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INNOVATION AND OPEN SCIENCE

The Public and Private Sectors in the Process of Innovation: Theory and Evidence from the Mouse Genetics Revolution

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How do public and private researchers respond to a breakthrough inducing new research opportunities? Modeling the process of step-by-step innovation as a control rights problem, this paper evaluates comparative research strategies of public versus private researchers as they respond to a common breakthrough that induces many potential follow-on research paths. While the opportunity may be common to all researchers, differences in the degree of freedom afforded researchers results in the endogenous sorting of research projects; as a result, public and private researchers will produce distinctive research outputs, as measured by publications and patents.

Our analysis builds on the multistage research model developed by Philippe Aghion, Matthias Dewatripont and Jeremy Stein (2008) where earlier stages of research are more efficiently carried out by researchers who enjoy full control rights over their research agenda (inducing the development of entirely new research lines), while later stages may be more efficiently pursued by private firms focusing on near term commercialization of breakthrough research opportunities. We use this model to generate predictions regarding how public and private

researchers react to new research opportunities and increases in the openness of key research inputs relating to those opportunities. Our first prediction is that “private sector” researchers focus on late stage projects (resulting in patents), whereas “public” (academic) researchers pursue longer research lines resulting first in publications (and some patents) which may then lead to downstream applications in subsequent periods. The effect of a research opportunity is therefore longer lasting in academia. As well, an increase in the degree of openness not only impacts the level of follow-on research, but also on the degree of exploration and diversity pursued by academic researchers. This more diverse range of new research lines may lead over time to a wider range of follow-on patents, by both public and private researchers.

We provide empirical evidence for these ideas by analyzing a specific breakthrough in the life sciences in the 1980s—the mouse genetics revolution. The development and diffusion of powerful research tools to genetically engineer research mice allowed researchers to produce a wide variety of mice relevant to both fundamental long term questions in biology and to short term drug discovery using a variety of tools (Ken Paigen 2003). We focus on two key technologies—Knock-out and Cre-lox. Knock-out mice, initially developed at the University of Utah by Mario R. Capecchi, have individual genes turned “off,” allowing researchers to examine the precise role played by that gene in biological function and disease. This technology was recognized with the 2007 Nobel Prize in Medicine. Cre-lox mice, developed at E. I. du Pont de Nemours and Company (DuPont), enabled scientists to differentially switch genes “on” inside specific cell types, making Cre-lox mice a powerful method for examining how

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specific genes impacted particular organs and body systems. Both technologies were disclosed through publication and also received patents; however an important difference was that the Knock-out patent was never enforced against follow-on research within the academic community, while DuPont initially used its Cre-lox patent to impose significant limitations on academics. Indeed, in Fiona Murray et al. (2009) we exploit a shift in the openness of Cre-lox technology in the late 1990s—as the result of a Memorandum of Understanding (MoU) between DuPont and the National Institutes of Health (NIH)—to examine how openness shaped the level and diversity of follow-on public sector research. Our empirical evidence is consistent with the control rights approach: public sector publications increase at an earlier time than the rise in patenting for both Knock-out and Cre-lox mice; private sector patenting exhibits a more transient path than either public sector publications or public sector patenting; and the Cre-lox openness shock leads to a significant boost in public sector publications, concentrated on more exploratory research.

I. Theoretical Approach

We consider multistage research processes, with each research line starting with an initial idea I_0 ; and eventually generating a marketable product with value V after k successful stages. Assume for simplicity that each stage requires only one researcher, who obtains a probability of success $p < 1$ at any stage if he follows a “practical” research strategy at that stage. The researcher can also pursue an “alternative” strategy with a zero probability of success. We interpret this strategy as either a research activity that the scientist enjoys but that does not pay off in monetary terms, or as the initiation of a new research line that nonetheless does not result in progress down the particular line for which he was funded.

There is an infinite supply of researchers at each stage, each with an outside option w . After being hired at stage j , the scientist is exposed to idea I_{j-1} , and then learns whether he would prefer following the practical or the alternative strategy. If he is able to undertake his favored strategy, he suffers no disutility from working. If, however, the scientist has to undertake the strategy that he likes less, he suffers a

disutility of z . The ex ante probability that a scientist prefers to follow the practical strategy is given by α . Assume further that the choice of the practical versus alternative strategy is ex ante noncontractible, so one cannot write a contract promising a bonus for following the practical strategy.

Academic research (or freedom) differs from private sector research in that it leaves control rights over the research strategy in the hands of the researcher. Thus if a research line is pursued in academia, the researcher is paid wage w and always works on his preferred strategy. This implies that with probability α , the scientist works on the practical strategy, and with probability $(1 - \alpha)$, he works on the alternative strategy. Thus the ex ante probability of advancing to the next stage is αp . Instead, when employed by the private sector, the researcher knows that the firm owner has the authority to force him to work on the practical strategy. Anticipating this, the researcher will demand a wage $w_p = w + (1 - \alpha)z$, where the latter term represents compensation for the fact that scientists now always have to adopt the practical strategy, whether they prefer that research direction or not (Scott Stern 2004).

A main finding in Aghion et al. (2008) is that academic freedom tends to dominate private sector focus at earlier stages of a research line, whereas private sector control dominates at later stages. To see this, consider a research line involving two stages, and suppose the first stage has been successful so that we are now at stage two, one step away from generating V . If this last stage of research is done in the private sector, the expected payoff is $E(\pi_2^p) = pV - w_p$. If instead it is done in academia, the expected payoff is $E(\pi_2^a) = \alpha pV - w$. Private sector research will therefore yield a higher payoff than academic research if and only if $(1 - \alpha)pV > (w_p - w)$; that is, if and only if $pV > z$.

Let Π_2 denote the maximum of $E(\pi_2^p)$ and $E(\pi_2^a)$. Moving back to stage one, we can compare $E(\pi_1^p) = p\Pi_2 - w_p$ and $E(\pi_1^a) = \alpha p\Pi_2 - w$ and see that private sector research yields a higher payoff than academic research at stage one if and only if $p\Pi_2 > z$. Since $\Pi_2 < V$, it follows that if private sector research is value maximizing at stage one of the two-stage research line, it is also value maximizing at stage two: it cannot be value maximizing to have academic freedom operate at later stages than private

sector research. The intuition is that, while academia's wage cost advantage is assumed to stay constant over research stages, its lower probability of success becomes more problematic as one approaches the final value V . This result can be generalized to lines of any length k (see Aghion et al. 2008).

What does the model have to say concerning the effect of a common shock inducing new research opportunities, and the effect of an openness shock such as the Cre-Lox MoU?

- First, a breakthrough such as mouse genetics should induce an increase in both private sector and academic activity, with a more sustained push in the latter, whose less focused nature will lead to a flurry of new early-stage research lines which lead to further academic exploration. By contrast, more focused, later-stage private sector research will typically lead to a short surge in near term projects that subsides over time. (Seongwuk Moon forthcoming)
- Second, an openness shock reduces the fixed costs associated with (academic) exploration, with a potential for downstream exploitation. This shock should lead, unsurprisingly, to a higher level of academic activity (because there will be additional profitable research lines). However, the complementarity between academic freedom and openness leads us to also expect sustained academic activity, and once again a sustained increase, due to the exploratory nature of open access academic research (Murray et al. 2009).

II. Data and Methods

The data for this study include two distinct research outputs: articles in scientific journals and patents. The articles capturing the flow of research building on mouse genetics technology are defined by the citations to a set of "mouse articles" (papers describing the development of a novel genetically engineered mouse captured in the Mouse Genome Informatics (MGI) database and published between 1987 and 1998 (the date of the NIH agreement covering Cre-lox mice)). Of the 13,000 mouse articles in MGI, we focus here on mouse articles describing two types of mouse engineering technologies: Cre-lox (28 mouse articles) and Knock-out (1,895 mouse

articles). We use PubMed and Thomson ISI Web of Science to collect detailed bibliometric information for all follow-on forward citing articles in scientific journals through the end of 2005. For each we gather institutions and key words allowing us to categorize each citing article as either public sector (academic, government, or nonprofit) or private sector (for-profit) research. The key words also allow us to define "new" and "old" research by subject area; "new key words" are those attached to forward citing articles which have not been used in a citation to that same mouse article in prior years. Conversely, "old key words" have been used as a descriptor in citations in a prior year. We aggregate these measures into technology-year observations by mouse-engineering technology by combining all the citations received by all the mouse articles for a given mouse-engineering technology in any particular year; these aggregates form the basis for our analysis of articles as a research output (see Murray et al. 2009 for details).

To analyze the research output captured in patents, we link the two mouse-engineering technologies of interest (Cre-lox and Knock-out) to particular US Patent Office patents based on the text description in granted patents. (This is preferable to the citation based approach because citations to the Cre-lox and Knock-out patents capture only follow-on research that directly builds on these tools and does not necessarily capture patents that use these technologies). As of December 2009, the database contains 2,711 patents linked to Cre-lox mice, and 2,605 patents linked to Knock-out mice. For each patent entry we gathered assignee information to differentiate between patents belonging to public sector and private sector research entities. As with citations, we then aggregate patents into technology-year observations, combining all the patents in a particular mouse-engineering technology which were submitted as applications to the US Patent Office in a given year.

Our theoretical framework suggests that the level, nature and timing of follow-on research depend not only upon the type of research inputs available but also on their degree of "openness." While we cannot simply implement a controlled experiment in which different knowledge inputs were randomly allocated to different degrees of openness, we are able to take advantage of existing institutional variations that shift a subset of key research inputs towards higher levels of

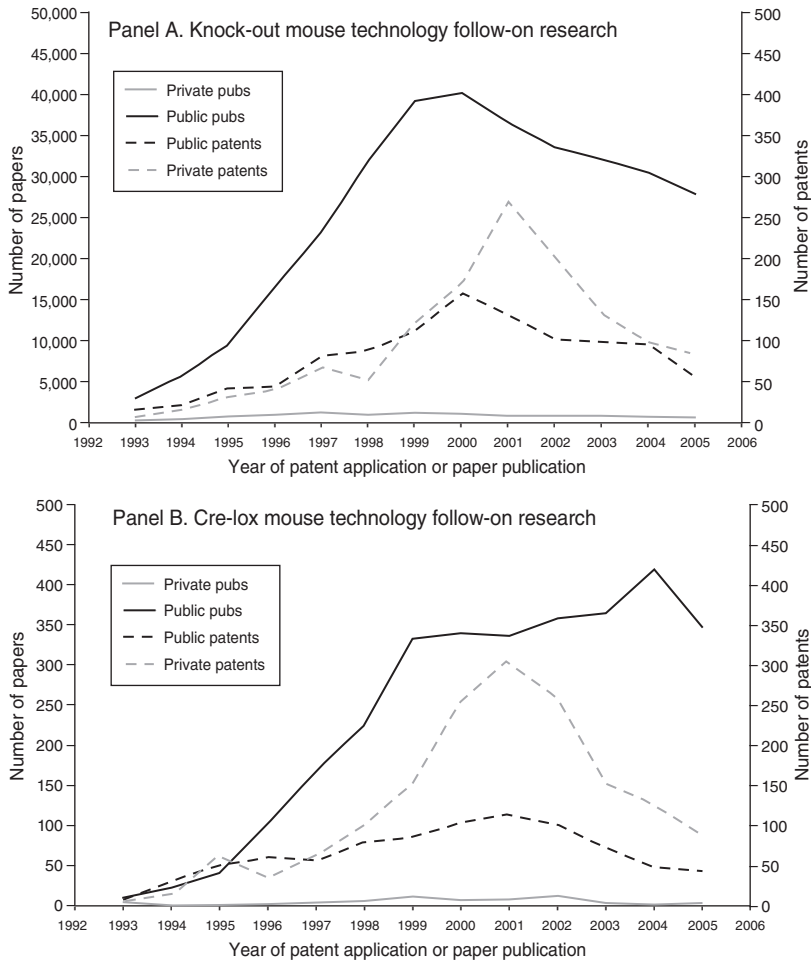


FIGURE 1

openness while leaving others unaffected. This difference-in-differences approach comparing follow-on use of the affected and unaffected research inputs before and after the shift in openness can be used to examine the impact of openness on the level and nature of follow-on research. In particular, we examine the impact of the shift in the openness of Cre-lox engineered research mice on the level and type of follow-on research (captured in the flow of articles citing our set of mouse articles) in the years before and after the shift, taking advantage of the fact that institutional changes to openness negotiated by the NIH affected Cre-lox but not Knock-out research mice (see Murray 2009 for qualitative research suggesting that the timing and extent

of this openness shock were largely exogenous, and Murray et al. 2009 for more details on our difference-in-differences empirical approach).

III. Results and Concluding Remarks

Our analysis of the responses of public and private researchers to the opportunity presented by the novel tools in mouse genetics engineering focuses on the publication and patent data outlined above. Figures 1a and 1b illustrate the annual levels of scientific research publications (left-hand axis) and patenting (right-hand axis) related to the use of mouse engineering tools divided according to whether the research was done predominantly by the private

sector or by the public sector (either alone or in collaboration). Figure 1a illustrates the different levels of knowledge production building on the opportunity presented by the Knock-out mouse technology. The publication data is based not on the number of Knock-out mice developed but rather the number of research articles that make use of such mice (traced through citations). Overall each Knock-out mouse article is, on average, cited by 22 articles each year, yielding more than 10,000 follow-on research articles annually; this dramatic impact on research is consistent with the 2007 Nobel Prize awarded for this breakthrough.

The rapid rate at which knowledge is produced and disclosed through publications is notable and rising steadily throughout the 1990s (as illustrated by the solid lines on the graph); most striking however is the overwhelming majority of the publications that are produced in the public sector. Less than 2.5 percent are produced in public-private collaboration, and publications authored exclusively by private sector researchers are at a negligible level. This public role in knowledge production and the continued output of academic research publications accords with our model that public sector researchers will respond to new opportunities through sustained participation and the expansion of the opportunity into a wide variety of (at times unexpected) sustained research lines. In contrast, patenting rises sharply (at a level of between 50 and 250 patents a year as illustrated by the dashed lines) with private sector researchers exhibiting a “gold rush” approach consistent with their rapidly moving in to undertake a series of one-stage projects using Knock-out mice; indeed, after 2002, private sector patenting activity falls off rapidly. In comparison to the publications which show little private sector involvement, patents are produced by both private and public sector researchers at a ratio of 1:1 until 1998 when the private sector moved ahead.

The patterns for Cre-lox mouse technology (see Figure 1b) are similar albeit at a different scale. In the period from its first discovery in the late 1980s to 1999, more than 50 different Cre-lox mice were developed, represented by 28 original mouse articles. Each one was subsequently used and cited in the academic literature at an average rate of over 14 times per year. These accumulated into more than 350 citing publications each year, again with the

overwhelming majority stemming from public sector researchers. While the level of publication is lower than for Knock-out, patenting levels are similar, with a peak of over 450 patents per year by both public and private sector researchers using Cre-lox mice. The pattern again accords with our model, with private sector researchers moving in rapidly with a much greater peak level of activity and then a more rapid drop-off, while public researcher patents show a more steady increase and slower rate of decline. In contrast, public sector research, mainly disclosed through publications, takes place at a sustained level over a long period of time suggesting that the research opportunity is extended along a wide variety of exploratory research lines.

It is also notable that for Cre-lox mice, the openness shock to the intellectual property surrounding the Cre-lox methods was complementary to the activities of public sector researchers. While private sector patenting does not seem to have been impacted by the NIH MoU (as we would expect given that the agreements were intended for the public sector), public sector researchers responded by increasing their levels of publication production in the post-openness period.

Drawn from our companion paper (Murray et al. 2009.), Table 1 examines how the level and nature of knowledge production using Cre-lox mice changes in the post-openness period. We also find that a 47 percent boost in the annual level of public sector research, but this increase is driven by an increase in follow-on publications using new key words and not those using key words that have already been connected to Cre-lox mouse articles. In other words, we do indeed see an increase in the level of diversity of research in the post-openness period.

Our research into the economics of the mouse genetics revolution reinforces a control rights approach to the process of innovation. In particular, this approach suggests that an important feedback mechanism (relative to a purely linear model of innovation) is the fact that researchers with discretion to pursue their own research direction often forgo near term commercial rewards to initiate entirely new research lines (pursued by themselves or others). In other words, the degree to which a single breakthrough discovery—such as the development of tools for mouse engineering—impacts a wide range of follow-on research reflects not simply the degree to which the breakthrough is “general

TABLE 1—NEGATIVE BINOMIAL CONDITIONAL FIXED EFFECTS

	Annual public sector paper citations	Annual public paper citations with new key words	Annual public paper citations with old key words
Effect of Cre-lox NIH agreement	[1.467]*** (0.115)	[1.399]* (0.202)	[0.879] (0.194)

Notes: Fixed effects for article (conditional), margin-age and margin-calendar year, window effects. Incident rate ratios in brackets; Block bootstrapped standard errors in parentheses.

purpose” but instead reflects how researchers and research funders contract with each other over academic freedom. It is of course possible to extend this logic to consider alternative forms of knowledge production, including emerging models for collaborative research and knowledge production such as open source software and Wikipedia. We leave such investigations as a further step along this research line.

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