-Academic Science"

The birth of the biotech industry in the late 1970s and the subsequent transition to what John Ziman describes as "post-academic science" – that is, science not driven by an

[15] Peter Weingart and Nico Stehr, *Practising Interdisciplinarity* (Toronto: University of Toronto Press, 2000): xiv.

abstract campaign to produce esoteric knowledge, but rather science as an interdisciplinary endeavour – has essentially laid to rest the stereotypical image of a strict dichotomy between fundamental and applied science. The understanding that scientific research involves an interaction between Mode 1 and a variant of Mode 2 of course does not suggest that *science*, as an epistemic enterprise, has moved from a previously noble and unbiased starting point to one motivated almost entirely by the desire to create products and maximise profit, but rather makes room for the recent trend in knowledge production being "…the outcome of a process in which supply and demand factors can be said to operate."[16] As will be discussed, these factors help to illustrate the socio-economic catalysts that drive research endeavours in the biomedical sciences.

To quote Gibbons et al., "the market for [scientific] knowledge – the number of places where it is wanted and can be used – is now wider and more differentiated than it has ever been."[17] In other words, the market in which Mode 2 knowledge and the problems it seeks to solve has expanded. In this particular case, the growing impatience (again, on behalf of the lay public, public funding institutions, government groups, and so on) for efficacious diagnostics, therapeutics, and preventative strategies with the potential to alleviate the proliferation of diseases negatively impacting public health in the United States constitute *demand factors*. Problems arise, however, given this commonly held lay assumption that developments in biomedicine and pharmacology occur in giant leaps made over short periods of time, when in fact, it is the incremental acquisition of fundamental knowledge that accrues over years (often decades) that permits researchers to grasp the significance of a discovery and to exploit it.

[16] Gibbons et al., *The New Production of Knowledge*: 4.
[17] Ibid: 49.

In response to these demand factors, namely the expectation for rapid biomedical and pharmaceutical product development, the increased emphasis on interdisciplinary research and translational science among the scientific community and various funding agencies, and the consequent inclusion of methodologies, techniques, funding sources, and actors from across the R&D spectrum in the research process (i.e. the expansion of Mode 2) constitute the *supply factors*. As Ziman notes, post-academic science is an extension of Mode 2 science: it no longer occurs *solely* in the context of academia, and it not only *produces* knowledge, it *constructs* knowledge "in accord with the commercial, political, or other social interests of the bodies that underwrite its production." [18] Thus the potential socio-economic appropriability of research projects is critical, particularly in terms of motivating research and securing funding.

While post-academic science is not inherently *pure* in the traditional sense – in that it is not undertaken solely with the objective to observe and produce knowledge regarding the natural world without any application in mind at the outset – it remains curiosity-driven and *mission-oriented*. Post-academic science is directed by the desire to gain an understanding of natural phenomena so as to solve a specific problem, the solution to which may be a tangible artefact (e.g. a marketable therapeutic agent) or something more abstract (e.g. a digital technology, such as a drug screening platform). It is characterized by an effort to "direct research towards economically and socially useful goals, [and to] organize research around national priorities."[19]

It is at this point that the discussion of Mode 2 (section 2.1.1) is particularly

[18] John Ziman, *Real Science: What It Is, and What It Means*: 173.
[19] Richard Whitley, *The Intellectual and Social Organization of the Sciences* 2nd ed. (New York: Oxford University Press, 2000): 296.

relevant. Applying the knowledge of interdisciplinary groups in a larger collaborative process to solve real-world problems requires the consideration of multiple supply and demand factors extending across the spectrum of research and development. To that end, translating knowledge and information – moving Mode 1 knowledge across disciplinary boundaries – is essential. Applying knowledge to contexts that may potentially satisfy national priorities (most often issues related to public health, the environment, and national security) occurs through the efforts of interdisciplinary teams of researchers, each providing epistemic contributions from relevant disciplines, which are then combined as part of a dynamic, holistic solution to a broader question. If the research discussed in this particular thesis is to be understood as "post-academic" and mission-oriented, then successfully translating scientific knowledge requires: (1) an understanding, based on the model of Mode 2 science previously discussed, that innovation and the application of knowledge occurs in the context of interdisciplinary collaboration; (2) an acknowledgement of various demand factors driving research (e.g. the economic and social burden of wide-scale chronic disease); and (3) the intent to solve real-world problems by applying knowledge to create or produce a product (tangible or otherwise) that pertains to a specific context of use, *as well as* the intent to understand the root causes of phenomena (i.e. the etiology or pathogenesis of disease) such that these products may be developed in future.

While additional economic factors must be taken into consideration when translating scientific knowledge, the aforementioned conditions constitute a set of base criteria upon which successful knowledge translation may be held to. The scientific

research in question in this thesis is an epistemic endeavour born of interdisciplinary collaboration, and is driven largely by socio-economic supply and demand factors.

2.2. The Commodification of Translational Science

The process of translating scientific knowledge, particularly in commercially salient fields, such as pharmacology and biotechnology, implies a "commodification" of knowledge itself. Narrowly speaking, commodification suggests a buying and selling of scientific expertise and research results. In this case, however, I employ a somewhat more abstract notion, in which "all kinds of scientific activities and their results are predominantly interpreted and assessed on the basis of [socio-]economic criteria."[20] As discussed in section 2.1, the way in which knowledge is applied to particular contexts in post-academic biomedical science is an interdisciplinary endeavour, and knowledge production is itself a response to supply and demand factors. The means of transferring knowledge and information across disciplinary boundaries are therefore similar to the circulation and exchange of goods in a market system. Simply put, "a market is a social institution for the systematic exchange of commodities for currencies between vendors and customers."[21] The market for knowledge and information "…is a notional market where the vendors are individual researchers, [and] the commodities are research results," and research results, inscribed in published papers, "…are treated as the quantifiable output of a 'knowledge production process,' arising from specific contracts for projects

[20] Hans Radder, "The Commodification of Academic Research," *The Commodification of Academic Research: Science and the Modern University*, ed. Hans Radder (Pittsburgh: University of Pittsburgh Press, 2010): 4.
[21] John Ziman, "The Microeconomics of Academic Science," in *Science Bought and Sold: Essays in the Economics of Science*, ed. Philip Mirowski and Esther-Mirjam Sent (Chicago: University of Chicago Press, 2002): 323.

funding research or employment."[22] In this particular context, the supply and demand factors discussed in section 2.1 fuel the exchange of commodities, and both public and private actors constitute the customers.

As such, information may therefore be sold in the intellectual property market and may be used to generate revenue, particularly if it has been patented. In the case of translating scientific knowledge, however, the commodities and currencies traded are not necessarily given any monetary value, and fundamentally *intangible* benefits may be appropriated at the same time as economic benefits, depending on the way in which knowledge moves from "supplier" to "customer:" actors outside the scope of the knowledge production process may benefit from the translation of knowledge. For instance, the public at large may benefit enormously from information circulating and moving across disciplinary boundaries, particularly when that information has the potential to alleviate wide-scale health issues with consequent deleterious economic effects. Private industry also benefits from the circulation of information across disciplinary boundaries: in the case of pharmaceutical development, for example, moving fundamental research results towards a stage wherein a candidate product may be developed and marketed is undoubtedly a means of generating future revenue.

The commodification of knowledge leads to incentive for public and private investment in translational research and an interest on behalf of those same actors (i.e. those not partaking in research) outside the process of knowledge production itself at either end of the production scale (at the outset, wherein knowledge may only be suggestive of a particular application, and ending with a tangible product). This incentive for public investment in translational research rests on the obvious social and economic

[22] Ibid: 332, 332.

benefits that may result (e.g. large-scale improvements in public health that lead to a decrease in the strain on public healthcare, increased productivity and life expectancy of a population, etc.).[23] Further, there is additional incentive for investment from private industry, as translational science increases the rate of knowledge diffusion from initial scientific discovery to clinical trial to the creation of a product with market value. As Hans Radder notes, "commodification enables the orientation of academic research toward technological advancement and socioeconomic priorities."[24] In this sense, the commodification that stems from knowledge translation involves not only appropriating monetary benefits (e.g. in terms of gaining profit from the sale of a particular therapeutic), but may also be regarded on a more abstract level, in which intangible benefits arise from the circulation and exchange of knowledge. Moreover, additional beneficiaries – particularly private pharmaceutical companies – often are quick to pounce on research or novel therapeutics emerging from public laboratories, and may rapidly develop new compounds with slight molecular variations at a much faster rate and at a lower cost to their own financial benefit. The benefits potentially derived from the commodification of fundamental scientific knowledge therefore provide incentive for private industry to accelerate the movement of research results from basic to applied settings, and by extension, in the case of NCATS, to work in conjunction with public research agencies so as to expedite this process.

This section will discuss the commodification of translational science, focusing on the properties of knowledge as a public good, and the implications of categorizing scientific knowledge as such. My aim is to briefly remark on the interests of public and

[23] John P. Bunker, "The role of medical care in contributing to health improvements within societies," *International Journal of Epidemiology* 30, no. 6 (2001): 1260-1263.
[24] Hans Radder, "The Commodification of Academic Research": 13.

private actors in the creation and circulation of that knowledge. In doing so, I highlight the significance of commodification as an inherent feature in the process of translating scientific knowledge.

2.2.1. Scientific Knowledge as a Public Good

Scientific knowledge translated under the auspices of the National Center for Advancing Translational Science (NCATS) may be categorized as a *public good*, owing largely to its commercial salience and intrinsic economic characteristics. Two particular aspects define the notion of a good in the economic sense: rivalry and excludability. In this sense, "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."[25] Moreover, a good is rivalrous when two or more actors are competing for its use. Conversely, then, 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. While public goods are typically seen as being tangible items (e.g. fresh water or traffic lights), we may consider scientific knowledge to be a public good.

Michel Callon qualifies scientific knowledge as a "quasi-public good," owing to the fact that it is to a certain degree appropriable in very specific situations; for example, if actor A sells unpublished information to actor B regarding the means of manipulating a certain gene pathway, B may enjoy exclusive use of that information.[26] For simplicity's sake, I argue that scientific knowledge may be considered as a public good. As Callon

[25] Michel Callon, "Is Science a Public Good?" *Science, Technology, and Human Values* 19, no. 4 (1994): 399.
[26] Ibid.

notes, the "ease of appropriation [of a good] appears to depend on the material or the base in which the information is inscribed."[27] In the case of scientific knowledge, information is made publically available when it is published in peer-reviewed journals (and thus legitimized, according to Mertonian norms), and this inscription consequently assures its non-excludability. Further, scientific knowledge is a quintessential non-rival good: putting knowledge inscribed in a particular form (a journal article, for example) to use does not prevent others from mobilizing the same knowledge at the same time (assuming these actors possess the same skills and expertise). Accordingly, scientific knowledge is "a durable [public] good, not destroyed or altered by its use," and this fecundity allows for information to be used in a broad range of applications.[28]

Let us proceed, then, under the assumption that scientific knowledge is a public good, in light of the fact that while it may still be circulated, exchanged, or engaged in commercial transactions it maintains its non-rivalrous and non-excludable properties. The implications of scientific knowledge as a public good are therefore far-reaching, particularly as they motivate the process of translating scientific knowledge itself (from bench to bedside). Competition (for profit) is a key market mechanism, and given that the market provides little incentive for private actors/institutions to produce non-rivalrous, non-excludable goods, it consequently cannot be relied upon to yield public goods (or to do so efficiently). The future economic value of fundamental scientific knowledge is speculative at best and particular uses for such knowledge are often conjectural as well: as Ziman notes, a large percentage of fundamental research results are "almost worthless

[27] Ibid.
[28] Ibid: 401.

commercially, and largely trivial."[29] This does not imply there are no privately provided public goods, however the onus falls largely on the government to do so. Take basic scientific knowledge, for example. There is little motivation for a private company such as Pfizer or Merck to undertake and invest in basic research endeavours with *potential* application value (therefore not guaranteeing revenue) or to make the results of this research publically available (thereby making it difficult to exploit and appropriate rent). The ultimate goal of private industry is to accrue profit from their respective products, and, as discussed previously, to place knowledge production at the disposal of financial interest undermines the validity of scientific knowledge itself.[30]

Of course, scientific research and development does not always follow a linear model; rather, research projects often begin and end with particular socio-economic supply and demand factors.[31] As will be discussed in ensuing sections, basic scientific research has traditionally been funded almost exclusively by public agencies (such as the National Institutes of Health), while private industry has taken on the development of tangible, marketable products (such as a particular therapeutic). As Dasgupta and David note, this occurs for several reasons, namely that (1) the market value of fundamental science is often difficult to forecast; and (2) "realization of economic rents ('profits') from a basic research advance…are intrinsically difficult to establish and defend," and as such "private returns to investment are highly uncertain."[32]

Translating scientific knowledge is motivated largely by the need to alleviate major socio-economic issues currently plaguing public health in North America; for example,

[29] John Ziman, "The Microeconomics of Academic Science:" 336.
[30] Ibid: 335.
[31] See section 2.1.1 above, "The 'New Production of Knowledge'."
[32] Partha Dasgupta and Paul A. David, "Towards a New Economics of Science": 490.

the rocketing cost-per-patient burden on the national healthcare system brought about by emerging, re-emerging, and chronic diseases, or the consequent decline in quality of life for those with untreatable health issues. This is done in theory by rapidly moving laboratory science to the bedside of the patient so as to create novel diagnostics and therapeutics with the potential to mitigate the socio-economic costs stemming from prevalent or insidious disease (in this case, cancer pharmaceuticals). By extension, then, NCATS is to produce *nearly* commercial science through funding research endeavours that yield publically available knowledge (i.e. early clinical trials, drug screening studies, and so on, inscribed in peer-reviewed journals). It is *nearly* commercial in that it is not quite at the stage where it can be marketed, though it has a designated application that has been tested to a degree. This knowledge is made a public good with government support (and retains its non-rivalrous and non-excludable qualities following publication), at which point private industry steps in to fund late-stage clinical trials, ultimately producing a marketable product.[33]

In terms of translational science as a discipline and the scientific knowledge produced thereof, its status as a public good and its categorization as "post-academic science" are not mutually exclusive, as it is generally created in the context of application and moved across disciplinary boundaries with this application in mind. Indeed, translational science is, by definition, mission-oriented. Undoubtedly, as will be discussed in ensuing sections, we see (1) an understanding, based on the model of Mode 2 science previously discussed, that innovation and the application of knowledge occurs

[33] The notion of translational science as a *good*, specifically in the context of developing novel cancer pharmaceuticals, will be elaborated in further detail in the final section of this thesis. As will be discussed, NCATS does not aim to only produce tangible, marketable products itself, but also seeks to support and accelerate the movement of knowledge across the basic/applied spectrum (from "bench to bedside).

in the context of interdisciplinary collaboration; (2) an acknowledgement of various demand factors driving research (e.g. the economic and social burden of wide-scale chronic disease); (3) the intent to solve real-world problems by applying knowledge to create or produce a product (tangible or otherwise) that pertains to a specific context of use, *as well as* the intent to understand the root causes of phenomena (i.e. the etiology or pathogenesis of disease) such that these products may be developed in future; and (4) the production of *nearly* commercial science and subsequent inscription/publication in publically available, peer-reviewed journals.

2.2.2. Science in Service of the Nation

Ziman aptly describes the current state of scientific research as *science in service of the nation*, with the aim of *utility* (social, economic, political, or otherwise) rapidly becoming a standard norm in the production of knowledge.[34] If we are to proceed with the concept of translational science is a public good ultimately aimed at alleviating or mitigating the socio-economic effects of wide-scale disease, we may also infer that an increasing and varied number of interest groups – including governmental groups and organizations, federal regulators, private and commercial firms, private healthcare providers, the media, patient advocacy groups, and the general public – have a stake in the knowledge translated under the auspices of the National Center for Advancing Translational Science (NCATS). Supposing, for the purposes of this section, that the public does indeed have a stake in NCATS-funded research, due to the potential social and economic gains to be derived from the knowledge consequently produced. It is beneficial to re-emphasize that (1) scientific knowledge inherently possesses commercial

[34] John Ziman, *Real Science: What It Is, and What It Means*: 74.

properties (i.e. information can be marketed, both literally and figuratively, and tangible commodities contributing to national prosperity may be produced thereof); and (2) it consequently serves that the public has a legitimate claim to potential benefits this knowledge may produce (e.g. in the form of diagnostics and therapeutics).[35] Clearly, then, public and private actors have a vested interest in the research funded by NCATS, particularly as there is potential for the knowledge produced by these research endeavours to yield marketable products that address social or economic demand factors. Efforts to translate science are, inherently, in service of the nation. As will be discussed, what is novel in the case of translational science is the coalescence of public and private funds and actors along the R&D spectrum.

Given the implicit role that public and private actors play in the field of translational biomedicine and the stake in publically-funded research they may legitimately make claims to, it therefore serves that research involving more prevalent diseases with larger populations to treat, and by extension to offset the costs of production, is more favoured in terms of funding than rarer conditions.

In theory, economic returns are increased when knowledge (in this case, research results) contributes directly to solving problems affecting large population percentiles. Diseases such as diabetes, chronic hypertension, and hyperlipidemia, for instance, have large target populations, while rarer diseases that may, in fact, be easier to target (e.g. those with single gene defects) are extremely costly, both for the pharmaceutical companies funding late-stage clinical trials and manufacturing therapeutics as well as for

[35] In this particular case, I define the *public* as both the tax-paying populace as well as government groups. Consequently, involvement in research funding therefore stems from taxation, government initiatives, and so forth, while public "ownership" of scientific knowledge is implied due to the financial contributions previously given.

health insurance providers. Imatinib, for example, was the first successful treatment for chronic myelogenous leukemia, a particularly devastating disease.[36] The population of those affected and the consequent market penetration of the drug, however, is relatively small, and the price per annual treatment course fluctuates between $90,000 and upwards of $138,000 depending on the brand.[37]

Prior to the growth of translational science, the formula for funding research aimed at developing pharmaceuticals was proportional to a number of factors, namely time for and cost of drug development, as the desire for healthy profit margins versus the actual costs of production and the number of patients in need of similar therapeutics plays a significant role in the sustainability of the national healthcare system. Consequently, close ties between the private pharmaceutical industries in the United States ensured that government funding for research conducted in public laboratories (including universities) favoured more prevalent (and more profitable) disease targets.[38]

In the case of translational science as a field of research and development, however, the nature of scientific knowledge production and its consequent status as a *nearly* commercial public good incurred through the process of translation alters the formula for funding drug development research. As I will discuss in sections 3.1 and 3.2, research occurring under the umbrella of NCATS is intended to fill the gaps between public research institutions and private industry that are traditionally created by the desire to solely (or predominantly) address diseases with commercial salience. Funding for

[36] Leslie Pray, "Gleevec: the breakthrough in cancer treatment," *Nature Education* 1, no.1 (2008): 37.
[37] C. Abboud, et al. "The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts." *Blood* 121, no. 22 (30 May 2013): 4439-42.
[38] See Paula E. Stephan, *How Economics Shapes Science*, and Elizabeth Popp-Berman, *Creating the Market University: How Academic Science Became an Economic Engine* (Princeton: Princeton University Press, 2012).

translational research is of course driven by the desire to streamline drug development (engendering health profit margins for private industry by extension). However, the status of scientific knowledge as a public good also highlights the role played by socio-economic considerations in expediting translational science *in service of the nation*, as research results have the potential to produce tangible commodities that may contribute to national prosperity, improve quality of life, and so on.

2.3. What Does it Mean to Translate Biomedical Science?

Recall, three questions were posed in the introduction of this thesis: (1) what does it mean to translate scientific knowledge?; (2) what role do socio-economic considerations play in research endeavours proposing notional "products" with applicatory potential (such as novel pharmaceutical targets or prototypes)?; and (3) is NCATS-funded research *translational* according to this definition?

From the preceding discussion, we may begin to answer two of these three questions. The ultimate aim of translational science is to accelerate the process of diffusing knowledge from the laboratory to the clinic to the medicine cabinet. The traditional definition of translational science put forth by the scientific community, wherein *translation* refers to "a unidirectional continuum in which research findings are moved from the researcher's bench to the patient's bedside and community," fails to address either the context in which this knowledge is produced, the means of moving research findings along the basic/applied spectrum, or the factors driving research.[39] Through an STS lens, this process requires some consideration for the conditions at the

[39] Doris McGartland Rubio, et al., "Defining Translational Research: Implications for Training," *Academic Medicine* 85, no. 3 (March 2010): 472.

outset of knowledge production, namely the socio-economic demand factors that motivate research, and the applicatory contexts that drive scientific experimentation. As discussed, *application* generally begets *interdisciplinarity*: applying knowledge to solve real-world problems requires the incorporation of expertise and knowledge bases from beyond the scope of a single discipline, each of which is combined as part of a dynamic, holistic solution. Translational science entails a transformation of research results – such that fundamental knowledge may be understood and applied in clinical settings – achieved through the process of transforming and inscribing basic research results into a particular base form (i.e. a published article) to consequently be diffused across disciplinary boundaries and into a particular context of application by heterogeneous groups of researchers.

Of overarching importance in this case is the categorization of scientific knowledge as a public good, owing to its non-rivalrous and non-excludable characteristics. The implications of this assertion highlight the necessity of public/private collaboration in translating scientific knowledge from "bench to bedside," as private industry is needed to move *nearly* commercial science from early clinical trials to the production of a marketable product. Moreover, as a result of its status as a public good, translating knowledge requires consideration for the socio-economic motivations for translating this knowledge, namely that actors from outside the research process (i.e. the lay public, public and private funding institutions, government groups, private industry, and so on) have a vested interest in translational science.

What, then, does it mean to translate scientific knowledge? I argue that translational science first requires fundamental knowledge to be produced under the conditions of

"post-academic" science. That is, research is embarked upon *in service of the nation*, with the intent to solve real-world problems by applying the knowledge and expertise of relevant disciplines to create or produce a product (tangible or otherwise) that pertains to a specific context of use, *as well as* the intent to understand the root causes of phenomena (i.e. the etiology or pathogenesis of disease) such that efficacious products may be developed more rapidly and the adverse effects of these products are more accurately predicted. Further, given that these real-world problems extend beyond the scope of a single discipline, research projects are undertaken in an interdisciplinary and applicatory context, incorporating methodologies, techniques, funding sources, and actors from beyond the context of the laboratory, and both knowledge production and problem solving are driven by very particular demand factors (namely, the socio-economic burden of wide-scale disease). The nature of this knowledge, produced under these conditions and in these specific contexts, may be categorized as a public good. To translate scientific knowledge, therefore, entails a remodelling of fundamental research results, produced by means of interdisciplinary collaboration, from a potentially applicable state to a *nearly* commercial, non-rivalrous, and non-excludable state, thereby producing a solution to a specific real-world problem.

What role do socio-economic considerations play in research endeavours proposing notional "products" with applicatory potential? I have argued that translational science necessarily requires a synthesis of socio-economic considerations in terms of how is produced and how real-world problems are solved – both prior to the launch of and throughout a particular research project. Given that public/private collaboration is needed to move nearly commercial science from the laboratory or early trial stage to late-stage

trials and marketable product, research is motivated by the desire to maximise profit (in the case of private industry), the need to address costly or neglected diseases (in the case of public actors funding basic research), and the overall need to streamline the movement of knowledge from "bench to bedside." This particular question will be elaborated on further in the discussion of NCATS itself.

Translational science in action will be discussed in the ensuing section of this thesis, specifically in the context of cancer research occurring at the National Center for Advancing Translational Science. In doing so, I will apply the aforementioned conclusions to research directed towards the development of novel oncologic therapeutics and diagnostics funded by NCATS. Specifically, I will address translational science and its socio-economic motivations in the case of systems pharmacology (and its principal fields of genomics, proteomics, and metabolomics), and examine a particular case study of research in cancer biology.

3. The National Center for Advancing Translational Science

In December of 2011, the U.S. National Institutes of Health (NIH) launched the National Center for Advancing Translational Science (NCATS), the mission of which is "to catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions."[40] The purpose of NCATS is twofold: (1) to refine the currently unsustainable modes of drug development from initial laboratory target discovery to FDA approval of a candidate product; and (2) to avoid the familiar scenario in which basic research findings with the potential to contribute in one way or another towards alleviating prominent socio-economic issues languishes in the laboratory or at the preclinical stage, its worth known only to highly specialized researchers while it is neglected by the masses of clinicians and private funding sources. In the idealized scenario of the NIH, the development of diagnostics and therapeutics is accelerated by introducing innovative translational techniques, with NCATS-funded researchers exploring new or prospective drug targets, or compounds previously overlooked or abandoned by private pharmaceutical initiatives, while simultaneously "bringing together similarly oriented mechanism-based researchers currently separated in the NIH's disease-specific institutes," and pursuing clinical trials thereafter.[41] Consequently, the timeframe in which knowledge moves from "bench to bedside" and is transformed into a tangible commodity from which social and economic benefits may be appropriated is, in theory, dramatically reduced. The NIH has identified three areas of translational research into

[40] "NCATS Mission Statement," *NCATS: The National Center for Advancing Translational Science*, NIH: The National Center for Advancing Translational Science, accessed 1 May 2014.
[41] Jerry Avorn and Aaron S. Kesselheim, "The NIH translational research center might trade public risk for private reward," *Nature Medicine* 17, no. 10 (October 2011): 1176

which NCATS-funded projects are divided into three stages of translation (designated as T1, T2, and T3).

> T1 research expedites the movement between basic research and patient-oriented research that leads to new or improved scientific understanding or standards of care. T2 research facilitates the movement between patient-oriented research and population-based research that leads to better patient outcomes, and the implementation of best practices, and improved health status in communities. T3 research promotes interaction between laboratory-based research and population-based research to stimulate a robust scientific understanding of human health and disease.[42]

In focusing exclusively on T1 research, this section will discuss the need for a federally funded research body specifically devoted to translational science, applying the concepts of applicability and interdisciplinarity, as well as the definition of translational science discussed in the preceding section to NCATS and several case studies in particular. This thesis focuses solely on studies that fall under the umbrella of cancer biology and systems pharmacology – many of which are projects nearing the cusp of commodity status – as knowledge application occurs at the interface between basic and clinical settings, where translating knowledge entails a transformation of fundamental research results produced by means of interdisciplinary collaboration to a *nearly* commercial, non-rivalrous, and non-excludable state with *potential* applicatory value. I endeavour to demonstrate the need for considering the conditions at the outset of knowledge production, namely the socio-economic demand factors that motivate research as a result of the status of knowledge as a public good, as well as the ways in which the model of post-academic science discussed in section 2 (namely, the applicatory, interdisciplinary contexts that drive scientific experimentation and move research results across the basic/applied spectrum) help to make sense of NCATS-funded research.

[42] Doris McGartland Rubio, et al., "Defining Translational Research: Implications for Training," *Academic Medicine* 85, no. 3 (March 2010): 473.

3.1. Accelerating Drug Development: The Need for a National Centre

Recall, section 2.1 addressed the means in which knowledge is produced in what John Ziman has termed post-academic science. As discussed, solving specific real-world problems involves *applying* the knowledge of relevant, *interdisciplinary* groups in a larger collaborative process to design research projects, systematize methodologies, and interpret data. NCATS is, essentially, a coordinated effort to bring together the requisite groups of researchers needed to solve these real-world problems, and in doing so, produces *nearly* commercial science and extends consideration to a range of socio-economic supply and demand factors. The focus of this section is firstly the bottlenecks plaguing the drug development process, and secondly the means by which NCATS intends to remove many of these bottlenecks by providing an environment in which post-academic knowledge production and translation may occur.

The path from initial laboratory bench work to the development of an FDA-approved candidate product is not, by any means, a linear one, nor is it dominated by one particular discipline. The time required to develop novel drug compounds, in addition to the requisite costs, have increased significantly in recent decades, and the current inefficiencies and lags in pharmaceutical development are exacerbated by ever-increasing public demand for efficacious therapeutic options. While studies targeting infectious and cardiovascular disease have had higher success rates (roughly 20%), those targeting central nervous system (CNS) diseases or oncologic studies are significantly less successful (roughly 5-8%), and studies of compounds targeting novel mechanisms have notably higher failure rates than studies of targets previously successful in drug

development.[43] Moreover, roughly 43% of compounds fail to progress past Phase III clinical trials (i.e. large-scale in vivo trials) and roughly 23% fail to pass registration, with the costs of developing a marketable product rising steeply with continued late-stage failures.[44]

Given the potential risks and the costs associated with failure, funding research in pharmaceutical development (i.e. stage one [T1] translational research) is fraught with uncertainties. The alarmingly slow rate of FDA approval for drugs addressing a novel target class presents private pharmaceutical companies with numerous patent expirations and economic strains, which in turn has led to a trend in the reduction of private investment in pharmaceutical R&D.[45] This climate has consequently necessitated collaboration between the NIH (the United States' primary medical research agency and funding body), private investment groups, and biotech industries. Prior to the establishment of NCATS, roughly 60% of the NIH budget was allocated towards basic research, while slightly less than 30% was spent on clinical research.[46] As well, the majority of private venture capital funding for drug development is typically directed at prototypes that have completed preliminary small-scale in vivo trials (i.e. Phase I trials), while funding for basic laboratory research (such as drug target validation) languishes.[47]

In creating programmes such as the Clinical and Translational Science Awards (CTSA), the Molecular Libraries Program (MLP), and Therapeutics for Rare and

[43] Ismail Kola, "The State of Innovation in Drug Development," *Clinical Pharmacology and Therapeutics* 83, no. 2 (February 2008): 228.
[44] Ibid.
[45] Francis S. Collins, "Reengineering Translational Science: The Time Is Right," *Science Translational Medicine* 3, no. 90 (6 July 2011): 2.
[46] Doris McGartland Rubio, et al., "Defining Translational Research: Implications for Training" *Academic Medicine* 85, no. 3 (March 2010): 474.
[47] John C. Reed et al., "The NIH's role in accelerating translational sciences," *Nature Biotechnology* 30, no. 1 (January 2012): 16.

Neglected Diseases, NCATS is intended to provide the necessary infrastructure for accelerating the translation of clinically relevant basic research occurring in the biological sciences into promising therapeutics and diagnostics, largely by working in conjunction with and bringing together partners in the regulatory, academic, non-profit, and private sectors, and, by extension, creating an environment in which actors from relevant disciplines may come together to solve problems of interest. Simply put, NCATS is attempting to solve real-world problems that cannot be solved by means of a single discipline.

In emphasizing the mediation between projects that fall between the upstream end of scientific research, wherein knowledge regarding the etiology of disease and drug metabolism (among other things) is produced (and traditionally funded by the NIH), and the downstream end, in which late-stage clinical trials occur (and are supported largely by the private sector), NCATS is ostensibly aimed at removing or bypassing the bottlenecks that occur in this middle ground. The attempt to bridge this gap results in the production of *nearly* commercial science, as the results of these research endeavours are not quite at the stage where they can be marketed, though they have a designated application, and yet the knowledge produced is to a degree publically-funded and consequently retains its non-rivalrous and non-excludable qualities following publication.

As discussed in section 2.1.2, translating post-academic knowledge requires in part the intent to solve real-world problems by applying knowledge to create or produce a product (tangible or otherwise) that pertains to a specific context of use, *as well as* the intent to understand the root causes of phenomena (i.e. the etiology or pathogenesis of disease) such that these products may be developed in future. For example, in addition to

funding basic research (e.g. studies attempting to develop monoclonal antibodies or nucleic acid-based drugs), the CTSA and MLP programmes further support investigating new and unvalidated therapeutic targets, which seek to repurpose extant compounds that failed to pass the clinical trial stage.[48] The questions raised by research endeavours in the CTSA and MLP programmes are examples of Mode 2 problem solving in action: for example, are protein- or nucleic acid-based therapeutics more efficacious in particular contexts? In what dosages? And at what costs? By extension, we see the relationship between contextual application of research projects and consequent interdisciplinarity of practice, as these problems (i.e. these research endeavours) cannot be undertaken solely under the auspices of a single discipline.

NCATS will further fill gaps in pharmaceutical research and development created by the divide between public research institutions and private industry, namely by funding projects aimed at diseases often neglected by the private sector (generally due to the desire for healthy profit margins versus the actual costs of production and the number of patients in need of a particular therapeutic). As detailed in section 2.2.2, an increasing and varied number of interest groups – including governmental organizations, federal regulators, private and commercial firms, private healthcare providers, patient advocacy groups, and the general public – have a stake in translating scientific knowledge from "bench to bedside," given the social and economic gains to be potentially acquired in the process. By explicitly including neglected disease targets in its mandate, NCATS is also aimed in part at bypassing the bottlenecks in the drug development process that occur when disease targets with smaller population percentiles are neglected by private industry.

[48] Ibid.

The MLP, for example, has initiated studies directed at neglected disease targets (e.g. antimicrobial resistance) often funded only through minor government grants (rather than investors), in addition to assay and biomarker development.[49] Thus, research occurring under the umbrella of NCATS is intended to fill the gaps between public research institutions and private industry that are traditionally created by the desire to solely (or predominantly) address diseases with commercial salience. Funding for translational research is of course driven by the desire to streamline drug development (engendering healthy profit margins for private industry by extension). However, in the case of NCATS, putting scientific knowledge to use in specific real-world applications requires consideration for the socio-economic interests of *both* public and private actors, especially given that this knowledge fits the criteria of a public good as discussed in section 2.2. As a result, research conducted under the mandate of this national centre is indeed *in service of the nation*, given that the results of these endeavours have the potential to produce tangible commodities that may contribute to national prosperity, improve quality of life, and extend beyond the interests of private industry.

Thus, NCATS will consolidate efforts to improve the translation process in one national centre by funding both basic research (e.g. in molecular biology, medicinal chemistry, and preclinical toxicology) and applied endeavours (e.g. efficacy testing and post-marketing research), as well as working in conjunction with private industry to ensure that the process of developing therapeutics and diagnostics proceeds as efficiently as possible with minimal expense lost. As discussed in section 2.2.1, given that it is a publically funded federal institution and the knowledge produced via NCATS/NIH funding necessarily possesses the qualities of a public good (namely it is non-rivalrous

[49] Ibid: 17.

and non-excludable), NCATS is producing *nearly* commercial science (to the point of phase II clinical trials), at which point private industry may step in to fund more costly, late-stage trials, ultimately producing a marketable product. In doing so, NCATS will, in theory, bridge the gap between basic research and clinical studies, ensuring that basic research findings with the potential to alleviate prominent socio-economic issues are not overlooked by clinicians and private funding sources. By extension, NCATS will also ensure the public reaps the benefits yielded by biomedical research. Consequently, we see here the descriptive model of post-academic science discussed in section 2 in action: firstly, in its attempt to accelerate the process of moving fundamental scientific knowledge from the laboratory bench through to clinical trial to candidate application, NCATS has engendered an environment in which *real-world* problems are solved through the process of *applying* the knowledge and expertise of relevant *interdisciplinary* groups in a larger collaborative process to design research projects, coordinate methodologies, and interpret data, while moving knowledge and information across disciplinary boundaries. Moreover, we see NCATS producing *nearly* commercial science through funding research endeavours that are not quite at the stage where results can be marketed (as tangible products, for example), though they have designated application and give consideration given to multiple supply and demand factors extending across the spectrum of research and development. As argued in section 2.3, to translate scientific knowledge entails a transformation of fundamental research results produced by means of interdisciplinary collaboration to a *nearly* commercial, non-rivalrous, and non-excludable state with *potential* applicatory value, thereby producing a solution to a specific real-world problem. In this section I have discussed the infrastructure provided by NCATS in

which the translation of scientific knowledge under these conditions may occur. Section 3.2 will apply this model of translation to several case studies of NCATS-funded research in action.

3.2. Translational Research in Cancer Biology and Systems Pharmacology

As detailed previously, post-academic involves an acknowledgement of various socio-economic supply and demand factors driving research. To recap, in the case of translational science, the growing impatience for efficacious diagnostics, therapeutics, and preventative strategies with the potential to alleviate the proliferation of diseases negatively impacting public health in the United States constitute demand factors, as do the current bottlenecks and inefficiencies in the drug development process. The commonly held lay assumption that developments in biomedicine and pharmacology occur in giant leaps made over short periods of time is yet another demand factor in this particular case. Conversely, the increased emphasis on application and interdisciplinarity by funding and research institutions, and the consequent inclusion of methodologies, techniques, funding sources, and actors from across the R&D spectrum in the research process constitute the supply factors. The creation of NCATS in and of itself is also a supply factor, given its mission to collaborate with private industry as well as to address diseases often neglected by the private sector. Thus, in the case of NCATS, post-academic research – rooted in applicability and interdisciplinary collaboration – is a response to these supply and demand factors.

Certain fields in biomedicine embody the characteristics of post-academic science, and therefore provide an excellent lens through which to examine the socio-economic and

epistemic factors that facilitate research endeavours in translational science. In particular, the increasing enthusiasm for and continuing advancements in genomics (and related disciplines of proteomics and metabolomics) in recent decades lends itself well to solving real-world problems by moving research results from the laboratory into clinical practice, particularly given its pertinence in a broad array of relevant fields from cardiology to oncology to hematology. The development of ibrutinib as a treatment for B-cell lymphoma or screening for *BRCA1* and *BRCA2* mutations, for instance, are prime examples of the successful clinical translation of fundamental research results in genomics and proteomics for diagnostic and therapeutic purposes.[50] The developments in each case are, essentially, responses to broad questions (e.g. how might clinicians identify women at risk of developing breast or ovarian cancer?), and these solutions were produced by *applying* the knowledge and expertise of multiple disciplines and motivated by particular supply and demand factors.

As will be discussed, these examples (and others) provide a context for applying the previously discussed concepts of applicability and interdisciplinarity to science in action, and further shed light on the notion of scientific knowledge as a public good. The intent of this section is to first provide a brief overview of pharmacology research conducted at the National Center for Advancing Translational Science, to highlight a selection of significant studies in cancer biology, and finally to demonstrate the ways in which these studies fit the model of translation previously argued.

[50] Yvonne Bombard, Peter B. Bach, and Kenneth Offit, "Translating Genomics in Cancer Care," *Journal of the National Comprehensive Cancer Network* 11, no. 11 (November 2013): 1343-1353.

3.2.1. T1 Research: Interdisciplinarity from Therapeutic Target Discoveries to Candidate Health Applications

Ongoing breakthroughs in cell and molecular biology, notably the development and implementation of the enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) as standard laboratory technologies in the late 1970s and early 1980s, respectively, have revolutionized biomedicine, particularly in terms of predictive testing and screening, and rapid diagnostic testing. These advances have enabled researchers to detect individual genetic polymorphisms, use specific protein biomarkers, or examine metabolite levels to develop more efficacious predictive and diagnostic molecular tests as well as therapeutic agents, and continued breakthroughs in molecular-based technologies, particularly those facilitating biomarker development, provide a basis for overcoming the obstacles currently impeding the drug development process. However, real-world problems, such as treating a particular disease or understanding its genetic expression so as to develop therapeutic targets, cannot be solved by a single discipline.

Consequently, current research in biomedicine and pharmacology generally aims to understand the effects of both disease and diagnostic/therapeutic agents on *systems* as a whole, rather than on its individual constituents – on the entire genome, the proteome, or the metabolome – hence the growth of *systems pharmacology* as a particularly salient field under the umbrella of translational medicine.[51] Approaching problems related to highly prevalent or particularly insidious forms of cancer (e.g. breast cancer, treatment-resistant lymphoma, and so on) from the molecular level involves applying the

[51] Peter K. Sorger, et al. "Quantitative and Systems Pharmacology in the Post-genomic Era: New Approaches to Discovering Drugs and Understanding Therapeutic Mechanisms," *An NIH White Paper, QSP Workshop Group* (2011): 8.

knowledge of multiple disciplines in laboratory work, pre-clinical, and clinical studies. To illustrate, systems pharmacology

> draws on several existing disciplines, including classic pharmacology, chemical biology, biochemistry and structural biology, …pathology, applied mathematics, and medicine, and has an intrinsic and extensive experimental component that incorporates approaches from tissue and organ physiology, pharmacology and cell biology.[52]

As discussed in section 2.1, solving problems (i.e. treating highly prevalent forms of cancer) requires the application of knowledge from relevant fields of expertise to address a broad array of questions answered by the epistemic contributions of relevant disciplines, which are combined for as part of a dynamic, holistic solution to a broader question.

In this case, drug development projects generally approach and assess the interactions of various agents with a specific target (e.g. a gene, protein, metabolite) as well as the inverse response of particular targets to various drugs and drug combinations *in vitro* first, before subsequently graduating to *in vivo* animal and human models in preclinical and clinical trials, wherein doses and dosage regimens may be refined.[53] Drug development is accelerated as a result *applying* the knowledge and expertise of *interdisciplinary* networks of researchers to design research projects, coordinate methodologies, and interpret data so as to allow for the flow of research from "bench to bedside." The relationship between identifying a contextual application for knowledge at the outset of research projects and the consequent interdisciplinarity of practice that occurs in the process of diffusing knowledge across disciplinary boundaries towards that

[52] Ibid.
[53] Douglas B. Kell, and Royston Goodacre. "Metabolomics and Systems Pharmacology: Why and How to Model the Human Metabolic Network for Drug Discovery," *Drug Discovery Today* 19, no. 2 (February 2014): 172.

particular application is especially evident in the case of NCATS-funded endeavours. The ensuing case studies in section 3.2.2 illustrate concrete examples of this relationship, and further exemplify the consideration given to socio-economic supply and demand factors in translating scientific knowledge.

3.2.2. A Case Study in Protein Kinase Inhibitors

Efficacious cancer therapies generally involve administering combinations of drugs, and in many cases combination therapies will include a protein kinase inhibitor. For example, ibrutinib and imatinib (marketed as Imbruvica and Gleevec, respectively) are FDA-approved protein kinase inhibitors used in the treatment of B-cell lymphoma, chronic myelogenous leukemia, and breast cancer (among others). Older cancer chemotherapeutics (such as such as vincristine) have not provided lasting remission rates for particularly aggressive forms of cancer, and, given the number of approved drugs and the number of possible drug pairings, alternative schedules of administration, and dosage variations, clinicians often must resort to trial and error when prescribing combination therapies. These constitute the real-world challenges presented to researchers in cancer biology and pharmacology whose work is directed towards developing novel therapeutics, brought about through the difficulties of treating drug-resistant cancers combined with bottlenecks in the drug development process, and knowledge cannot be applied towards solutions to these challenges *solely* by pharmacologists or *solely* by geneticists, but rather by interdisciplinary groups. To illustrate, if the real-world problem of a particular research project is treating a particularly insidious form of lymphoma, the aim of this endeavour is to *apply* the knowledge of relevant fields of expertise to address

a broad range of questions for a holistic solution: for instance, what can previously unstudied genetic mutations tell us about the ways in which cellular malignancies appear and diffuse in this case? How can a given chemical agent target these mutations? How can extant therapeutics be used to target dysregulated chemical activity responsible for tumour growth, and in what dosages? [54] What are the costs associated with pre- clinical and clinical testing? Answers to these questions draw upon the *application* of contributions from multiple disciplines to a particular context, and these contributions each address a specific aspect of the overarching problem to be solved.

As discussed, NCATS seeks to provide researchers with the necessary infrastructure to solve these real-world problems. Moreover, as will be discussed further, in solving these problems we see a production of *nearly* commercial science: public science, possessing the necessary non-rivalrous, non-excludable characteristics, that supports the late-stage trials and marketing of private industry. This section will present a number of case studies of NCATS-funded research in cancer biology, focusing specifically on the use of protein kinase inhibitors as a unifying technology. I will detail several key terms and concepts, examine a selection of clinically significant examples of translational science in action, and finally apply the previously discussed definition of translational science to these particular case studies.

Protein kinases refer to a family of ubiquitous enzymes present in all eukaryotic cells that are responsible primarily for transferring a phosphate group from a triphosphate molecule (e.g. adenosine triphosphate, or ATP) to protein in a cell, a process known as *phosphorylation*. In doing so, kinases play a significant signalling and regulatory role in

[54] See Akintude Akinleye, Muhammad Furqan, and Oluwaseyi Adekunle. "Ibrutinib and Indolent B-Cell Lymphomas," *Clinical Lymphoma, Myeloma & Leukemia* (15 November 2013): 2152.

the functioning of the nervous and immune systems and in mediating homeostasis, and essentially acting as an on/off switch for various cellular activities such as apoptosis (programmed cell death), cell signalling, and cellular differentiation.[55] Protein kinases (particularly the subfamily of *tyrosine kinases*) are known to mutate on rare occasions and remain constitutively in the "on" position (known as proto-oncogenes and oncogenes), thereby causing unregulated cell growth and initiating (or progressing) tumourigenesis. Further, protein kinases represent approximately 20% of the druggable genome, and thus kinase inhibitors that reduce enzyme activity or correct enzymatic function – thereby delivering focused chemotherapy while minimizing systematic side effects – have been targeted as potentially successful anti-cancer therapies.[56]

NCATS-funded studies focusing on protein kinases have ranged from the most basic laboratory bench work (e.g. studies identifying genes with the potential to promote tumour growth) to small- and medium-scale in vivo clinical trials in humans (Phase I and II trials). On the far end of the basic/applied spectrum, NCATS has supported researchers examining the role of particular gene or protein pathways responsible for cellular malignancies. Zhao et al., for example, identified a specific receptor protein (referred to as *RON*) as an activator of the c-Abl proto-oncogene, a non-receptor tyrosine kinase that is frequently overexpressed in many cases of advanced breast cancer, and is translocated in all cases chronic myelogenous leukemia.[57] Building on previous studies that highlight the role of c-Abl in tumourigenesis when unregulated, Zhao et al. demonstrated a novel

[55] G. Manning, et al., "The Protein Kinase Complement of the Human Genome," *Science* 298, no. 5600 (December 6, 2002): 1912-1913.
[56] S.K. Grant, "Therapeutic Protein Kinase Inhibitors," *Cellular and Molecular Life Sciences* 66 (2009): 1163-1164; see also Bert Klebl, Gerhard Müller, and Michael Hamacher, eds, *Protein Kinases as Drug Targets* (Weinheim: Wiley, 2011).
[57] See H. Zhao, et al., "The Ron receptor tyrosine kinase activates c-Abl to promote cell proliferation through tyrosine phosphorylation of PCNA in breast cancer," *Oncogene* 33, no. 11 (13 March 2014): 1429-1437.

pathway in which the RON receptor tyrosine kinase regulates and activates c-Abl, which in turn catalyzes phosphorylation leading to cellular malignancies.[58] The results of this study highlight the cellular mechanisms that prompt malignant cell growth and proliferation, particularly in breast cancer. Moreover,

> …understanding [these] signalling mechanisms can allow this event [Ron-Abl induced phosphorylation] to be used not only as a prognostic marker for disease development, but also as a therapeutic target of combination treatment in multiple cancer types and to help overcome the frequent challenge of drug resistance in cancer therapy.[59]

A similar study by Maxson et al. identified mutations in the proto-oncogene CSF3R (colony stimulating factor-3 receptor) as a factor behind chronic neutrophilic leukemia and atypical chronic myelogenous leukemia, and further concluded that these mutations act as markers of CSF3R signalling pathways for tyrosine kinase inhibitors – and thus provide a novel therapeutic target.[60] Other studies have examined the mechanisms of successful inhibition of kinase activity and leukemic cells of the recently FDA-approved second-generation tyrosine kinase inhibitor nilotinib (marketed as Tasigna) in cases of drug-resistant c-Abl kinases (occurring in some cases of chronic myelogenous leukemia).[61]

Towards the more applied end of the spectrum, NCATS-funded researchers recently completed a groundbreaking drug-screening study, the significance of which is twofold: the project developed a novel combination drug-screening platform capable of selecting the most potentially successful drug composites from a long list of possible

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[58] Ibid: 1433.
[59] Ibid: 1435.
[60] See Julia Maxson, et al., "Oncogenic *CSF3R* Mutations in Chronic Neutrophilic Leukemia and Atypical CML," *The New England Journal of Medicine* 368, no. 19 (9 May 2013): 1781-1790.
[61] See Suneet Shukla, et al., "Synthesis and Characterization of a BODIPY Conjugate of the BCR-ABL Kinase Inhibitor Tasigna (Nilotinib): Evidence for Transport of Tasigna and Its Fluorescent Derivative by ABC Drug Transporters," *Molecular Pharmaceutics* 8, no. 4 (1 August 2011): 1292-1302.

combinations using the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib and diffuse large B-cell lymphoma (DBCL) as model. Further, the screening platform identified several combinations of ibrutinib and a variety of other drug classes that successfully suppress models of DBCL cells.[62] The platform performed assays using diseased cells, treating each with a combination of one of 459 different drugs in various dosages whose mechanisms have previously been studied, analyzed the results, and produced a list of 30 drug pairs.[63] On a larger scale, the short list of drug combinations provides a cornerstone for immediate and future clinical trials, a compelling prospect given the aggressive and common nature of DBCL, which comprises approximately 30% of all new cases of B-cell lymphoma diagnosed in North America each year.[64] NCATS funding has also been directed towards more advanced clinical trials. A recent medium-scale (Phase II) clinical trial examined the efficacy of an inhibitor of the tyrosine kinase proto-oncogene Src (*Src* being short for sarcoma) in men with advanced prostate cancer, highlighting the significance of pharmacokinetic analyses in early clinical trials.[65]

This selection of case studies may be categorized along various points of the basic/applied spectrum, from studies of genetic pathways and drug-protein interactions (basic) to Phase II clinical trials (slightly more applied). Section 2 of this thesis highlighted the interdisciplinarity associated with applying knowledge to solve particular real-world problems, as well as the role of socio-economic considerations involved in

[62] See Lesley A. Mathews Griner, et al., "High-throughput combinatorial screening identifies drugs that cooperate with ibrutinib to kill activated B-cell-like diffuse large B-cell lymphoma cells," *Proceedings of the National Academy of Sciences* 111, no. 6 (11 February 2014): 2349-2354.
[63] "Screening Platform Is a Launch Pad for Novel Treatment Combinations," *NCATS: National Center for Advancing Translational Science*, (14 February 2014), Accessed 28 May 2014.
[64] "Overview: Diffuse Large B-Cell Lymphoma (DLBCL)." *Diffuse Large B-Cell Lymphoma*. Lymphoma Research Foundation. Accessed 2 May 2014.
[65] See Emmanuel S. Antonarakis, et al., "A phase 2 study of KX2-391, an oral inhibitor of Src kinase and tubulin polymerization in men with bone-metastatic castration-resistant prostate cancer," *Cancer Chemotherapy and Pharmacology* 71, no. 4 (April 2013): 883-892.

translating scientific knowledge (in terms of how and why knowledge is initially produced). As noted, the concept of *Mode 2* or post-academic science provides the basis for the overarching argument of this thesis, namely that the translation of scientific knowledge necessitates a transformation of fundamental research results, produced by means of interdisciplinary collaboration, from a potentially applicable state to a *nearly* commercial, non-rivalrous, and non-excludable state, thereby producing a candidate product (or the suggestion thereof). Moreover, translational science entails a synthesis of socio-economic considerations in terms of how and why knowledge is produced, particularly in terms of what motivates public and private actors throughout this process, and involves the collaboration of actors and institutions from across the research and development (R&D) spectrum.

Recall, section 2.1 concluded with several key assertions about the nature of post-academic science, namely that there are various supply and demand factors driving research, research endeavours are undertaken with the intent to both create tangible products (such as diagnostics or therapeutics) and to understand the mechanisms of phenomena (in this case, multiple types of cancer), and that the application of knowledge to a specific context necessarily begets interdisciplinarity. These case studies demonstrate first and foremost a production of Mode 2/post-academic science. The study published by Zhao et al., for example, is intended to addresses the overarching issue of how to effectively treat breast cancer: this question is far too broad to be answered by a single group of researchers. Attempting to understand the means in which a particular receptor protein (*RON*) "promotes cell proliferation and what signalling pathways downstream from the Ron receptor are important in this process" requires first an awareness of the

role of c-Abl in tumourigenesis when unregulated, as well as an understanding of the means in which proto-oncogenes are affected by certain receptor proteins and cellular mechanisms responsible for malignant cell growth and proliferation (among many other things). These prerequisites extend beyond the scope of a single research group. Demonstrably, this process necessitates the *application* of the knowledge and expertise of multiple fields (from cancer biology, to pathology and laboratory medicine, to molecular and biomedical pharmacology) to produce information that may be combined as part of a dynamic solution to the broader challenge of developing a combination therapy for multiple cancer types, and to alleviate the difficulties presented by drug resistance in cancer therapy.[66] As discussed in section 2.1, applying the knowledge of interdisciplinary groups in a larger collaborative process to solve real-world problems requires the consideration of multiple supply and demand factors extending across the spectrum of research and development. In this particular case, the range in fields of methodologies, techniques, and actors involved in applying knowledge and expertise to solving this problem constitute the supply factors. The nature of NCATS itself (the primary funding agency behind this project), with its mission to provide the necessary infrastructure for accelerating the development of candidate health applications from clinically relevant basic research further constitutes a supply factor supporting and motivating translational research (such as that of Zhao et al. and Maxson et al.). As discussed in section 3.1, this organizational structure is achieved and maintained through collaboration between public research agencies funded by NCATS and private industry, with drug development streamlined as a result. Conversely, the growing impatience (on behalf of the lay public,

[66] H. Zhao, et al., "The Ron receptor tyrosine kinase activates c-Abl to promote cell proliferation through tyrosine phosphorylation of PCNA in breast cancer": 1430.

government groups, private industry, and so on) for efficacious diagnostics, therapeutics, and preventative strategies with the potential to alleviate the proliferation of diseases such as breast cancer or B-cell lymphoma (among others) negatively impacting public health in the United States constitute demand factors. Moreover, the need for novel approaches to particularly insidious or treatment resistant cancers, or for increasingly efficient means of drug screening may account for additional demand factors, as does the problem of unpredictability in terms of success rates in drug development trials which further motivates the public/private collaboration favoured by NCATS. These approaches may be particularly costly, however, especially when the population affected by a particular form of cancer is relatively small (e.g. in the case of myelogenous leukemia), and thus NCATS provides an ideal setting (a supply factor) for moving research results across the basic/applied spectrum, especially given its intent to work in conjunction with private industry. These same supply and demand factors hold true in all of the case studies previously discussed, and we see research endeavours undertaken with the intent to both create tangible products and to understand the mechanisms of phenomena. Further, we see the concepts of interdisciplinarity and applicability playing a critical role throughout each case; translational research, particularly research attempting to solve real-world problems stemming from disease from the molecular level, necessarily requires the expertise of networks of researchers contributing the skill-set and specialist knowledge base of their respective disciplines, applied to a specific context. The study completed by Mathews Griner et al., for example, involved not only a range of scientists needed to interpret and synthesize data, but also computer scientists and researchers specializing in informatics to coordinate the more technological aspects of the project.[67] To quote John

[67] See Lesley A. Mathews Griner, et al., "High-throughput combinatorial screening identifies drugs that

Ziman once again, post-academic science does not only *produce* knowledge, it *constructs* knowledge "in accord with the commercial, political, or other social interests of the bodies that underwrite its production," and evidently the interdisciplinarity and potential socio-economic relevance of research projects is critical, regardless of how fundamental they may be.[68]

Section 2.2 addressed the commodification of translational science, focusing specifically on the properties of knowledge as a public good, the implications of categorizing scientific knowledge as such, and the interests of public and private actors in the creation and circulation of that knowledge. The development of a novel drug-screening platform by NCATS-funded researchers clearly demonstrates the production of *nearly* commercial science: the knowledge produced through this study has been made publically available, and possesses the necessary non-rivalrous, non-excludable characteristics. NCATS "has given the broader scientific community access to the control software, interface and data generated in ongoing experiments," such that any research group in the world may now use the drug-screening technology created, with no single research group holding a monopoly over or gaining profit from this technology[69] Though some of the case studies discussed highlight instances of notional suggestions of products (such as those that fall along the more basic end of the spectrum), while others produce or make use of more tangible technologies (such as the development of a drug-screening

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cooperate with ibrutinib to kill activated B-cell-like diffuse large B-cell lymphoma cells."

[68] John Ziman, *Real Science: What It Is, and What It Means*: 173.

[69] "Screening Platform Is a Launch Pad for Novel Treatment Combinations," *NCATS: National Center for Advancing Translational Science*; see also "Tripod Development: Cheminformatics Proving Ground," *Division of Preclinical Innovation*, National Center for Advancing Translational Science, accessed 8 June 2014, where this technology has been made available, where "the name Tripod can be thought of as an acronym for Therapeutically Relevant Informatics for Prioritization, Optimization, and Development. It also symbolically represents a support structure—which consists of biology, chemistry, and informatics—for a typical therapeutic project."

platform or early clinical trials), each produces knowledge that supports the late-stage trials and marketing of private industry and further embodies the characteristics of science *in service of the nation* as discussed in section 2.2. As a result, actors from across the R&D spectrum have much to gain from instances of translational science in action such as these, and therefore have incentive to invest in the production of fundamental research that will eventually move from "bench to bedside."

Clearly, then, the development of efficacious cancer therapeutic and diagnostic technologies involves more than just the movement of research results from the bench to the patient's bedside and community when closely examined through the lens of STS. In examining case studies of research in cancer biology and systems pharmacology funded by NCATS, the relationship between the consideration given to contextual application at the outset of research projects and the consequent interdisciplinarity of practice and varying epistemic roles of actors involved in the research process is apparent. Moreover, the diffusion of research results and information across disciplinary boundaries to "real world" applications occurs in response to particular supply and demand factors that extend across the R&D spectrum. NCATS has provided an environment in which real-world problems may be addressed by interdisciplinary groups, and has further ensured that, given its role in funding these research endeavours, knowledge produced through these endeavours retain the non-rivalrous, non-excludable properties of a nearly commercial good. We see that this research is *nearly* commercial in that it is not quite at the stage where it can be marketed, though it has a designated application that has been tested to a degree, and retains its non-rivalrous and non-excludable qualities following publication. As I have argued, translational science entails a remodelling of fundamental

research results, produced by means of interdisciplinary collaboration, from a potentially applicable state to a *nearly* commercial, non-rivalrous, and non-excludable state, thereby producing a solution to a specific real-world problem.

4. Conclusions: Why Study Translational Science?

In the first section of this thesis three questions were posed: first, what does it mean to translate scientific knowledge? What role do socio-economic considerations play in research endeavours proposing suggestions of "products" with applicatory potential? And finally, is NCATS-funded research *translational* according to this definition? The ensuing discussion outlined the epistemic and socio-economic characteristics of this translational science as a whole. Section 2 concluded with the argument that translating scientific knowledge entails a remodelling of fundamental research results, from a potentially applicable state to a *nearly* commercial, non-rivalrous, and non-excludable state, thereby producing a candidate product (or the suggestion thereof). Moreover, I argued that translational science necessarily entails a synthesis of socio-economic and epistemic considerations in terms of how and why knowledge is produced and real-world problems are solved, particularly in terms of what motivates public and private actors throughout this process, as well as the ways in which actors and institutions from across the R&D spectrum collaborate. Thus socio-economic factors play a significant motivating role in prompting the development of novel therapeutics for costly or neglected diseases, and further bring together a range of actors and funding sources in this endeavour, even in instances of projects that result in notional suggestions of products, rather than tangible, marketable goods.

Evidently, then, NCATS-funded research, highlighted in part by the cases discussed, is indeed translational according to this argument. Why study translational science through the perspective of science and technology studies then? Of what use is it to the scientists actually participating in the process of translating scientific knowledge to

call attention to concepts such as interdisciplinarity, applicability, and commodification? As emphasized throughout this thesis, current modes of drug development are unsustainable and the need for novel diagnostics and therapeutics with the potential to combat increasingly prevalent or particularly insidious diseases will continue to grow, regardless of whether pharmaceutical R&D continues to lag behind. There is an urgent need to bridge the gap between fundamental and clinical studies to ensure that promising biomedical research results are not overlooked by private industry, and thereby accelerate drug development and alleviate the social and economic burden of wide-scale disease. Clearly, NCATS has begun to reconcile the basic/applied disparities by working to remove bottlenecks in the development process stemming from issues of funding to failures of interdisciplinary communication. That being said, if science is to be "in service of the nation," understanding the social and economic forces that motivate and sustain scientific research in relevant fields is consequently crucial. Accordingly, we must look at factors such as interdisciplinarity and applicability, as well as the implications of scientific knowledge as a public good, to help solve the real-world challenges currently hindering the application of science in service of the nation. Utility (social, economic or otherwise) of knowledge is preceded by an understanding of its means of production and communication, and indeed an appreciation of the epistemic and socio-economic nature of research and innovation (as afforded by science and technology studies) will help to overcome impediments to scientific ingenuity.

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