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The revolution re-visited: Clinical and genetics research paradigms and the productivity paradox in drug discovery

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ABSTRACT

Breakthroughs in genetics and molecular biology in the 1970s and 1980s were heralded as a major technological revolution in medicine that would yield a wave of new drug discoveries. However, some forty years later the expected benefits have not materialized. I question the narrative of biotechnology as a Schumpeterian revolution by comparing it to the academic research paradigm that preceded it, clinical research in hospitals. I analyze these as distinct research paradigms that involve different epistemologies, practices, and institutional loci. I develop the claim that the complexity of biological systems means that clinical research was well adapted to medical innovation, and that the genetics/molecular biology paradigm imposed a predictive logic to search that was less effective at finding new drugs. The paper describes how drug discovery unfolds in each paradigm: in clinical research, discovery originates with observations of human subjects and proceeds through feedback-based learning, whereas in the genetics model, discovery originates with a precisely-defined molecular target; feedback from patients enters late in the process. The paper reviews the post-War institutional history that witnessed the relative decline of clinical research and the rise of genetics and molecular science in the United States bio-medical research landscape. The history provides a contextual narrative to illustrate that, in contrast to the framing of biotechnology as a Schumpeterian revolution, the adoption of biotechnology as a core drug discovery platform was propelled by institutional changes that were largely disconnected from processes of scientific or technological selection. Implications for current medical policy initiatives and translational science are discussed.

1. Introduction

The past forty years have witnessed significant changes in the landscape of bio-medical research. Breakthroughs in genetics and molecular biology in the 1970s and 1980s made possible the application of basic science to medical discovery, and innovative bio-informatics techniques vastly increased the analytical power that could be harnessed to the complex task of finding new drugs (Scannell et al., 2012). These developments transformed the process of drug discovery as well as the institutional landscape of bio-medical research.

The new biotechnologies were framed in the popular press as well as the scholarly literature as a revolutionary technology in drug discovery (Cockburn, 2006; Henderson et al., 1999; Hopkins et al., 2007; Rosenberg, 2009). Biotechnology was characterized as a rational, science-driven approach to discovery, in contrast to the trial-and-error, chemical-based research platforms of the pharmaceutical industry. This framing was a powerful force in its adoption by both firms as well public sector policies. Billions of dollars and a great deal of scientific resources were invested in rapidly sequencing the human genome, fuelled by the promise of radical progress in medical innovation. Changes in policy to allow patenting of genetic material facilitated commercialization and private-sector adoption of the new technologies. The Schumpeterian character of the technology was exemplified by a US model of commercialization that centered on entrepreneurial start-up firms founded by university scientists and backed by venture capital (Gittelman, 2006; Kenney, 1986; Zucker et al., 2002).

Some forty years have passed since the initial discoveries were made, yet the expected benefits in medical discovery have not materialized (LeFanu, 2012). It is estimated that in real terms, the number of new drugs approved in the US per billion dollars of R&D spending has declined by half every nine years since 1950, with the steepest declines in the 1980s and 2000s – precisely the era that the new scientific paradigm emerged (Scannell et al., 2012). As blockbuster drugs lose patent protection, the rate of discovery of new drugs has not been sufficient to maintain a robust R&D pipeline

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(Kola and Landis, 2004). In the face of a perceived R&D productivity crisis, many large pharmaceutical firms are reducing R&D and shuttering entire branches of research (Jack, 2011).

The problem of declining productivity of discovery is puzzling, a paradox even: why have scientific breakthroughs in biology, as well as vastly improved analytical techniques, failed to yield the expected gains in medical innovation? Current medical policy addresses this question by pointing to institutional failures, as well as time lags, in the translation of basic science to clinical settings (Cockburn, 2006; Collins, 2011; Mullard, 2011). This paper develops a different perspective, to consider the role of different scientific research paradigms in the productivity of drug discovery. I contrast two distinct paradigm in medical research: patient-oriented clinical research and discovery based on the science of genetics and molecular biology. The former was central in the post-war institutional landscape, whereas the latter emerged as important in the 1980s and 1990s. The two paradigms represent distinct and competing logics of discovery: genetics-based approaches represent a predictive, theory-driven search logic that abstracts from natural complexity, whereas clinical research is an experiential, feedback-based search process using study objects as they exist in the natural world. They are distinguished by an epistemic divide in their beliefs about the usefulness of understanding *disease causality* as a starting point of discovery. As a result, the origin points and subsequent search unfold differently in each of the two paradigms. A core argument is that these practices have implications for the relative performance of each search paradigm in medical discovery.

The comparison of the two paradigms is guided by the larger debate about the relative merits of predictive and experiential search and learning routines for technological innovation. Prior research in the management literature has stressed the power of predictive science and analytics for innovation when technological problems are complex (e.g., Arora and Gambardella, 1994; Fleming and Sorenson, 2004). However, the idea that more science yields better technology has been challenged by the claim that the logic of basic science is fundamentally ill-equipped to solve many complex technological problems, and indeed may conflict with technological learning. This perspective stresses different evolutionary logics of scientific and technological knowledge, such that discovery in each unfolds largely independently of the other (Nelson, 2003; Nightingale, 1998; Pavitt, 1998; Gittelman and Kogut, 2003; Vincenti, 1993). In line with this perspective, many in the medical policy literature have pointed out that most major medical discoveries originated at the bedside rather than the bench, and that the application of genetics and molecular science to medical discovery could hinder, rather than accelerate, progress (LeFanu, 2012; Gelijns and Rosenberg, 1994; Gelijns et al., 1998; Rees, 2002a; Vos, 1991). This claim partly reflects the remarkable postwar record of clinical research: the period following World War II 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).[1]

The historical centrality of clinical research in medical discovery and its subsequent decline raises the question of how and why a new scientific paradigm emerged in the research landscape. Did clinical research face diminishing returns, with the low-hanging fruits of discovery already picked, such that the emergence of genetics and molecular-based approaches represented a radical shift toward a new and more productive research paradigm? Or was its role in medical research diminished by changing institutional forces that were largely independent of technological selection (Ahrens, 1992; Nathan, 2002)? Understanding the answer to this question is important for an effective diagnosis of the productivity decline in drug discovery, as well as the design of effective organizational and public policies to address it.

This paper tackles the link between research paradigms and discovery by analyzing the two paradigms from both a conceptual as well as a historical perspective. I describe how the process of drug discovery unfolds in the genetics and clinical research paradigms. The two paradigms are distinguished by differences in their origin points and the types and timing of feedback that guide sequential decision-making: in the clinical research paradigm, observation from humans forms the starting point of investigation, and feedback from patients is used to guide further investigations. In the genetics model, models of interactions at the sub-cellular/molecular level form the initial point of discovery, with information from intact human subjects entering at the testing stages. A central claim is that the highly uncertain and variable nature of human biology means that early feedback from human subjects is important in the discovery process, such that models of fundamental causality at the molecular level – while valuable for further *scientific* research – are of limited utility in as guides to *technological* search. The implication is that the clinical research paradigm is comparatively advantaged at discovering drugs that will operate effectively in humans, and that this advantage is robust to advances in fundamental biological science. In this perspective, the historically central role of doctors in medical discovery does not reflect a lag in basic science, but the persistent limitations of basic science and predictive theory to develop technologies that will be effective in highly complex, variable natural phenomena.

The second part of the paper questions the dominant narrative of biotechnology as a Schumpeterian revolution that emerged to overtake a largely exhausted research trajectory based on random, trial-and-error discovery. This framing neglects the substantial US investment in the postwar period to build an institutional infrastructure that would provide support for academic clinicians working in a network of Academic Medical Centers, in close collaboration with chemists in pharmaceutical firms. I describe the multiple factors that, following the rise of the clinical paradigm in biomedical research in the 1950s and 1960s, led to its weakening in the 1970s and 1980s: changes in healthcare and insurance and policies that put budgetary pressure on teaching hospitals and shortened in-patient care cycles; increased bureaucratization of academic hospitals; and declining career opportunities for young physician-researchers. Concurrent with these changes, recombinant DNA and related techniques were discovered in university laboratories which previously had little or no application to medical research. In the US, translation of the basic science to medical applications was propelled by a Silicon Valley model adapted from the technology sector, characterized by venture-capital backed firms spun off from university research.

The history reveals the decline of support for clinical research can be tied to institutional and policy shifts that were largely

[1] 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.

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