Medical Research Paradigms and Useful Inventions: An empirical analysis of clinical and basic researchers in licensing at two Academic Medical Centers

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Abstract

The integration of scientific knowledge with health-enabling technologies (medical innovations) has been identified as a key policy challenge; there is a perception that the pace of medical innovation has lagged advances in basic research in the life sciences. This problem has been framed as one of translation: the application of knowledge at the "bench" to the "bedside". We propose that the lab and the clinic represent fundamentally different research paradigms, and that research conducted by physicians remains a central paradigm in medical discovery. We analyze patent and licensing data from two prominent academic Medical Centers over a 30 year period. Our findings show a strong "MD effect": inventions by teams composed solely of MDs and teams with MDs MDs as team leaders are more likely to be licensed than inventions by teams composed of or led by PhD researchers. Inventions by teams that combine MDs and PhDs are not more likely to be licensed, calling into question the translational model of combining expertise to bridge different domains. These results are robust to a number of controls that account for the technological and scientific orientation of the research project and the investigators. Our results help inform policy about the relationship between basic and applied research in medical innovation. Our paper adds to the small body of studies that show that clinical research continues to play a critical role in medical innovation, even in an era of burgeoning molecular science and increasingly data-driven methods in the life sciences.

1. Introduction

Since the 1970s, a major shift has occurred in medical research. The period has witnessed a rapid expansion of fundamental knowledge about the genome; a sharp increase in digital information processing and analytics; and the development of highly efficient tools, technologies, and diagnostics. Teams, rather than individual investigators, have become more important in the discovery process, reflecting both the rise of "big data" and new high-throughput analytical techniques in the life sciences, as well as increased specialization as the sheer volume of scientific knowledge has expanded (Collins, 2010; Wuchty et al, 2007). As expressed by NIH director Francis Collins, "the power of the molecular approach to health and disease has steadily gained momentum over the past several decades and is now poised to catalyze a revolution in medicine . . . The foundation of success in biomedical research has always been, and no doubt will continue to be, the creative insights of individual investigators. But increasingly those investigators are working in teams, accelerated by interdisciplinary approaches and empowered by open access to tools, databases, and technologies" (Collins, 2010).

This new era in medical research has centered on molecular-level research and data-driven discovery that has promised to yield a wave of new health-enabling technologies and treatments. However, there is a widely-shared perception that scientific advances in the life sciences have not been matched by a corresponding increase in the rate of medical innovation: that discoveries made at the "bench" have not been effectively translated into useful applications at the "bedside" (Collins, 2011). The lack of progress has been diagnosed, in part, as a problem of *translation*: a lag between advances in basic science and analytical techniques and their impact on new products (Contopoulos-Ioannidis et al, 2008; Morris et al., 2011). In this

interpretation, the integration of these complex domains of knowledge has been identified as a central policy objective, so that the expected benefits of basic science can flow to the clinic (Cockburn, 2006). "Translational research" policies to improve the flow of scientific knowledge to clinical applications have become an important centerpiece of medical policy in Europe and the United States.

The NIH defines the job of translational scientists as "taking basic discoveries about the causes of a disease and transforming this knowledge into a new treatment and demonstrating that it tangibly improves human health"[1]. In 2005, the NIH issued its Roadmap for the future, with stronger integration of basic and clinical sciences at its core; in 2011, it founded the National Center for Advancing Translational Sciences (NCATS) to implement this vision. The first new Center at the NIH in many decades, it attests to the importance of the translational model in bio-medical research policy. Several European policy initiatives similarly seek to foster integration of basic science with clinical applications through translational research.

It is worth noting that the translational model of medical innovation is not rooted in historical linkages between science and medicine: the application of scientific methods to medical innovation is relatively recent, and the hospital, not the laboratory, was the primary source of discovery for most of medical history. Even before the development of a formal medical profession, hospitals provided physicians with "buildings and bodies" – opportunities to not only observe and treat the sick, but to dissect and learn from the dead (Bynum, 1994; Weiner and Sauter, 2003). The introduction of modern scientific methods to medical research can be traced to Paris hospitals in the 19th century under the guidance of the great experimental

[1] http://www.ncats.nih.gov/about/about.html. Translational research may also have a public health aspect, when framed as a process of diffusion and uptake of evidence-based medical knowledge in clinical care (Woolf, 2008). We refer to translational research in the first sense: the application of basic scientific knowledge to the development of health-enabling technologies and treatments.

physician Claude Bernard, whose dictum to "go first to the hospital" reflected his belief that the laboratory was the handmaiden to the clinic in medical discovery.

The clinical research paradigm formed the centerpiece of medical policy in the post-World War II period, particularly in the United States (for a review of the history, see Gittelman, 2015), a period in which clinicians working in Academic Medical Centers played a dominant role in spearheading research and medical innovation (e.g. Ahrens, 1992; Gelijns et al, 1998; Rees, 2002; Swazey and Fox, 2004). This period has been called the "Golden Age of Clinical Research" because of the unprecedented wave of treatments and health-enabling technologies that were developed by scientists working in clinical research settings (Ahrens, 1992; Mitra, 2009, Swazey and Fox, 2004)[2].

In addition to the discovery of new treatments, clinical research was important in generating fundamental insights in biology (LeFanu, 2012; Mitra, 2009; Swazey and Fox, 2004). Among the most notable example was Oswald Avery's discovery of DNA, made while working with a team of clinicians at Rockefeller Hospital to develop a cure for pneumonia. In their detailed history of the oncogene paradigm – the linking of genetics to cancer – Keating and Cambrosio (2001) show that the new genomics paradigm emerged from the work of clinicians whose unique access to human subjects enabled them to make the bridge between biological and medical knowledge.

[2] Mitra (2009) details the unprecedented wave of drugs and other innovations discovered in clinical settings in the post-war period: penicillin and other antibiotics; streptomycin for tuberculosis; cortisone for immune system disorders; chlorpromazine, which changed understanding and treatment of psychiatric disorders and laid the basis for modern psychiatry; chemotherapy drugs; immune-suppressants for organ transplantation; polio vaccine; and contraceptive medications. Treatments and devices included cardio-pulmonary bypass and open heart surgery, cardiac catheterization, organ transplantation, joint replacement, renal dialysis, intra-ocular lens implant, cochlear implant, in vitro fertilization; the invention of the ventilator and intensive care of infants; the operating microscope, fiber-optic endoscope, cardiac pacemaker, laser, ultrasound, isotope scan, CT, MRI, and PET scans, and the linear accelerator.

We argue that the bedside to bench model of medical innovation *remains* an important discovery path in medical discovery, even in a period of rapid advances in the biological sciences. Our claim is a challenge to the perspective that the declining rate of medical innovation can be diagnosed as insufficient application of basic science to medical knowledge. We propose that doctors working in hospitals remain central to medical innovation because they have unique opportunities for insights that emerge from the joint activities of research combined with interactions with living patients. We compare the research paradigms of clinicians working with observational data of patients with that of basic scientists who work with data at the intra-cellular and molecular level, and propose that the clinical research paradigm is uniquely adapted to medical innovation. A startling extension of this claim is that the decline in the rate of technological progress in medicine (particularly in drug discovery) as compared to prior periods is not due to too little basic science, but to prioritizing basic science, big data, large teams, and high-throughput analytical techniques over clinical methods in medical innovation.

The role of the clinic in medical policy has been a central topic in the medical policy literature (e.g. Gelijns et al, 1998; LeFanu, 2012, Mitra, 2009; Rees, 2002; Scannell et al, 2012; Williams, 2005) as well as the literature on the economics of technology (Gittelman, 2015; Hopkins et al, 2007; Nelson et al, 2011; Nightingale, 1998; Nightingale, 2004). Our study is among the first to empirically identify the relative contributions of clinical and basic research to medical innovation. By identifying the training of scientists as well as their scientific specialties, our analysis helps tease out the impact of distinct research *paradigms* from the skills and specialized knowledge that different team members bring to the project.

The context we study is Academic Medical Centers (AMCs). These organizations, which emerged in the research landscape in the mid-20th century, bring together clinicians, basic scientists, patients, support staff, and state of the art technologies and laboratory facilities in an

institutional setting that is devoted simultaneously to medical practice and rigorous scientific research. They allow for inter-disciplinary collaborations in an environment that cannot be duplicated in university departments or private R&D labs (Bercovitz and Feldman, 2011; Nathan, 2002; Rosenberg, 2009). Discoveries with commercial potential are frequently patented and licensed to firms for further commercial development. Academic Medical Centers thus provide a fruitful context in which to study the contributions of basic and clinical research to medical innovations.

Our analysis is focused on two world-class AMCs: the Mass General Hospital and Brigham Women's Hospital, both affiliated with Harvard Medical School. These have been the sites of important health-enabling inventions, including the first organ transplant and limb reattachment, diagnostic tests, numerous new drugs, and cosmetic lasers. We analyze licensing to firms as an indicator of an invention's commercial potential. While not all licensed inventions eventually become products, a license is an indicator of commercial value that is not captured in patent or bibliometric data. We analyze the probability of a patent being licensed as a function of the research background of its inventors, as indicated by their training as clinicians (Medical Doctors, MDs), basic scientists (Doctor of Philosophy, PhDs), or a combination (MD-PhDs). While prior work has studied the role of patenting and publishing on scientists' contribution to innovation in biomedicine (e.g., Subramanian et al, 2013, Baba et al, 2009), and the characteristics of inventing teams on innovation outcomes (e.g., Bercovitz and Feldman, 2008; Bercovitz and Feldman, 2011), ours is the first to identify training in clinical and basic research as a key variable predicting the market performance of inventions.

Our study covers a time period from the late 1970s to the mid-2000s when molecular biology, genetics, and large-scale analytical methods took increasing importance in bio-medical research at AMCs, and indeed our data reflect such a rise. We leverage the composition of

inventive teams to study whether the training of researchers affects the probability of a license, conditional on a patent being issued. We find a strong "clinician effect": the presence of an MD or MD-PhD on an invention significantly increases the chance of its being licensed, whereas inventions by PhD scientists are less likely to be licensed. The only time that PhD scientists have a positive effect on licensing is when the scientist is also a clinician (MD-PhD). We control for a number of technological, field-specific, organizational and individual factors that might influence the distribution of research domains as well as the commercial success of patents; our results are robust across a range of such controls. The results suggest that clinical research remains an important paradigm in medical innovation, even in an era in which basic research, cross-disciplinary teams, big data, and large-scale analytical techniques have become central in medical research.

2. Basic and applied research in technological innovation

Basic research and technological innovation can usefully be understood as two distinct paradigms of learning characterized by different sets of practices and search routines[3]. These differences have been explored in the context of communication and codification practices; methods of validation and experimental conditions; decision-making processes; and the extrinsic and intrinsic motivations of investigators (Aghion et al, 2008; Allen 1984; Nelson 2003; Nightingale, 1998; Rosenberg, 1990; Sauermann and Roach, 2014). Broadly, basic research can be characterized as aimed at uncovering cause-effect relationships to produce knowledge that facilitates understanding of natural phenomena. To accomplish this, basic science reduces phenomena to their essential states, constructing experimental settings that are abstractions of the complexity that characterizes most phenomena as they exist in nature. Learning proceeds with

[3] Gittelman (2015) in this Special Issue contains a longer discussion of research paradigms and application to medical research.

predictive models, validation of prior theories, and "offline" experimentation that simulates, rather than replicates, real-world phenomena (Nelson, 2003).

Technological innovation, on the other hand, is concerned with producing artefacts that must function reliably across a variety of unpredictable real-world contexts. Problem solving therefore focuses on uncovering robust design principles rather than validating theory. Experimentation involves objects that closely resemble their real-world analogs, and feedback-based, experiential learning provides clues to mechanistic solutions that work in variable states of nature. Fundamental understanding may occur as a by-product of technological search, but is not a central object of learning; indeed, causal understanding of a problem is frequently unhelpful in finding technological solutions (Vincenti, 1990).

In sum, search in basic science seeks to reduce natural complexity in order to develop and test universal cause-effect relationships. Technological learning studies phenomena in their full complexity to uncover understandings of functional, rather than causal, relationships to design artefacts that function well in variable states of nature. Because of different orientations towards the production of knowledge and the production of artefacts, early writers emphasized that interactions between basic science and technological innovation are episodic and sporadic in nature, rather than a smoothly occurring transfer (Allen, 1984, De Solla Price, 1965; Mansfield and Lee, 1996).

Nelson (2003) proposes that while learning-in-practice ("techno") and fundamental understanding ("logy") co-evolve, the most valuable scientific fields for technological innovation are the applied sciences whose methods and objectives study complex phenomena as they exist in nature, and thus more closely resemble technological learning than they do basic science. Thus the specialized practices of scientific fields is a key variable in theorizing the ways in which science usefully engages with technology,, in particular, the degree to which researchers study

complex phenomena in their natural states (or close analogs thereof) or rely on predictive theory and abstract models..

3. *Basic and clinical research in medical innovation*

Apart from case histories, there is scant statistical evidence of the relative contribution of these paradigms to the productivity of medical innovation. Partly, this reflects the great difficulty in tracing the origins of an innovation that may have taken decades to develop into a treatment. Gelijns et al. (1998) study blockbuster drugs as well as two major devices in 1993 and find that secondary uses – a major source of medical innovation - had been discovered for nearly all of them, and that these secondary uses accounted for nearly half of sales within two years. These new discoveries were made both at the bench as well as the bedside, and illustrate the importance of clinical data as a starting point in triggering new medical discoveries. A recent study examined the sources of discovery of new off-label uses for drugs, and found that 59% of the innovations came from clinicians practicing in the field rather than from drug companies (De Monaco et al, 2006).

Recent empirical investigations of the biopharmaceutical industry – which relies heavily on science for innovation – suggest patterns that are consistent with the proposition that applied science contributes more to private-sector innovation than basic science. However the evidence remains indirect. Several studies have found a negative relationship between highly cited scientists (or highly cited papers) and valuable patents (Gittelman and Kogut, 2003, Rothermel and Hess, 2007, Subraminan et al, 2013). Instead, a number of studies [Gittelman and Kogut, (2003), Subramanian et al (2013), Baba et al (2009), Rothermel and Hess (2007)] find that boundary spanning scientists who engage in both scientific and technological activity make a greater contribution to innovation than scientific "stars", suggesting that individuals who span

the worlds of research and technology are more valuable to firms than those who specialize in research.

Even though these studies have typically been restricted to a single field, they do not account for the training of the scientists. As a result, it is difficult to ascertain from these findings whether the boundary spanners are applied scientists or are basic scientists engaged in translation to a market. They provide indirect evidence that applied research is more useful than basic research for innovation, since it is plausible that scientific "stars" are more likely to be basic researchers: journals in applied sciences tend to be less prestigious and receive fewer citations than basic science journals, and paper-based citation trails in applied disciplines are shorter than in the basic sciences (De Solla Price, 1970). However, while studies are suggestive of a negative (positive) effect of basic (applied) science on successful innovation, the evidence is indirect and the question remains open regarding which types of scientific research are associated with successful invention.

Much of the theoretical literature seeking to understand the contributions of basic and applied research to discovery focuses on the level of uncertainty of the problems being solved, or the "upstream" versus "downstream" nature of problem solving (e.g., Aghion et al, 2008). While helpful in understanding how incentives in firms and universities can lead to an efficient division of innovative labor, variation in the uncertainty of problems is less useful for understanding the contributions of basic and clinical research to medical innovation: we propose that it is not the *level* of uncertainty of problems that matters for performance, but the idea that each group confronts complexity in a different manner[4].

[4] Moreover, the utility of categories such as "upstream" and "downstream" inventions is limited in the case of medical innovation, where scientific insights can have immediate utility. For instance molecular probes, diagnostics, devices, and new drug compounds may all emerge from basic science. A PhD scientist patented an "inexpensive, readily manufacturable" device that detects apnea by measuring the amount of CO2 in a person's

Both basic and clinical scientists working in academic hospitals study complex problems and use clinical data in their work. We propose that clinical research adheres to a logic of discovery that hinges on a unique combination of medical education, interactions with living patients, and research. The phrase "living patients" is important, since PhD scientists also utilize clinical data; however, their disease models and data abstract from the context of the full organism, while clinicians, in contrast, work with "naturally-occurring disease models", e.g. pathological states as expressed in the human body, and utilize data from observations of living subjects (Crowley and Thier, 2001).

Clinical and basic researchers inhabit different epistemic cultures that privilege distinct and sometimes conflicting priorities: data versus cases; models versus observation; theories versus induction; genes over patients. Dougherty and Dunne's (2011) ethnographic research uncovers a sharp contrast between two groups of scientists, whom they refer to as "digital" and "therapy" scientists. These groups correspond to those working in the basic and clinical paradigms, respectively. Digital scientists frame problems and products using abstract, systematic maps of the search space, based on identifying and following "knowns", e.g. gene maps to identify well-specified targets. Therapy scientists work differently: they focus on local search of "unknowns", studying concrete, emergent processes. They are more involved in physical interaction with tangible materials and study the body's functioning in real-world contexts.

The central role of clinical research in solving medical problems hinges on the idea that developing solutions for complex medical problems does not commonly originate in the laboratory: the immense complexity of biological systems interacting with a variable

breath (patent number 4,648,396). Indeed, inventions involving human subjects frequently face high regulatory, testing and bureaucratic hurdle before they may be considered proof of concept, and thus may be more "upstream" than those that emanate from a laboratory.

environment, coupled with the relative gaps in scientific understandings of biological processes, means that predictive, abstract models are limited in their utility. Instead, close observation and study of humans by physicians trained in research is a useful starting point for discovery. Clinical researchers spend several years studying medicine, physiology, and pathology, and their practice involves ongoing interactions with afflicted human subjects. They therefore have the opportunity to observe complex physiological phenomena as they exist in various states of nature. Basic scientists receive deep scientific training but do not engage in interaction with living patients as part of their professional practice. They are specialized in studying biological sub-systems at a more fundamental and specialized level than is presented in complex biological systems, e.g. intra-cellular or molecular structures and processes. Both groups study complex processes, but only clinicians study complexity as it exists in nature. By adopting a focused, reductionist approach, basic researcher have fewer opportunities than their clinical counterparts to make valuable connections between the lab and clinical observation. We propose that this difference will be expressed in the success of the inventions of these two groups.

To illustrate this difference in search logics, we contrast inventions by two anesthesiologist specialists in our dataset. A novel painkiller was patented by Dr David Borsook, an MD-PhD who works extensively with patients suffering from neurological pain. Dr. Borsook's laboratory research involves using advanced imaging technologies to develop clinical, observational measures of patients suffering from disease-related pain. He was involved in a clinical trial testing a cancer drug, and noticed that administering the drug to patients decreased their pain. According to the description in the patent (5905069)[5], "The invention is based on the unexpected discovery that administration of a spicamycin derivative to a patient suffering from

[5]Borsook, D. and J.W. Clark, "Methods of decreasing or preventing pain using spicamycin or derivatives thereof", U.S. Patent 5905069, filed January 26, 1998 and issued May 18, 1999

pain resulted in a significant decrease of that pain". Borsook's inventions was possible because he was able to observe the operation of the drug in the human body and theorize why it worked, leading to his subsequent invention.

His work differs markedly from Dr. Charles Serhan, PhD, who has several patents for anti-inflammatory drug compounds. Dr. Serhan's research focuses on "the cellular and molecular mechanism(s) that govern endogenous anti-inflammation and resolution mechanisms in inflammation.Dr. Serhan's approach in elucidating the molecular map or resolution circuitry involves a multidisciplinary systems biology approach employing lipid mediator informatics, cellular and molecular analyses integrated in a systems approach to elucidate critical biochemical pathways in the resolution response in vivo.[6]" Both researchers employ clinical *data* in their work: however, Borsooks research hinges on observations of intact patients using new imaging technologies, while Serhan's methods rely on large-scale analysis of intra-cellular and molecular data.

In sum, we propose that iterations between observation and study of patients with research provides valuable opportunities to make connections about treatments that are not available to scientists specializing in research only. We therefore expect that the inventions of clinical researchers will be more likely to be valued in a market than inventions of basic researchers, and that this difference is not attributable to the level of uncertainty, field specializations, or closeness to the final market of the inventions.

While we expect that the clinical paradigm provides unique opportunities for medical discovery, teams that combine the clinical, patient-oriented perspective with expertise in basic science could have fruitful opportunities for diverse knowledge sharing, creativity and discovery

[6] http://research.bwhanesthesia.org/research-groups/cetri/serhan-lab accessed October 19, 2015

Moreover, the analytical models and data-analytic approach of basic life scientists can augment and complement the "small-n" observational studies of clinicians. Indeed, cross-disciplinary teams that combine clinical and basic science are at the core of translational medicine. The translational model hinges on the idea that combinations of clinical and basic researchers on teams will increase the inventive performance as compared to teams comprised of one or the other paradigm.

However, our assertion that these groups adhere to different logics of discovery mean that combining them on teams does not "solve" the problem of medical innovation: teams are not merely the sum of the knowledge of their individual members. We theorize that even when teams combine clinicians and basic researchers, team leaders will be important in setting in motion the intellectual paradigm of the project as a whole, clinical or basic research, which will shape the problem-solving approach and opportunities for creative discovery. Therefore, we expect that the research training of the team leader will be predictive of its commercial potential, and that, following on the above discussion, inventions that are led by clinicians are more likely to succeed than inventions where the project is led by a basic researcher, even if the team combines both types of researchers.

4. *Empirical context*

a. Academic Medical Centers: The Mass General and Brigham Women's Hospitals

Modern academic medical centers were designed to combine state-of-the art medical technologies and lab facilities, offering researchers the opportunity to engage in trans-disciplinary research motivated by practical problems. These individuals were conceived as key agents in the integration of laboratory science with clinical applications and were the main

beneficiaries of NIH policies to increase grant funding of biomedical research in universities (Nathan, 2002).

At the institutional core of the Academic Medical Center is the physician-scientist, "individuals with an MD degree who are engaged in research as their primary professional activity" (Ley and Rosenberg, 2005). The institutionalization of physician-scientist career track was an American innovation of the early 20th century when medical schools, which had been practice-based, for-profit institutions, were joined with research universities under the guidelines of the Flexner report. The Flexnerian goal, enshrined in the "Full time plan", was to create a career path in academic hospitals that allowed physicians to devote themselves to research on an equal footing with university faculty, freed from the financial need to practice private medicine (Bryan and Stinson, 2002). These individuals were conceived as key agents in the integration of laboratory science with clinical applications and were the main beneficiaries of NIH policies to increase grant funding of biomedical research in universities (Nathan, 2002). Generally, clinical researchers only have MDs, but increasingly they also have PhD degrees; and by the mid-2000s the number of MD-PhDs applying for NIH research grants was almost equal to the number of MD-only applicants (Ley and Rosenberg, 2005).

Our study focuses on the Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH). In 1994, these two AMCs became the founding members of Partners HealthCare, the largest healthcare provider in Massachusetts. In terms of quantity of NIH funding, MGH consistently ranks first and BWH second among all hospitals. [7] In 2014, the two hospitals had a combined research revenue of over $1.4 billion.[8] Both of these Academic

[7] http://www.report.nih.gov/award/index.cfm accessed November 30 , 2015

[8] Partners HealthCare Research Management, Annual Report 2012. http://navigator.partners.org/ResearchSupportOffices/Research-Management-Annual-Report-FY12.pdf accessed April 11, 2014

Medical Centers are Harvard teaching hospitals, and are ranked among the top 10 hospitals by US News and World Report in 2013.

Both institutions have been at the forefront of academic research and clinical innovation worldwide. MGH, founded in 1811 as the third US hospital, has been the site of the first demonstration of the use of ether for surgical procedures in 1846, the identification of appendicitis in 1886 and the first severed limb reattachment in 1962. Similarly, in 1923, the first heart valve surgery in the world was conducted at Peter Bent Brigham hospital, predecessor to Brigham and Women's hospital. The same hospital was also the site of the world's first organ (kidney) transplant in 1954.

Both have been at the forefront of basic research in the life sciences. MGH's molecular biology department was founded in 1982 with a grant of $70 million by Hoechst, and it is the home institution of Nobel Prize winner Jack Szostack, who created the first artificial chromosome (Culliton, 1982). Innovative products that were invented at these two institutions include the drugs Enbrel, Liraglutide, Pepcid, Sensipar and nitric oxide for use in the treatment of newborns in respiratory distress; diagnostic tests and devices including tests for Alzheimer´s, pre-eclampsia; vitamin-E infused polyethylene prosthetics for knee and hip replacements, Fraxel lasers for skin rejuvenation as well as numerous research tools, genes and genetically modified organisms. Inventions like these that are patented have generated approximately $110 million in licensing income in 2012 (RVL Annual Reports, various years).[9]

b. Basic and clinical scientists in AMCS

There are three main types of scientists working in Academic Medical Centers: MD, MD-PhD, and PhD. In the United States, MD ("Medical Doctor") degrees are awarded by medical

[9] Partners Research Ventures and Licensing (RVL) Annual Reports for years 2005-2012 http://innovation.partners.org/resource_center/annual_reports, accessed April 1, 2014

schools that require four years of training, and graduates must complete and additional three to eight years of work in a hospital in their specialty as a physician-apprentice (resident). Medical schools are practice-oriented and students learn biological science but do not receive training in research methods. For a variety of reasons, the majority of MDs do not elect for careers in research: the number of physicians whose primary activity was research declined from about 5 per cent of all physicians in the early 1980s to less than 2 per cent in the mid-1990s (Ley and Rosenberg, 2005). MD-PhDs are clinicians who have opted for additional training, in the form of a PhD, to develop research expertise within a field of specialty. The MD-PhD degree was created and funded by the NIH to address the gap in research training at medical schools, and was intended to encourage physicians to engage in research careers. PhD scientists work in non-clinical specialties; though they may encompass fields of biology (e.g. biochemistry) they do not involve patient care, and students receive greater training in research methodology, statistical methods, and basic science. The emergence of fields such as genomics, proteomics, and large-scale analysis of genetic data have increased the role of PhD scientists in bio-medical research.

We associate MDs with clinical research and PhDs with basic research. While they may work on similar types of problems or diseases, e.g. oncology, pharmacology, hematology, their training differs sufficiently to warrant the distinction in the work that they do: MDs are trained in medicine and related fields, and have experience in patient-oriented research, while PhDs are formally trained in fundamental disciplines and sophisticated analytical techniques in such fields as molecular biology, genetics, biochemistry, and bio-statistics. We interpret MD-PhDs as clinicians who also have deep knowledge of a research specialty.

c. Licensing

The importance of licensing technology, particularly from academic institutions, has been expanding in recent years. Arora and Gambardella (2010) review data from various sources to

arrive at a size of approximately $100 billion in 2002 for the global market in technology, about double their earlier estimate of $35-50 billion in the mid-1990s. (Arora et al. 2001; Arora and Gambardella, 2010, cf. Athreye and Cantwell, 2007; Robbins, 2006). Other survey based studies point to the increasing importance and rate of out and in-licensing by firms (Sheehan et al, 2004; Zuniga and Guellec, 2008; Tsai and Wang, 2009).

Licensing markets are particularly important in bio-medical fields, where many early-stage discoveries originate in university setti

ngs, and medical schools are particularly central in university licensing (Bercovitz and Feldman, 2008; Mowery and Ziedonis, 2002). During the 1980s, universities became increasingly aware of the commercial potential of their faculty's research and disclosure became a normal faculty practice (Bercovitz and Feldman, 2008; Sampat, 2006). At the same time, private firms in bio-medicine shifted towards more out-sourcing of research, leading to active vertical markets for technology involving universities, medical schools, biotechnology firms and large pharmaceutical firms (Stuart, Ozdemir and Ding, 2007). In a survey of firms using university technology, Thursby and Thursby (2004) find that more than half of the respondents use university technology in new product development and 23% note that in-licensed patents from universities were crucial in the development of their products.

5. Sample, Variables and Methods

Our objective is to analyze the relative contributions of clinical and basic research to the commercial potential of an invention. Our data consists of patented inventions, and we focus on licensing of those inventions to firms as a measure of commercial potential. It is an imperfect proxy. It does not indicate whether a product emerged from the license; however, it does indicate

that a firm perceived a potential for commercialization and was willing to pay in order to develop the technology further.

Data was collected on all patents issued to the two AMCs between 1977 and 2007, along with their associated licenses.[10] Multiple patents are sometimes issued for a single invention, called a case. Patents from the same case are almost invariably licensed together as a portfolio, have the same inventors and come from the same parent patent application through patent divisions, continuations and continuations-in-part. To avoid bias created by including related patents in our estimations that are identical to others in the same case for many key variables, our unit of analysis is the case, rather than the individual patent.

We do not include all inventions in our sample. We exclude co-assigned cases in which the invention was assigned to multiple institutions such as other firms or non-profit organizations.[11] We also exclude inventions that are the result of company sponsored research agreements (SRAs). Such inventions are likely to reflect the research agendas of the sponsor rather than the independent research of the scientists. While interesting in its own right, this could bias our results, as the company interests, rather than the scientists alone, would impact the selection of research question, the team, and the research agenda. Furthermore, patents from

[10] We collect the data from the Technology Licensing Office in charge of the intellectual property at the two academic medical centers. Faculty members at the AMCs are required to submit an invention disclosure to the TLO if they believe they have conceived of an idea that is novel and has a potential for commercialization. After extensive review regarding the patentability of this invention a decision is made by the TLO about whether to file an application for one or more patents. Once a patent is filed, the TLO actively researches potential licensees for the invention; inventors may also initiate contacts. In cases of company-sponsored research, the sponsoring firm usually has an automatic right of first refusal to any inventions emanating from the research.

[11] Under US patent law, co-assignees are allowed to use or license the invention to others without consulting each other. Since we only observe licensees to the MGH or BWH, we cannot be sure that we are capturing all licenses to co-assigned patents. Information about the institutional assignment of patents comes from the patent front page. We check assignments against USPTO assignments website, which is more complete (and correct) than the front page of the patent.

sponsored research are almost always automatically licensed to the sponsoring firm, or grant the right of first refusal to the sponsor.

In total there are 495 inventions, where each observation represents a case in which at least one patent has been granted between 1977 and 2007, and for which the hospitals are the sole patent assignees[12]. Of those inventions, 382 have only one patent associated with them, while the remaining 113 have multiple patents associated with the same case.

a. Dependent variable: Licensing

We use the date of the earliest license to measure the licensing event, which we interpret as evidence of an attempt to commercialize or use by a firm. Patents may be licensed multiple times; some are licensed through non-exclusive agreements, some are sublicensed by the first licensor. Additionally, licenses may be terminated and the invention then can be relicensed to a different entity. Our estimations do not include these complex transactions but only focus on whether an invention was ever licensed to any firm, conditional on a set of explanatory variables.

Our data is right censored; inventions continue to be at risk of licensing after our study period expires. Moreover, inventions both enter and exit the risk set over time as they are newly patented (entry) or licensed, abandoned or expire (exit)[13]. Because we have right censored data

[12] Some prior research has used invention disclosures as the level of observation, including invention disclosures that have not been patented (Kotha et.al, 2013). We do not include them because in our case they automatically remain unlicensed. Public disclosure of the unpatented inventions is certain and fast since they are emanating from academic institutions where secrecy is not a preferred form of intellectual property protection and where dissemination of ideas and publication of results is the currency of career advancement. Furthermore by focusing on patented invention disclosures we ensure that all inventions in our sample have passed a threshold for patentability, based on the USPTO requirements. Inventors themselves are academics who often will file their latest paper as an invention disclosure and are generally less equipped than TLO officers and patent attorneys to be unbiased judges of the patentability or commercial potential of their own research.

[13] Abandonment of a patent occurs if the TLO decides, post-grant, that it is no longer desirable to pay the maintenance fees to keep a patent in force. These decisions may be made at 3.5, 7.5 and 11.5 years after the patent has been granted. Abandonment is equivalent to expiration, as an abandoned patent is not available for licensing. In cases where we have multiple patents per case, the case is at risk for licensing until the last patent is abandoned or has expired. We gather abandonment information from the USPTO supplemented with IP Thompson's Delphion information on patents in force.

with exit and entry over time, we employ a survival model that measures time to first license; the Cox Hazard model estimates the hazard of licensing by combining information about entry and exit of inventions with information about whether the exit was associated with licensing. An invention disclosure enters the risk set beginning at the priority (or provisional filing date) of the first filed patent. We exclude an invention from the risk set after the first license.

b. Explanatory variables

To capture the effect of different research paradigms on inventions, we identify the degrees of each inventor listed on all patents within each case. An inventor on a patent, by law, must have contributed "to the conception of the invention" i.e. to at least one of the claims of the patent. We are therefore confident that we are capturing individuals who made a meaningful contribution of their knowledge to the invention.

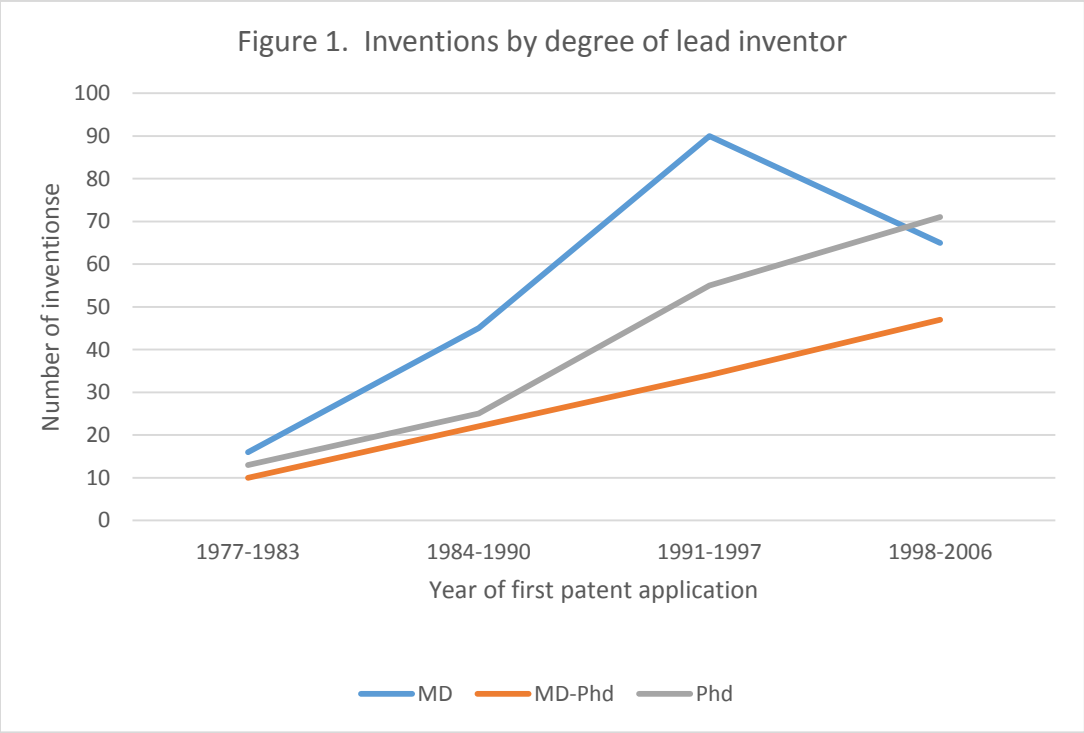
We use a variety of sources to identify inventors' degrees as either MD, MD-PhD, or PhD. The main source is the invention disclosure itself. Each degree is further checked against a variety of other sources[14]. Inventors that had only a Master's degree or a Bachelor's degree are classified as "other".

Lead inventor degree – We expect that the research paradigm of an invention will be reflected in the degree of the lead inventor on the invention (Bercovitz and Feldman, 2011). We use the first listed inventor on the inventor disclosure form (labelled "Lead Inventor") who is generally (though not always) also the Primary Investigator of the project. Therefore, we interpret the degree of the lead inventor as defining the paradigm of the research that initiated

[14] These include internal directories, ProQuest Dissertations and Theses Database, CVs and university biography webpages. Published articles were also used to identify a researcher's degree. Where possible, graduation dates were identified; in a few cases there were people in an MD or a PhD program at the time of patent filing – they were considered MDs or PhDs respectively.

and guided the invention. We create a series of dummy variables that indicate the educational degree of the lead inventor, again using the categories MD, PhD and MD-PhD.

Figure 1 shows the number of cases in our dataset by the degree of the lead scientist.[15] The graph shows that inventions for which the Lead Inventor had a PhD rose steadily since the



early 1990s, while inventions led by MDs declined in the late 1990s. However, the number of inventions with Lead Inventors with MD-PhDs grew in the late 1990s, which likely reflects changes in the degree composition of physician-researchers over this period, reflecting a trend in which junior clinical investigators seeking a career in research (versus practice only) are more likely to pursue an MD-PhD than in the past (Ley and Rosenberg, 2005). Overall, the data show

[15] 13 teams whose first inventors are coded as "Other" or are not available are excluded from the graphic.

the strong increase in PhD scientists' contributions to invention in the late 1990s, likely propelled by the rise of molecular biology,genetics and other basic fields in medical research.

Invention team type– Inventions can include MDs, PhDs, MD-PhDs as inventors, in a variety of combinations. We measure this in two main ways[16]:

Single Domain inventions consist of those in which all scientists share the same degree, and can be either *Single Domain Clinical* (all MDs) or *Single Domain Research* (all PhDs). The presence of an MD-PhD on a case automatically disqualifies it from either category.

Cross-Domain Inventions combine clinical and PhD scientists. This can happen in two ways. If an invention includes different individuals who are MDs and PhDs, the invention is called *Cross Domain Distributed*. If an invention includes at least one MD-PhD, plus any other combination of degrees, we label it *Cross Domain Integrated* because at least one team member spans both disciplines.

About 30% of cases have only one inventor; these are categorized using the above criteria. Only the Cross-domain distributed category is by construction required to have more than one researcher.

c. Control Variables

Inventor characteristics

Lead Inventor Experience - Faculty at AMCs are on an academic career track, and many are engaged in the discovery of inventions and collaborations with firms: there is a great deal of variation in the degree to which they have a "taste" for commercialization, and some are more

[16] The inclusion of a scientist with a another degree besides MD, PhD or MD-PHD did not change the team type as long as there was at least one MD, MD-PhD, or PhD on the team. However, teams that have only inventors with another degree are classified as "Other degree." Only six inventions are classified as "Other degree".

inventive than others. We want to capture the involvement of faculty in commercialization that is independent of their specialty, field of research, and scientific standing. We construct a time-varying variable that counts the number of prior patented inventions of each lead scientist up to the time of the current invention.

Scientific specialization– In addition to the technological characteristics of the invention, we want to capture the areas of work that the scientists are engaged in. This helps to control for the observation that differences in PhDs and MDs might correlate with different types of research specializations. Using a variety of sources, but mainly relying on publications in the Web of Science, we collect data on the departmental affiliation of each inventor at the time the case was filed. Departments evolve over time, and different departments often cover overlapping subjects. We therefore assign keywords to these departmental affiliations that best capture the specialty of the department as indicated in its name, e.g. Oncology, Molecular biology, Pediatrics, Pathology, Surgery, Psychiatry, etc. Each invention is coded as having a specialization if there is at least one inventor with that specialization on any of the patents; inventions may thus contain more than one specialization.

Star Inventor This variable captures whether any of the inventors on an invention is a highly-cited scientist, as listed by the Institute for Scientific Information, which identifies individuals whose citations place them at the pinnacle of their respective fields. This variable captures the effect of scientific excellence and high-impact science on invention; while we have not hypothesized a specific effect, prior empirical literature as discussed above has found a negative effect, which we speculate may be due to the fact that highly cited scientists are more likely to engage in basic research. We include it in our estimations to explore this relationship further. We also create a variable that indicates if the star is also a clinical scientist.

Single inventor – This is a dummy variable that indicates whether the invention has only one inventor.

We also include an additional variable, *"Number of inventors"* to account for the number of unique inventors listed on the case.

Patent characteristics

Technology Type – The inventions span a wide array of technologies, reflecting the variety of knowledge that contributes to innovation at the two AMCs. The technology of an invention might impact demand for the technology and the time to licensing. For example, inventions might include software for an MRI machine, a new catheter or a diagnostic test for Alzheimers. A medical device may be licensed more quickly than a drug molecule because it has a different development and clinical trial requirements affecting FDA approval timeline and return on investment. Similarly, a research tool such as a genetically altered mouse is likely to have a different licensing profile than a drug molecule. We include time-invariant dummy variables to capture these effects within each of the types of technology represented by the inventions.

We use the main (first) USPTO assigned patent class to categorize each invention into six main groups: Drugs, Molecular biology, Surgery, Chemistry, Imaging and "other". We further divide all inventions into device and non-device inventions. We define a medical device as an object or apparatus that has human body contact and/or is used on the human body and requires an FDA approval as a medical device. Even though there is a wide variation within medical devices with regard to their complexity and novelty, this classification is nevertheless useful as the approval process is similar for most devices, and licensing of devices might differ systematically from non-devices across the technology fields we identify.

Figure 2 examines the composition of inventions by technology over time. Overall, the data indicate a rise in basic research, with chemistry and molecular biology increasing; "other", which in this graph includes imaging and other categories with very few cases, is also increasing. There has been a sharp fall in drugs, this is likely to be driven in part by an increasing shift toward sponsored research in drug discovery at AMCs; sponsored research inventions are excluded from our sample. Surgery remains an important class of inventions throughout the period.

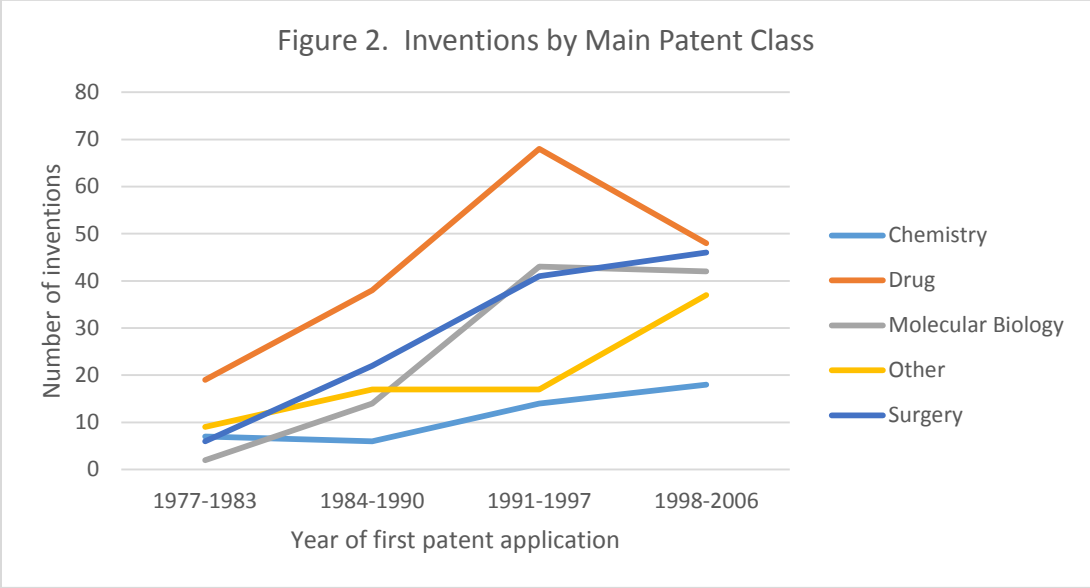
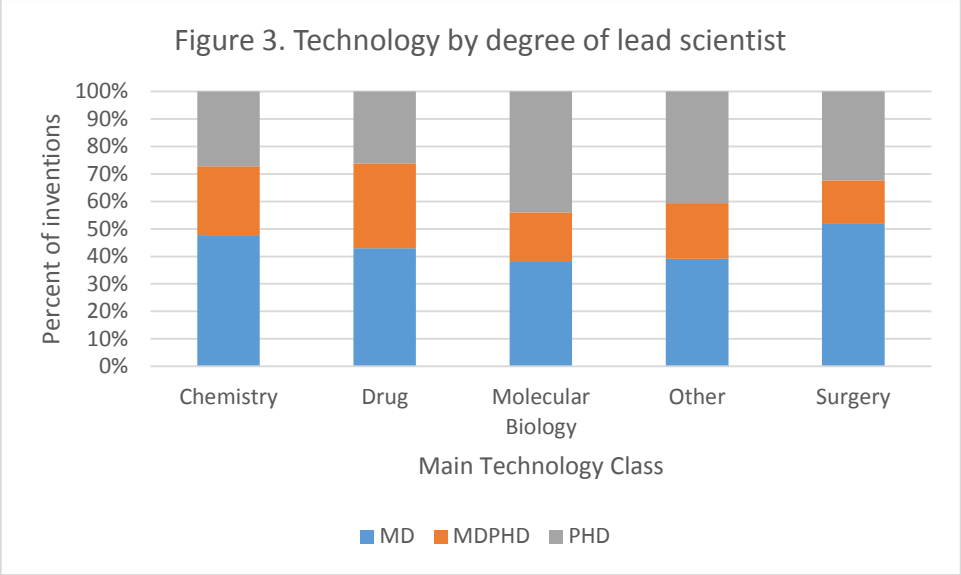


Figure 3 explores the distribution of technologies by the degree of lead inventor. This is important for our conceptual claim that differences between inventions by clinical and basic researchers stem from distinct processes of discovery, not different *fields* of discoveries. Empirically, we are concerned that our statistical estimates of "Basic" and "Clinical" variables be independent of field effects. If scientists self-select into certain kinds of projects, it will be difficult to know if the results are driven by research paradigms or unobserved variation across technology fields. We don't see such a pattern in the univariate data: molecular biology, which is



associated with basic research, has the highest concentration of leads in a single degree type - PhDs, however this maximum is only 55%; the remainder have a clinical degree. Overall the data show that PhDs, MDs and MD-PhDs are distributed widely across technologies, such that these categories do not allow for a clean distinction between "basic" and "applied" fields of research. This likely reflects, in part, the opportunities at Academic Medical Centers to merge basic and clinical research across an array of medical fields.

To further explore our claim that it is the logic of discovery, rather than the fields of inventions, that sets clinical and basic scientists apart, we look for an indication that clinical researchers are involving human subjects to a greater extent than PhD scientists across all their inventions. We search the abstracts of all patents for clinical keywords and code whether an invention (which may consist of multiple patents) has a clinical keyword in its abstract. We find that inventions that have a clinician as the team leader (MD or MD-PhD) are far more likely to include a clinical keyword than teams led by PhD scientists: 44 per cent versus 30 percent, respectively[17]. A similar pattern is found when looking at the composition of teams: the highest incidence of clinical keywords is found in inventions that include an MD-PhD on the team (48%), followed by teams composed only of MDs (40%); teams that combine PhDs and MDs (31%) and teams with only PhDs (28%). These data indicate that despite the fact that there do not seem to be major differences in the fields of inventions, clinicians are much more likely to engage in research that involves human subjects, from which we build the claim that they are likely to follow a different logic of discovery that is more conducive to creating commercially successful inventions.

Bibliometric variables

We include other characteristics of the patents that may correlate with the probability of licensing; valuable patents frequently have bibliometric characteristics that correspond to the effort put into the invention. That effort, in turn, can affect the probability of licensing. *Backwards citations* are the maximum number of patents cited by any patents in a case; this measure correlates positively with the scope of the claims on the patent, which suggests greater

[17] The Web of Science was used to generate a list of clinical keywords. These were: patient; clinical; vertebrate; human; full living; organism; subject; protocol; consent; administer; trials; mammal; blinded. This is an error-prone measure, insofar as inclusion of a clinical keyword in the abstract does not mean that humans were involved in the discovery. However, this would tend to work against the large difference we already find between clinicians and basic researchers in use of these keywords.

strength of intellectual property protection and increased chance of licensing. We also include *forward citations* up to 2011; highly-cited patents have been used to measure important technologies in bio-medical innovation (Gittelman and Kogut, 2003). In cases with multiple patents, we use the maximum forward to any single patent in the case. To account for age bias on citations, we calculate this variable as "forward cites per year" which is cumulative forward citations divided by the number of years since grant date through 2011. *Number of inventors on case* – This variable measures the number of unique inventors listed on a case. Inventions with more inventors may signal more effort and costs involved in a project (Gittelman and Kogut, 2003; Subramanian et al, 2013), and larger-scale projects may be more likely to be licensed. Large-scale projects are also more likely to include inventors with diverse research backgrounds who have links to potential licensors, so it's important to net out that effect when estimating the relationship between team composition and the probability of licensing. *Number of Patents per case* - A higher number of patents could signify important inventions with a higher probability of licensing.

MGH – A dummy variable that indicates whether the invention was made at the Mass General (1) or Brigham and Womens' Hospita (0)l.

Year – We control for time with variables that indicate whether the invention was disclosed in the 1980s or 1990s; the 2000s (when there are far fewer inventions due to right truncation) is the omitted category.

6. Proportional hazard models of licensing

We estimate a semi-parametric proportional hazard model, the Cox Hazard Model, in which time to first license is the dependent variable. The model is semi-parametric because it estimates a baseline non-parametric hazard function from the data, without assuming a specific

underlying distribution.[18] The covariates enter the model linearly, i.e. they modify the hazard function multiplicatively, giving it the name proportional. In the Cox Hazard model estimation formula below, $h(t|x_j)$ is the hazard of licensing computed by using the baseline hazard $h_0(t)$ estimated from the data without distributional assumptions and modified proportionally by the vector of independent variable coefficients - b_x.

$$h(t|x_j) = h_0(t)e^{b_x x_j}$$

6a. Models of specialized and cross-domain inventions

Model 1 includes the controls and fixed effects for technology class as well as the scientific specialization of the researchers on the patents. The effect of scientific stars is not significant; however, the effect of lead inventor experience in prior patenting is significant ($p<.01$), indicating the scientists' "taste" for invention and their success in patenting is predictive of successful licensing. Several of the controls for patent importance are also significant, indicating a correlation (rather than a causal relationship) between many bibliometric measures and the ex-post success of a patent (Gittelman, 2008). Forward citations and number of patents on a case (which correlate with technological importance) are both positive and significant ($p<.001$) but the number of inventors on a case is not significant.

In Model 2 we include a dummy variable that distinguishes between stars who are clinicians and others (mostly PhDs). It is positive and significant ($p<0.1$), and the main effect of star is now negative. This result suggests that stars engaged in clinical research are associated with licensed inventions, but those in basic science are not. However, our measure on clinical stars does not remain significant in models that follow which overlap on the clinical research

[18] Our results are robust to alternative hazard models with distributional assumptions (Weibull and Log-Normal) as well as to alternative hazard specifications such as Accelerated Failure Time (AFT).

dimension; we note however that the impact of highly cited scientists on innovation does appear sensitive to whether scientists are clinicians or Phds.

In Model 3 and 4 we explore the idea that inventions associated with clinical researchers are more likely to be licensed than those associated with PhDs. In Model 3 we first estimate the hazard of licensing of inventions composed only of MDs (Single Domain Clinical) against the omitted category of all other invention types combined, and find that these teams do have a higher hazard of licensing ($p<0.01$). Model 4 shows that, conversely, inventions composed only of PhDs have a *lower* hazard of licensing compared to all others ($p<0.01$). Taken together, the results provide strong support for our proposition that inventions associated with clinical research are more likely to be licensed than inventions by PhDs. It is important to underscore that these effects control for the technology of the invention, as well as the departmental specialization of the researchers.

There are many teams that are distributed, including those that mix both MDs and PhDs or include at least one inventor with an MD-PhD. We estimate how these combinations affect the hazard of licensing. Model 5 estimates the effects of cross-domain teams of both types: inventions on which MDs and PhDs collaborate (Distributed) and inventions that include an individual with MD-PhD (Integrated). The Single Domain inventions are the omitted categories. These models show there is no difference in the hazard of licensing between the cross-domain inventions and the single-domain inventions; integration of basic and clinical research alone does not increase the hazard of licensing as compared to inventions by single domain teams. The results do not supportthe common wisdom that integrated teams perform better than single domain teams.

In Model 6, we further probe the effect of integrating clinical and basic knowledge on inventions; the omitted category is inventions with all PhDs. Therefore, the remaining inventions all have at least one clinician, and have some combination of MD, MD-PhD, and

PhD. Again, we find that teams with only MDs are more likely to be licensed ($p<0.01$), however, teams that combine MDs and PhDs or have MD-PhDs have a higher hazard of licensing but the results are not statistically significant. These results contradict the premise of the translational model that combining basic and clinical research will be associated with greater innovation performance.

In model 7 we explore the effect of team leaders on licensing. These models capture our proposed "paradigm effect" insofar as the lead scientist determines the overall orientation of the research that led to the invention (Bercovitz and Feldman, 2011). If our proposition that these are different logics of research is correct, the lead inventor should matter to outcomes even after controlling for the team type, type of technology and the scientific specialization of the scientists. In Model 7 we control for team type by including variables that indicate whether the team included both MDs and PhDs (as we did in Model 5). We include dummy variables for inventions with MD leaders or MD-PhD leaders as compared to the omitted category of PhD leaders; we find that the latter is at a significantly lower hazard of licensing than teams with MD or MD-PhD leaders ($p<0.05$). This lends further support that the clinical research paradigm, as expressed by the team leader, increases the hazard of licensing.

7. Discussion and conclusion

This paper addresses an important gap in our knowledge about the relative contributions of basic and clinical research in medical innovation. We consider clinical research as a research paradigm distinct from basic science, which is unique in affording interactions with afflicted patients as part of the research process by scientists trained in both medicine and research. We contrast this with basic science, typically performed in a lab, which is engaged with understanding fundamental cause-effect relationships using reductionist, abstract models. Historically, most medical discoveries were made at the bedside; however, recent advances in knowledge about molecular biology as well as vastly powerful information-processing tools have

transformed the model of medical research. A new paradigm has emerged, in which large-scale data, teams, and basic research play a more central role than in the past.

Despite these shifts, the rate of medical innovation has not witnessed the expected boost in productivity (LeFanu, 2012). Current policy has diagnosed the problem as one of failure to translate basic research findings to clinical settings, and new institutions and policies have been designed to build bridges between the "bench" and the "bedside", for instance by encouraging cross-disciplinary teams. We propose that given the complexity of many medical problems, basic research has limited direct utility to technological innovation; instead, we propose that the clinical paradigm remains important in medical discovery because its search logic is embedded in the complex and variable context in which disturbances occur: the human body.

Our results provide support for the proposition that research by clinicians remains an important element in medical discovery. We find a pronounced "clinician effect": inventions by teams of clinicians are more likely to be licensed by firms, whereas inventions by basic researchers have a lower chance of being licensed. Moreover, collaborations between clinicians and PhDs do not add to the hazard of licensing. We found this result surprising, as we expected a positive impact of combining both domains of knowledge. The only case in which basic research increases the probability of licensing is when it is embodied in a team leader who spans both clinical and basic science (MD-PhD).

Our findings are intriguing, given that our context consists of two major Academic Medical Centers which are dedicated to the integration of clinical and basic research. We find that the distinctions between clinical and basic research matter, even in an institutional environment where the distinctions between them should be less pronounced than they would between (for instance) universities and medical schools, or universities and firms. In an AMC we expect that PhD scientists would have a greater-than-average "taste" for clinically applicable research than their counterparts in university laboratories, and that MDs would have a greater

than average "taste" for basic research than their practitioner counterparts. In other words, we expect that both PhDs and MDs in Academic Medical Centers are "Pasteur scientists" – conducting scientific research but with an eye to practical utility. Our data on technological fields bears this out, revealing PhD scientists invent in what would be considered "applied" fields (e.g. surgery and devices) and MDs invent in basic science fields (molecular biology). Despite the expectation that they would be similarly oriented and work on similar problems, and controlling for field and specializations, we nonetheless find a difference in the commercial potential of their projects. We interpret these differences as evidence that researchers in the clinical and basic research domains are driven by different logics of search, and those paradigms matter for the commercial potential of their inventions. Our findings that teams led by clinicians perform better than those led by PhDs – even controlling for whether they are mixed teams – gives more support to our claim that research paradigms, and not just scientific specializations, are important drivers of inventive success.

It might be argued that the fruits of basic research take years to translate to a market and that more time is needed for their value to be observed. This argument can be countered on three levels. First, these inventions are patented inventions so have been deemed to have practical utility by the Technology License Office and the USPTO. They span a range of technologies, rather than a few patent classes that might be considered "basic" (e.g. molecular biology). Our time period spans some thirty years, and our results show that the differences are robust over the time period.[19] Finally, the characterization of basic research as "early stage" implies an evolution from bench to bedside that is inaccurate in terms of the process by which medical innovations are discovered (Gelijns et al, 2001). As our results highlight, despite the close links

to science, applied research methods have formed a fruitful starting point for discovery and commercial development (Nelson, 2003).

Our findings help shed light on prior empirical research on boundary spanners as well as star scientists, and their differential contributions to innovation. As discussed earlier, it remains ambiguous whether the prior findings of a positive (negative) relationship between boundary spanners (stars) and technological innovation stem from differences across basic and applied scientific fields. Our findings suggest that these effects may, in fact, matter: academic stars only have a positive impact on innovation when they are clinicians, suggesting that the negative relationship found in prior work could reflect a proxy for basic research. Regarding boundary spanners, we propose that the "Clinician effect" in our data supports the idea that boundary spanners matter to innovation because they are more likely to be engaged in applied science and engage in technological learning, not the more general case of joint activities of scientific research and invention. Indeed, insofar as both MDs and PhDs in Academic Medical Centers may both be considered boundary spanners, we show that only one group of boundary spanners increases the rate of licensing. We propose that, taken together, our results help to unpack this important source of unobserved heterogeneity across inventing scientists, a topic that is now emerging as an important stream of research in its own right (e.g. Sauermann and Roach, 2014; Sauermann and Stephan, 2013). We leave to future research to further investigate these distinctions across groups of scientists who contribute both to research and to technological innovations.

Our findings have implications for the growing importance of teams and "big data" in science that necessitate specialized resources and skills to gather and analyze (Jones, 2009; Wuchty et al, 2007). We conceptualize basic and clinical research domains as not just different types of knowledge but distinct paradigms of research, and find that clinical research, which has historically been the key locus of medical innovation, continues to be important, even in a period

of burgeoning basic research and data-analytical frameworks in the life sciences. Our results show that the lead inventor has an additional effect over and above team composition on the success of the invention. We interpret our results to mean that scientists are not just bits of specialized knowledge and skills that may be combined and changed as the task requires; they are committed to specific professional identities and scientific paradigms that shape the questions they ask, the data and methods they employ to address them, and whether they adhere to a predictive or learning-in-practice logic of search. Our results question the idea, central in the translational model, that a more intensive application of basic science to innovation is needed to spur innovation, and that clinical researchers should partner with basic research. Instead, we find that the clinical research paradigm remains important in the development of useful new treatments and health-enabling technologies.

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Table 1: Estimates of the Hazard of Licensing, Cox Hazard Model

VARIABLES	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Single Domain Clinical			0.515***			0.756***	
			(0.193)			(0.255)	
Single Domain Research				-0.544**			
				(0.230)			
Cross Domain Integrated					-0.0570	0.396	-0.415
					(0.206)	(0.263)	(0.325)
Cross Domain Distributed					-0.0977	0.321	-0.146
					(0.244)	(0.291)	(0.249)
Lead MD							0.482**
							(0.207)
Lead MD-PhD							0.752**
							(0.350)
Lead Other							0.504
							(0.660)
Clinician Star Scientist		0.912*	0.710	0.624	0.882*	0.569	0.724
		(0.484)	(0.497)	(0.501)	(0.492)	(0.506)	(0.504)
Star Scientist on Team	0.0790	-0.619	-0.503	-0.346	-0.581	-0.367	-0.515
	(0.245)	(0.455)	(0.461)	(0.475)	(0.462)	(0.473)	(0.471)
Lead Inventor Experience	0.0503***	0.0511***	0.0497***	0.0524***	0.0498***	0.0502***	0.0553***
	(0.0152)	(0.0153)	(0.0151)	(0.0153)	(0.0154)	(0.0153)	(0.0158)
Forward Cites per Year	1.122***	1.069***	1.062***	1.032***	1.070***	1.051***	1.008***
	(0.282)	(0.283)	(0.284)	(0.284)	(0.285)	(0.285)	(0.289)
Prior Art	-0.000327	0.000268	0.000921	0.000322	0.000308	0.000356	0.000442
	(0.00565)	(0.00565)	(0.00573)	(0.00572)	(0.00578)	(0.00588)	(0.00586)
Num Patents on Case	0.223***	0.225***	0.231***	0.252***	0.220***	0.249***	0.242***
	(0.0527)	(0.0530)	(0.0533)	(0.0555)	(0.0537)	(0.0552)	(0.0550)
Num Inventors on Case	0.0366	0.0205	0.0922	0.0420	0.0606	0.0835	0.0933
	(0.0918)	(0.0926)	(0.0956)	(0.0936)	(0.0979)	(0.0980)	(0.100)
Single Inventor Case	-0.0266	-0.0729	-0.0954	0.0634	-0.0545	-0.0200	-0.0307
	(0.220)	(0.221)	(0.223)	(0.227)	(0.229)	(0.229)	(0.232)
Device	-0.181	-0.186	-0.200	-0.147	-0.142	-0.193	-0.223
	(0.251)	(0.250)	(0.253)	(0.253)	(0.254)	(0.254)	(0.260)
MGH	-0.204	-0.116	-0.187	-0.164	-0.115	-0.208	-0.188
	(0.182)	(0.188)	(0.190)	(0.189)	(0.189)	(0.191)	(0.192)
Filed in 1980s	0.185	0.181	0.167	0.152	0.170	0.159	0.203
	(0.281)	(0.281)	(0.283)	(0.283)	(0.283)	(0.283)	(0.285)

Filed in 1990s	0.206 (0.234)	0.219 (0.235)	0.179 (0.235)	0.166 (0.237)	0.194 (0.236)	0.168 (0.236)	0.193 (0.237)
Technology Fixed Effects	YES	YES	YES	YES	YES	YES	YES
Department Fixed Effects	YES	YES	YES	YES	YES	YES	YES
Observations	491	491	486	486	486	486	483

Table 2: Summary Statistics for Main Variables

	Num of Observations	Mean	Std. Dev.	Min	Max
Invention Licensed	491	0.427699	0.49525	0	1
Single Domain Clinical	486	0.253086	0.435228	0	1
Single Domain Research	486	0.228395	0.420231	0	1
Cross Domain Integrated	486	0.339506	0.47403	0	1
Cross Domain Distributed	486	0.179012	0.383758	0	1
Lead MD	488	0.42418	0.494725	0	1
Lead PhD	488	0.329918	0.470666	0	1
Lead MD-PhD	488	0.227459	0.419622	0	1
Clinician Star Scientist	491	0.089613	0.285918	0	1
Star Scientist on Team	491	0.12831	0.334775	0	1
Lead Inventor Experience	491	5.162933	5.053785	1	28
Forward Cites per Year	491	0.382885	0.336362	0	2.5
Prior Art	491	9.370672	13.31522	0	142
Num Patents on Case	491	1.356415	0.933096	1	12
Num Inventors on Case	491	2.183299	1.163653	1	9
Single Inventor Case	491	0.311609	0.463623	0	1
Device	491	0.219959	0.414641	0	1
MGH	491	0.600815	0.49023	0	1
Filed before 1990	491	0.230143	0.421353	0	1
Filed in 1990s	491	0.576375	0.494636	0	1
Technology Class: Molecular Biology	491	0.199593	0.400102	0	1
Technology Class: Drug	491	0.348269	0.476908	0	1
Technology Class: Chemistry	491	0.083503	0.276923	0	1
Technology Class: Surgery	491	0.224033	0.417369	0	1
Technology Class: Imaging	491	0.069246	0.254132	0	1

Table 3: Correlations Between Main Variables

	Single Domain Clinical	Single Domain Research	Cross Domain Integrated	Cross Domain Distributed	Lead MD	Lead PhD	Lead MD/PhD	Star Clinician	Star	Lead Inventor Experience	Forward Cites per Year	Prior Art	Num of Pats per Case	Num of Inventors	Single Inventor Patent	Device	MGH	Filed before 1990	Filed: 1990-1999	Tech: Molecular Biology	Tech: Drugs	Tech: Chemistry	Tech: Surgery	Tech: Imaging
Single Domain Clinical	1																							
Single Domain Research	-0.32	1																						
Cross Domain Integrated	-0.42	-0.39	1																					
Cross Domain Distributed	-0.27	-0.25	-0.34	1																				
Lead MD	0.619	-0.46	-0.29	0.153	1																			
Lead PhD	-0.41	0.754	-0.35	0.073	-0.6	1																		
Lead MD/PhD	-0.32	-0.3	0.762	-0.26	-0.47	-0.38	1																	
Star Clinician	0.015	-0.17	0.123	0.02	0.15	-0.18	0.032	1																
Star	-0.06	-0.01	0.073	-0.02	0.041	-0.04	0.008	0.817	1															
Lead Inventor Experience	0.022	0.024	0.005	-0.06	0.031	0.01	-0.04	-0.05	0	1														
Forward Cites per Year	0.116	-0.03	-0.16	0.099	0.035	-0.04	-0.03	0.004	-0.04	-0.01	1													
Prior Art	0.075	0.01	-0.08	0	-0.02	0.021	-0.02	-0.04	-0.07	0.034	0.465	1												
Num Pats per Case	-0.02	-0.01	-0.03	0.074	0.02	0	-0.01	0.102	0.095	0.05	0.203	0.14	1											
Num of Inventors	-0.3	-0.17	0.155	0.337	-0.01	0.032	-0.03	0.199	0.212	0.031	-0.04	-0.02	0.033	1										
Single Inventor Patent	0.301	0.171	-0.17	-0.32	0.037	0	-0.01	-0.11	-0.14	-0.05	0.029	0.051	-0.02	-0.7	1									
Device	0.151	0.079	-0.19	-0.02	0.013	0.044	-0.12	-0.15	-0.19	0.009	0.311	0.234	-0.02	-0.09	0.069	1								
MGH	0.078	-0.06	0.043	-0.08	0.029	-0.08	0.026	-0.02	0.067	-0.12	0.048	0.054	-0.05	0.032	-0.03	-0.05	1							
Filed: 1977-1989	0.008	-0.01	-0.03	0.033	0.002	-0.04	0.038	-0.03	-0.06	-0.15	0.125	-0.08	0.018	-0.13	0.105	0.048	0.115	1						
Filed: 1990-1999	0.049	-0.06	0.005	0.004	0.091	-0.05	-0.05	0.093	0.129	0.136	0.048	-0.03	0.073	0.124	-0.05	8E-04	-0.06	-0.63	1					
Tech: Mol Biology	-0.15	0.122	0.044	-0.02	-0.05	0.122	-0.05	0.021	0.174	-0.08	-0.27	-0.22	-0.03	0.112	-0.11	-0.25	0	-0.11	0.027	1				
Tech: Drugs	-0.08	-0.12	0.118	0.081	-0.01	-0.09	0.141	0.187	0.125	0.143	-0.05	-0.1	0.207	0.005	0	-0.34	-0.05	0.081	0.057	-0.37	1			
Tech: Chemistry	0.016	-0.04	0.054	-0.04	0.046	-0.05	0.014	-0.07	-0.09	0.015	-0.19	-0.17	-0.07	-0.04	0.038	-0.16	0.032	0.019	0.011	-0.15	-0.22	1		
Tech: Surgery	0.195	0.008	-0.17	-0.02	0.066	0	-0.09	-0.13	-0.18	-0.03	0.351	0.316	-0.07	-0.04	0.044	0.538	0.03	-0.05	0.028	-0.27	-0.39	-0.16	1	
Tech: Imaging	-0.04	0.147	-0.06	-0.04	-0.12	0.142	-0.05	-0.06	-0.08	-0.06	0.163	0.114	-0.08	-0.12	0.098	0.3	-0.06	0.012	-0.14	-0.14	-0.2	-0.08	-0.14	1