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## Of Mice and Academics: Examining the Effect of Openness on Innovation<sup>†</sup>

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JULIAN KOLEV, AND SCOTT STERN\*

*This paper argues that openness, by lowering costs to access existing research, can enhance both early and late stage innovation through greater exploration of novel research directions. We examine a natural experiment in openness: late-1990s NIH agreements that reduced academics' access costs regarding certain genetically engineered mice. Implementing difference-in-differences estimators, we find that increased openness encourages entry by new researchers and exploration of more diverse research paths, and does not reduce the creation of new genetically engineered mice. Our findings highlight a neglected cost of strong intellectual property restrictions: lower levels of exploration leading to reduced diversity of research output. (JEL I23, O31, O33, O34)*

Over the past three decades, there has been a significant increase in the scope of formal intellectual property (IP) rights, such as patents, over scientific knowledge traditionally maintained in the public domain (Mowery et al. 2001; Murray 2002; Heller 2008). This dramatic expansion of IP rights for early-stage research tools has spurred a wide-ranging policy debate, with particular attention paid to the impact that IP plays in shaping both fundamental scientific advances and the incentives for follow-on research (Merges and Nelson 1990; Gallini and Scotchmer 2002).

The impact of IP rights on the rate and direction of scientific research is subtle. When strong and broad IP rights are available in a sequential-innovation setting, early-stage researchers can capture the value of their innovation by imposing access fees, thus enhancing the incentives for early-stage research but imposing a tax on follow-on research activities (Arrow 1962, Scotchmer 1991). In its simplest form, this perspective focuses attention on the trade-off between enhancing incentives for

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development of existing innovations via follow-on research (achieved by relaxing IP protection), and providing incentives for the creation of new early-stage research (achieved through tighter IP protection).

While this trade-off is important, it neglects the distinctive nature of cumulative discovery within the academic research community. Building on an emerging body of research in the new economics of science (Dasgupta and David 1994; Stern 2004), Aghion, Dewatripont, and Stein (2008, henceforth ADS) emphasize the role of intellectual freedom: granting control rights to allow researchers to select their own research agenda. A control-rights approach focuses attention on the role of exploration: scientific discoveries are not only *sequential*, but also *multi-purpose*,<sup>1</sup> and new follow-on research directions can be discovered when scientists freely explore the potential applications of existing research. In an “open” research environment, researchers have low-cost and independent access to prior discoveries and research tools. Such an environment encourages not only direct (perhaps commercially oriented) exploitation by follow-on researchers, but also the exploration of new research directions and entry by researchers who are new to an emerging research area.

The main prediction analyzed in this paper is that in a research setting characterized by a high level of intellectual freedom, greater openness will not simply increase the level of research output, but will also shift the *composition* of follow-on research toward more diverse and exploratory projects. We evaluate this idea in a very distinctive research setting: the invention, development, and application of genetically engineered (transgenic) mice by academic scientists (mainly biologists) in the period from 1980 to 2010. While mice might seem to be a niche research tool, the invention of methods to precisely engineer mice to exhibit particular characteristics (e.g., to be predisposed to a specific disease) enabled scientists to dramatically expand their ability to explore the biological basis of disease or evaluate the impact of different drugs. Scientists developed three complementary but distinct methods for mouse engineering, known as the Onco, Cre-lox, and Knock-out technologies. As emphasized by a leading researcher, “...at the end of 1980, in a period of a few months, an entirely new era in mouse genetics began, with the creation of the first transgenic mice... What ensued was an explosion of knowledge when a myriad of new biological and molecular insights appeared over the following years” (Paigen 2003, as quoted in Murray 2010). The new tools were used to develop a wide range of specialized research mice, which in turn led to a large body of both basic and applied follow-on research. It was no surprise that the developers of one of the methods—the Knock-out technology—ultimately received the Nobel Prize in 2007.

Within this setting, we evaluate the impact of openness on innovation by exploiting a natural experiment from the late 1990s that affected researchers seeking to access genetically engineered research mice created using two of the three technologies mentioned above (Cre-lox and Onco). Specifically, in 1998 and 1999, the National Institutes of Health negotiated two Memoranda of Understanding with DuPont that granted academic researchers low-cost, royalty-free, and independent access to both the use of DuPont’s methods and the transgenic mice created with

<sup>1</sup> These multipurpose discoveries often combine potential commercial application with a simultaneous contribution to fundamental scientific knowledge, placing them in “Pasteur’s Quadrant” of scientific research (Stokes 1997).

them. These agreements created a simple and standardized one-page contract for gaining access to the mice, and facilitated their availability through the Jackson Laboratory, the world's largest nonprofit research mice repository. The unanticipated agreements between the NIH and DuPont constituted a clear openness shock for the mouse genetics research community: the research tools covered by the patents—hundreds of varieties of Cre-lox and Onco mice developed in the early 1990s—shifted abruptly from a regime of high access costs to one where mice were readily available (at essentially marginal cost) to the academic research community.

Our empirical approach takes advantage of several key aspects of these NIH agreements and the nature of mouse genetics research to develop a difference-in-differences estimate of the impact of increased openness on both the level and nature of follow-on research. First, each genetically engineered mouse is associated with a journal article that describes its initial development; we refer to these linked publications as “mouse-articles.” We are able to construct a treatment sample based on mouse-articles affected by the NIH agreements and a control sample of mouse-articles unaffected by the agreements (composed of mice that were created using two alternative methods—“Knock-out” or “Spontaneous”).<sup>2</sup> Second, the precise timing and scope of the NIH agreements were unanticipated by the mouse genetics community. In effect, there was a sudden and permanent reduction in access costs associated with the mice in our treatment sample, with no change in access costs for our control sample.<sup>3</sup> Finally, we take advantage of detailed bibliometric data for follow-on citations to the mouse-articles to characterize how the openness shock changed the nature of subsequent research along a number of important margins.

In implementing our empirical analysis, we study the citations to a sample of more than 2,000 mouse-articles; approximately 10 percent of these are associated with the Cre-lox and Onco technologies, and so were impacted by the shift in openness that resulted from the NIH agreements. By comparing citations to the mouse-articles before and after the agreement (and comparing them to the evolution of citations in the control sample), we are able to isolate the causal impact of a shift in access costs on the level and nature of research. In addition to examining whether there is a net increase or decrease in the level of citations, the bulk of our analysis examines how the *composition* of citations differs after the openness shock. Specifically, we construct measures capturing whether the research community using a particular mouse in any given year is composed of new authors joining the community (e.g., the number of new authors citing the mouse-article), whether a particular mouse is generating new and previously

<sup>2</sup>While the NIH agreements we study had no direct impact on our control group, certain aspects of our results, such as the movement of researchers into and out of research using specific mouse-articles, bring up the possibility of substitution from our control group to our treatment group, potentially leading to a double counting of impact in our difference-in-differences framework. We perform a number of robustness tests tracking the precise movements of researchers within our sample, and find that substitution patterns between different mouse technologies are small compared to our measured treatment effects.

<sup>3</sup>Our natural experiment involves the shift of some mouse-articles from a high-access-cost regime to a low access-cost regime, and the control group is in the low-access-cost regime throughout the sample. Though not an ideal counterfactual (we would have preferred to observe some mouse-article remain in the high-access-cost regime throughout the sample), we are able to directly test for the validity of our control group, and find no evidence of differential trends between our treatment and control groups in the pre-shock period for any of our dependent variables (see Section II for a discussion, and Table 7).

unexplored directions of research (e.g., whether the citations include keywords that had never before been linked to a particular mouse-article), and whether that follow-on research is published in journals that are linked to more basic or more applied research. Finally, we directly examine the impact of the NIH agreements on the creation of new mouse-articles. While the reduction in access costs paid to early-stage researchers would normally decrease the incentives to create new mice and publish their associated mouse-articles, a setting where free exploration is central to the production of scientific knowledge would be consistent with a neutral or positive effect of increased openness on mouse creation.

Our results are striking. The NIH agreements are not simply associated with a uniform increase in the level of follow-on research, as expected under the classical tension between early- and late-stage IP rights.<sup>4</sup> Analyzing the composition of follow-on research, we find that the bulk of these increased citations are associated with research produced by “new” researchers and institutions. Specifically, the boost in citations to a given mouse-article in the post-NIH-agreement period comes from researchers that had not cited that mouse-article prior to the NIH agreement. In addition, the NIH agreements resulted in a significant increase in the diversity of follow-on research: there is a decisive increase in the diversity of the journals in which mouse-articles in the treatment group are cited, and in the number of previously unused “key words” describing the contributions of the citing research. Intriguingly, our data suggest that the NIH agreements are *not* associated with a reduction in the creation of new mouse-articles (i.e., the use of the Cre-lox and Onco technologies to develop new mice); instead, the development of new genetically engineered mice either remained the same or increased after the agreements. Taken together, these findings are consistent with the view that exploration is a central component of academic innovation. In light of these results, we suggest that the classical tension between early- and late-stage research incentives does not capture the full range of factors that determine the outputs of academic innovation, and propose that openness and exploration are also primary drivers of the research process.

The paper is organized as follows. Section I motivates the analysis by elaborating on the effects of openness on scientific knowledge production. Section II describes the experiment we use to explore the effects of increased openness on the level and composition of research flows. Section III outlines our identification strategy. Section IV presents the data and summary statistics. Section V presents the empirical results, and Section VI concludes.

<sup>4</sup> As we discuss in Section IIA, our qualitative examination of this scientific community suggests that the changing IP rights had little effect on early-stage researchers seeking to develop novel methods to engineer mice themselves. From the start of this revolution in molecular biology, scientists involved in developing new techniques were driven more by their potential to develop powerful new tools and enable diverse follow-on research than by the direct rewards of intellectual property. Further, in this case, patentability itself was a surprise—at the time of the development of the three mouse engineering technologies, the researchers did not anticipate that mice were potentially patentable. Indeed, the patent that was ultimately granted on the Onco-Mouse was the first patent granted on a genetically engineered mammal.



## I. The Impact of Openness on Scientific Knowledge Production

The primary focus of this paper is on how the degree of openness associated with scientific research tools impacts the level and nature of research using those tools. Our theoretical analysis combines the basic tradeoffs of IP policy in Green and Scotchmer (1995) with the analysis of freedom and exploration in ADS (2008), and develops novel predictions for the role of openness in scientific research. Green and Scotchmer view early-stage research as providing a set of tools that serve as inputs to later-stage work. Under a regime of strict IP rights, upstream tool developers are tool-specific monopolists, and so are able to impose significant access charges when a specific research tool is required for a follow-on research project. The natural trade-off in this environment is between providing incentives for tool creation through strong and long-lasting IP rights, and facilitating later-stage development by relaxing IP rights and providing low-cost access to existing tools. As long as IP rights holders cannot engage in perfect price discrimination with potential follow-on researchers (e.g., because of asymmetric information), a regime of strict IP rights for upstream tools will be associated with higher prices and lower quantities relative to the social optimum. In this framework, increased openness will (in equilibrium) decrease the rate of tool creation, while increasing the amount of follow-on research generated by each tool.<sup>5</sup>

However, as emphasized in ADS (2008), this linear view of innovation neglects two fundamental aspects of the scientific research process: the potential for multipurpose discoveries, and the role of researcher freedom, or control rights, in the innovation process. When considering discoveries that may have multiple follow-on applications, a nonlinear approach allows for an analysis of the heterogeneity among these follow-on research paths. Further, when there are multiple paths of innovation available, the level of researcher freedom becomes a key determinant of innovative output, even as it is endogenously determined within the structure of research organizations (Stern 2004; ADS 2008).

Building on the above discussion, our basic idea is that openness, by making it easier for a researcher to access others' ideas, gives researchers more incentive to start new and speculative research lines.<sup>6</sup> It does so by allowing other researchers to continue working on these lines, thereby increasing the probability that a new line will realize its full potential. In the online Appendix, we extend ADS (2008) to develop a simple model of how openness and freedom in research interact with one another.<sup>7</sup> We model research as a multistage process where each stage requires a researcher, and the ultimate stage leads to a commercializable output. The researcher

<sup>5</sup>For the full details of this theoretical framework, see Scotchmer (1996; 2004). This model of innovation has found support in empirical studies such as Furman and Stern (2011) and Williams (2013).

<sup>6</sup>For more background, Merton (1973), Dasgupta and David (1994), and David (2003) offer rich and comprehensive discussions of the role of openness and freedom in the context of Open Science.

<sup>7</sup>The formulation in the online Appendix is one of many that can yield broadly similar predictions. It is meant to offer a close connection to our empirical setting while also providing a useful perspective into the more general phenomenon of the impact of openness on innovation. The original ADS model focuses on the differences between academia and the private sector, with the former endogenously offering a higher level of freedom to its researchers. While this paper focuses on the impact of openness within the academic research community, we also explore the role of private sector innovation in mouse genomics when considering patent filings in our related work, Aghion et al. (2010).

is employed by a manager who decides how much effort to devote to monitoring the research agenda.<sup>8</sup> The lower the probability of monitoring, the higher the researcher's freedom. In each stage on the line, the researcher can choose between a practical strategy that leads to the next stage on the research line with some positive probability, and an alternative strategy that does not induce progress on that research line but yet may be what makes the researcher happier (and which may also lead to the creation of a new research line). The key insight of the model is that monitoring will be weaker in earlier stages in a research line than in later stages: the intuition being that the benefit of focused research increases as one moves toward later stages on the line and closer to its terminal payoff.

By developing a framework of the research process that is both sequential and multipurpose, this model generates predictions on the impact of an increase in openness on the flow and nature of innovation.<sup>9</sup>

First, openness directly lowers the cost of accessing the ideas of others, allowing free researchers to improve upon them when the original inventor lacks the expertise or desire to do so. Openness therefore increases the pool of contributing researchers for a given research line.

Second, through this larger pool of potential contributors, openness allows for better matching between researchers and projects. This increases the likelihood that any given stage of the project will succeed, particularly if it requires a different field of expertise from the previous stage. Because this effect is cumulative, its effect is strongest on projects that are multiple stages from producing their terminal output. Thus, increased openness will favor earlier-stage research and long-horizon projects.

Third, openness will be particularly important for more exploratory research lines that are characterized by a branching structure, where value is dispersed across a range of newly-generated research directions. In these contexts, access costs are likely to be incurred for every branch in addition to every stage, making exploratory research lines differentially more sensitive to the level of openness.<sup>10</sup> Thus, when a single discovery induces multiple follow-on research paths, a lack of openness will be most detrimental to the most speculative paths, i.e., those that involve previously unexplored research directions.

In addition to offering these new predictions, the above approach also implies a mitigation of the usual tradeoff in IP rights between the developers and the users of scientific tools. Specifically, because increased openness facilitates exploration, it can lead to an expanded set of applications for IP rights holders of existing innovations. While the lower access costs might decrease the IP holder's revenue in the short run, the long-run expansion of possible (commercial) applications works to counteract this decline. This countervailing effect is stronger the more freedom researchers enjoy, i.e., at earlier stages of the research process where the potential

<sup>8</sup>For an alternative perspective based on the decision to publish or patent a discovery, and an empirical investigation of the role of organizational forms in genetic research, see Moon (2011).

<sup>9</sup>See the online Appendix for formal derivations of these predictions, based on our extension of the control-rights approach developed in ADS (2008).

<sup>10</sup>Indeed, in the edge case where each new research direction can lead to yet more branching, total access costs rise exponentially, rather than linearly, with the distance to the terminal output.

for discovery of new applications is greatest.<sup>11</sup> In contrast to the predictions from traditional models, our analysis suggests that a policy of increased openness *need not* reduce the rate of innovation by the researchers facing reduced IP rights.<sup>12</sup>

As we move toward testing the above predictions, it is useful to state the relevant null hypothesis. Under the linear model, openness is expected to result in a *proportionate* increase in all types of follow-on research activities. Since all types of research are equally likely to depend on a given research tool, they would experience the same reduction in cost after an openness shock. Consequently, the linear model implies that there would be no systematic differences in the impact of openness across different types of follow-on applications. Specifically, the null hypothesis expects no difference between the output of new and old researchers, no difference between short-term and long-term research directions, and no difference between innovations in established fields and those exploring new research directions.

In contrast to the null hypotheses above, we predict that an increase in openness, by reducing the costs of accessing key research inputs, will: (i) widen the potential pool of researchers and institutions conducting follow-on work on any given research idea; (ii) favor long-horizon research lines, which require significant development before reaching the private sector; and (iii) increase the likelihood that researchers operating under high levels of freedom (e.g., academics) will engage in speculative exploration that broadens the diversity of research directions being pursued. Finally, because it expands the range of potential follow-on research applications, increased openness *need not* reduce the rate of innovation by early-stage researchers.

When considering the above predictions, it is worth noting that under a model where innovation is both sequential and multi-purpose, an increase in openness will have an impact that goes beyond a temporary one-off effect. Its initial effect is an increase in research that advances existing lines to the next stage of their progression, but its impact will likely persist because the development and exploration of existing lines can lead to further discoveries of new research directions. Thus, there is a positive probability of a long-term flow of new research lines that continue long after the lines covered by the original openness shock have ended.

The remainder of this paper examines the above predictions in the context of a specific natural experiment: the change in openness resulting from NIH agreements covering genetically engineered mice, which took effect in the late 1990s. In the following section, we elaborate on the details of this empirical setting.

<sup>11</sup> While it would be relatively difficult to increase the payoffs to a given IP holder by uniformly lowering the cost of access for *all* parties interested in using the technology, the benefit of exploration is greatly amplified if an IP holder can lower access costs for academic follow-on researchers while maintaining high access costs for commercial applications. If differential pricing is not possible, the discovery of early-stage research inputs could also be rewarded through direct public subsidies, or through public buy-outs of (private) patents as in Kremer (1998).

<sup>12</sup> Bessen and Maskin (2009) highlight a closely related effect in the context of the software industry: “if a patent holder is not as well-informed about a rival’s potential future profits as the rival is himself, she may have difficulty setting a mutually profitable license fee, and so... licensing may fail, thereby jeopardizing subsequent innovation.” While a detailed analysis of the software industry is beyond the scope of this paper, we believe this is an important theoretical insight, and that there are important commonalities between these two different settings that are worthy of future exploration.



## II. Empirical Setting: Shifts in the Openness of Genetically Engineered Mice

This section offers an overview of our empirical context and, in particular, the natural experiments that significantly shifted the level of openness for two broad categories of genetically engineered mice.<sup>13</sup> Mice play a central role in the study of cancer and other human diseases due to their genetic likeness to humans, with whom they share 99 percent of their genes.<sup>14</sup> Throughout the twentieth century, scientists in mouse genetics relied on spontaneous mutations for their disease studies: researchers bred mice that naturally exhibited particular disease-linked symptoms or behaviors.<sup>15</sup> In this line of research, scientists require significant numbers of live mice to ensure sufficient sample sizes for their experiments, e.g., when studying a given cancer's sensitivity and resistance to chemotherapy, as a function of the particular oncogene(s) that brought about the disease.<sup>16</sup> To facilitate their efforts, the research community developed open-access institutions, notably the Jackson Laboratory (a mouse repository in Bar Harbor, Maine) to classify, breed, and distribute specialized research mice to the academic community (Rader 2004).

In the early 1980s, advances in molecular biology and in the ability to manipulate embryonic stem cells allowed researchers to develop a set of systematic and precise methods for engineering specialized mice as research tools, greatly expanding the application of research mice in life sciences research.<sup>17</sup> Three breakthroughs were particularly important. First, with partial funding from DuPont Corporation, Professor Phillip Leder at Harvard University developed the "OncoMouse" method in June of 1984 (Stewart, Pattengale, and Leder 1984), which provided a means for inserting genes into an embryo, thereby making mice susceptible to particular forms of cancer and other diseases. Second, in a discovery that was subsequently awarded the 2007 Nobel Prize in Medicine, Mario Capecchi of the University of Utah and his collaborators developed the Knock-out technology (Mansour, Thomas, and Capecchi 1988); instead of insertion, this method enabled researchers to delete specific genes, with the first viable mice appearing in January of 1989 (Thompson et al. 1989). Finally, researchers in the life sciences division of DuPont, including Brian Sauer, completed the development of the Cre-lox technology in July of 1992 (Lakso et al. 1992); this method allowed for precise cutting and pasting that turns off genes in specific tissues or organs. In practical terms, these advances allowed researchers to develop three new types of research mice: Knock-out, Cre-lox, and

<sup>13</sup>Murray (2010) provides a detailed overview of the mouse genetics revolution and the role of intellectual property and openness within the mouse genetics research community. See also Rader (2004).

<sup>14</sup>See Rosenthal and Brown (2007) and Simmons (2008) for a full discussion of mouse models of human disease.

<sup>15</sup>Given the value of such mutations, researchers also developed techniques to significantly increase the rate of mutation of research mice, such as exposing pregnant mice to high levels of radiation (Murray 2007 and 2010).

<sup>16</sup>As discussed in Rader (2004), most experiments require several dozen to over 100 mice, and typical research labs have mouse populations in the thousands at any given time, covering multiple mouse strains.

<sup>17</sup>These methods of mouse engineering are complex and costly. To create a mouse with particular genes inserted within a mouse genome, scientists must first inject foreign DNA into mouse eggs, transplant the eggs into female mice, and, if successful, monitor and breed the incorporation of the genes into the offspring. During our sample period, the development of a mouse line from scratch likely involved at least 18 months of laboratory research and a significant investment of time and attention by a principal investigator (Rader 2004; Murray 2010).

Onco mice, which, along with the previously available spontaneous mice, could serve as critical scientific research inputs.

### A. Intellectual Property in the Mouse Genetics Revolution

The revolution in mouse genetics coincided with two important shifts in the role of IP rights in life sciences research. In 1980, the Supreme Court decision in *Diamond v. Chakrabarty* established the patentability of genetically engineered organisms, and the Bayh-Dole Act affirmatively allowed universities to seek patents over federally funded research starting in December of 1980.<sup>18</sup> While many observers took universities' growing patent portfolios as an indicator of their evolving role as engines of innovation (Henderson, Jaffe, and Trajtenberg 1998), some argued that strong IP rights could lead to rent-seeking and undermine research productivity (Heller and Eisenberg 1998). This debate was particularly salient for researchers within the mouse genetics revolution. Each of the three main new technologies (Knock-out, Onco, and Cre-lox) received a relatively broad patent.<sup>19</sup> In the case of Knock-out mice, the University of Utah received a patent in 1987 but did not place strict IP restrictions on their use by follow-on researchers. Instead, Knock-out mice were made available at relatively low cost through the Jackson Laboratory.

Before proceeding we should note that for mouse genetics researchers, the potential to patent the novel mouse genetics methods (and thus control the mice produced with them) does not seem to be the key incentive in the development of any of the three technologies. First, most of the research was initiated prior to the Bayh-Dole Act and was therefore started in a period before academic researchers considered the patentability of their inventions. Second, while *Diamond v. Chakrabarty* upheld patents on genetically engineered organisms, none of the research scientists considered mice (mammalian organisms rather than the *e. Coli* bacteria of the original case) to be patentable subject matter at the time they were conducting the original research. Indeed, the patent that was ultimately granted on the OncoMouse was the first patent granted on a genetically engineered mammal. Third, all the scientists involved have described the powerful scientific incentives that motivated their research. They were in pursuit of new genetic engineering methods that could render the simple mouse a more powerful research tool, and make possible a wide range of important new experiments (Murray 2010). This was true for the development of the Knock-out technology by Capecchi, who had received partial funding from the Cystic Fibrosis Foundation as well as the NIH. It was also the case for Leder and his funders (DuPont), as evinced by the lack of specific direction imposed in DuPont's funding arrangement and by Leder's lack of involvement in patenting decisions related to the Onco technology.<sup>20</sup> For the Cre-lox technology, Sauer initiated the work on its development while still at the National Cancer Institute. Thus, all of the

<sup>18</sup>These legal and policy shifts reflected, in part, increasing appreciation that certain types of academic research were increasingly dual in nature: fundamental scientific discoveries that could simultaneously have a high degree of commercial utility (Murray and Stern 2007).

<sup>19</sup>Knock-out mice were covered under US Patent 4,687,737, Onco mice under US Patent 4,736,866, and Cre-lox mice under US Patent 4,959,317.

<sup>20</sup>See Murray (2010) for a more thorough analysis of these issues.

genetic engineering methods in our sample were developed in the absence of any incentives offered by the possibility of receiving IP rights.

While the development of all three of the new techniques was driven primarily by the potential to develop powerful new tools and enable diverse follow-on research, the patents that were eventually granted over the Onco and Cre-lox technologies proved to be much more controversial than the patent over Knock-out mice (Merges and Nelson 1990). As a result of their partial funding of Harvard's OncoMouse discoveries and their internal development of Cre-lox technology, DuPont gained exclusive control over patents for these technologies. In contrast to the University of Utah, DuPont chose to exercise strict control over the distribution and use of mice that exploited the techniques covered by their patent portfolio.<sup>21</sup> During the early 1990s, researchers (and their institutions) were obliged to obtain a license from DuPont when they sought to use an Onco or Cre-lox mouse. The detailed licensing agreement required annual disclosures to DuPont regarding experimental progress, limits on informal mouse exchange among academic researchers, and reach-through rights allowing DuPont to automatically receive licensing revenue from any commercial applications developed using either Cre-lox or Onco technology.

These requirements—amounting to very high access costs for follow-on researchers—caused widespread discontent within the academic community.<sup>22</sup> There were a number of attempts to subvert or blunt the impact of the DuPont licensing regime: notably, in 1992, Dr. Ken Paigan, then-director of the Jackson Laboratory, announced he would make Onco mice openly available without a license, directly contravening DuPont's IP rights. While some researchers took advantage of informal sharing or chose to access Onco mice from the Jackson Laboratory (opening themselves to a potential infringement suit by DuPont), most researchers (and their institutions) were wary of the legal repercussions that could arise from using these mice. In the case of Cre-lox mice, prior to 1998, researchers had no means of access through the Jackson Laboratory or any other open-access depository: DuPont maintained a near-monopoly on their distribution.

Thus, by the mid-1990s, researchers seeking to use a particular genetically modified mouse faced one of several access-cost regimes. If the follow-on research required a Spontaneous and Knock-out mouse, it would generally be directly available from the Jackson Laboratory or another depository at relatively low cost.<sup>23</sup> If the research required an Onco mouse, the mouse might be available informally

<sup>21</sup>It is worth noting that DuPont targeted only follow-on researchers seeking to use mice created using the techniques it had patented. It made no significant attempts to restrict the creation of new mouse strains using these techniques by early stage researchers, seeking only to ensure that all new mice were subject to the same strict control in the context of follow-on work. Though DuPont's enforcement strategy was geared toward IP rights over downstream applications, even early stage projects had the potential to eventually lead to commercial outputs; because of this, mouse researchers expressed significant concern about the uncertain scope of DuPont's potential enforcement strategy and claimed that they had fewer incentives to use Onco and Cre-lox mice as a consequence (Murray 2010).

<sup>22</sup>DuPont's practices were seen as "an enormous obstacle to free and open distribution of information and materials... it was a whole new way of doing science... it really affected the way the mouse research community works" (Murray 2010).

<sup>23</sup>In addition to the unenforced Utah patent on knock-out technology, a small number of additional patents were granted over specialized knock-out mice. However, the intellectual property restrictions associated with these mice seem to have been negligible; further, their openness was not directly influenced by the NIH agreements we exploit in our empirical work.

through the researcher's peer-to-peer network or through the Jackson Laboratory. However, to use such a mouse was in direct contravention of DuPont's licensing requirements, and the risk of litigation served to increase the effective cost of access for follow-on researchers. If a Cre-lox mouse was needed, it might be available through informal exchanges among colleagues, but these too were beset by high access costs: Cre-lox developers invested considerable time and resources in the creation of the mouse, and often required co-authorship (or other types of nonmonetary payment) in exchange for access. In addition, the exchange of such mice took place in the shadow of potential infringement suits by DuPont, as well as contravening the official policy rules of most universities.<sup>24</sup> It was of course possible to access Cre-lox and Onco mice by signing DuPont's licensing agreement. However, relatively few institutions or researchers did so prior to the NIH agreements of the late 1990s. Finally, it was possible for research teams to develop a new mouse within their laboratory as part of the research process. This approach could delay a project by at least 18 to 24 months, require significant resources (e.g., a full-time post-doc), involve investment in specialized mouse engineering skills, and, in any case, did not eliminate the risk of litigation based on infringement of the DuPont patent portfolio.

### B. *The Openness Shocks on Cre-lox and Onco Mice*

The degree of openness associated with Cre-lox and Onco mice shifted dramatically following their respective NIH agreements in 1998 and 1999.<sup>25</sup> In the wake of a nearly decade-long campaign of pressure from the academic community, NIH Director and Nobel Laureate Harold Varmus successfully negotiated two "Memoranda of Understanding" among DuPont, the Jackson Laboratory, and the NIH. These agreements greatly decreased the access costs of the genetically engineered mice they covered for academic researchers. The Cre-lox agreement, effective on July first of 1998,<sup>26</sup> allowed the Jackson Laboratory and universities to distribute and share Cre-lox mice with a simple licensing process: a standardized one page material transfer agreement and an institution-wide license.<sup>27</sup> In addition, the Jackson Laboratory announced its commitment to acquire, breed, and distribute Cre-lox mice on an open access basis. A similar agreement for Onco mice was reached one year later, taking effect on July first of 1999;<sup>28</sup> notably, the impact of this agreement was somewhat less dramatic as the Jackson Laboratory had already been

<sup>24</sup> As described in Murray (2010), "The mice were fragile, and breeding lines had not been stabilized. This made it difficult to share in large numbers. One scientist who had managed to make Onco mice in the late 1980s recalled: 'I had a few requests for mice and offers of co-authorship. But I did not send them the mice...I was having to slow my own work down because they were breeding very poorly and so it was impossible to ship them around.'"

<sup>25</sup> We use the word "open" in the sense of these mice being widely accessible with clear and limited restrictions. The NIH agreements specified both a renouncing of the right to sue and reach-through rights to later work. It is useful to emphasize that, while initiated by the NIH, the terms of the agreement represented a voluntary choice on the part of DuPont.

<sup>26</sup> Full text of the Cre-lox agreement is available at: [www.ott.nih.gov/sites/default/files/documents/pdfs/cre-lox.pdf](http://www.ott.nih.gov/sites/default/files/documents/pdfs/cre-lox.pdf).

<sup>27</sup> While the actual NIH agreements pertained only to those with NIH funding, in reality this meant that virtually all academic researchers had direct access to the mice. However, the agreements had no effect on collaborative projects between academic and industry researchers, or on purely industry-run projects.

<sup>28</sup> Full text of the Onco agreement is available at: [www.ott.nih.gov/sites/default/files/documents/pdfs/oncomouse.pdf](http://www.ott.nih.gov/sites/default/files/documents/pdfs/oncomouse.pdf).

distributing Onco mice to researchers since 1992, albeit in violation of DuPont's IP requirements.

Over a two-year period, life sciences researchers experienced a significant decrease in the total costs of access for Cre-lox and Onco mice, while experiencing no shift in these costs for Knock-out and Spontaneous mice. These increases in openness provide the key source of variation we exploit in our empirical analysis. Three features of this increase in openness are particularly salient, and deserve elaboration. First, though the academic community lobbied continuously for increased openness regarding the Onco and Cre-lox mice, there is significant evidence that the precise timing and scope of the two NIH agreements were largely unanticipated.<sup>29</sup> Given that academic lobbying efforts for easier access to these mice spanned nearly a decade, it is unlikely that researchers were simply shifting publication dates for already-performed research in anticipation of a comprehensive agreement eliminating reach-through rights. Instead, researchers deterred by the licensing restrictions imposed by DuPont undertook different research projects.

The second important feature of the NIH agreements is their broad scope: they impacted more than 50 mice that had been developed and disclosed in the scientific literature using the Cre-lox technology, and more than 160 different Onco mice that were similarly disclosed. Importantly, these mice represented the entire population of strains covered by DuPont's IP rights, meaning that there was no potential for selection bias through the NIH targeting only the most valuable mouse strains. Moreover, given the general-purpose nature of DuPont's genetic modification techniques, the mice affected by the agreements were broadly applicable to a wide range of disease areas, covering both basic research characterizing fundamental biological processes and applied work assessing specific disease treatments.

The two features above allow us to effectively estimate pre- and post-NIH agreement citation rates to the treated mouse-articles in our sample. The third feature of the openness shocks relates to the validity of our control group. Specifically, the mouse technologies owned by DuPont and covered by the NIH agreements were only part of the mouse genetics revolution described in the previous section. When these technologies were developed, there was no *ex ante* reason to expect any single one to emerge as more or less valuable than the others. All four categories of mice were based on general-purpose techniques, and served as broadly applicable inputs for follow-on research; the most significant distinction among them was the different patterns of access costs *before* and *after* the NIH agreements, as described above. As such, we take advantage of a large sample of untreated mouse-articles (Knock-out and Spontaneous mice) to estimate the counterfactual citation rate that would have occurred if the NIH agreement has not been signed. This interpretation carries the implicit assumption that citations to both our treatment and control mouse-articles are subject to the same age and calendar-time dynamics. Notably, we make this assumption despite the fact that both Knock-out and Spontaneous mice were governed by low-access-cost regimes throughout our sample; therefore, we do not observe any low-openness mouse-articles after the calendar year of 1999 or

<sup>29</sup>We discuss this point in more detail in Section VB.



past the age of 12 years. A true counterfactual of mouse-articles that remain under a low-openness regime is therefore not possible. However, our analysis in Table 7 finds strong support for the above assumption, namely, that the calendar-time and age dynamics of citations to mouse-articles differ only by a constant of proportionality. Specifically, we test for and find no evidence of a difference in pre-shock trends between our treatment and control groups across any of our dependent variables.

As we outline in detail below, the mice in both our treatment and control samples were developed and disclosed during the pre-agreement period, and their use by follow-on researchers can be meaningfully captured by citations to the original mouse-articles.

### III. Empirical Strategy

#### A. Identification Strategy

We examine the impact of a sudden reduction in access costs for genetically engineered mice (arising from the NIH agreements described above) on the level and composition of follow-on research. Building on Furman and Stern (2011), our approach addresses a fundamental inference problem associated with traditional cross-sectional approaches to the evaluation of shifts in openness and related institutional arrangements: if more open inputs are used more extensively by follow-on researchers, does this follow from the fact that they are open or from the fact that openness tends to be associated with higher quality inputs and materials? Any effective estimation strategy must disentangle the selection effect (i.e., the correlation between openness and overall research impact) from the direct impact of openness.

Ideally, causal identification of the impact of openness would rely on a controlled experiment in which different knowledge inputs (such as particular research mice) are randomly allocated to distinct institutional environments with varying degrees of openness.<sup>30</sup> A practical route capturing the essence of such an approach takes advantage of institutional variations that shift key research inputs toward higher (or lower) levels of access costs in a way that is exogenous both to their initial production and to their incorporation into follow-on research lines.

We implement this idea by taking advantage of the institutional changes to openness negotiated by the NIH that affected some (but not all) research mice in our sample.<sup>31</sup> As described in the previous section, new specialized research mice are disclosed through publication in scientific articles that describe their production and distinctive characteristics (we refer to these disclosures as mouse-articles). In constructing our sample, we identify mouse-articles for mice affected by the NIH

<sup>30</sup>See Williams (2013), which cleverly exploits a natural experiment similar to this ideal experiment that occurred in the context of sequencing the human genome.

<sup>31</sup>Our approach builds on recent work applying a differences-in-differences econometric framework to analyze the institutional and microeconomic foundations of knowledge accumulation (Furman and Stern 2011; Murray and Stern 2007; Huang and Murray 2009; Rysman and Simcoe 2008).

agreements (i.e., Cre-lox and Onco mouse-articles) and for mice that were unaffected (i.e., Knock-Out and spontaneous mouse-articles).<sup>32</sup>

In our analysis, we trace out the scientific impact of each mouse-article over time through the citations to that mouse-article by follow-on research published in the scientific literature. While an imperfect and noisy indicator of overall impact, citations offer a systematic reflection of the process by which researchers acknowledge how their efforts at any given research stage build on the tools and knowledge developed by researchers in prior stages. In the case of mouse-articles, our qualitative research suggests that citations to a given mouse-article involve the use of that article's specialized research mouse in a scientific experiment, and that follow-on researchers almost always include a citation to the original mouse-article whenever its associated mouse is used in their project. Our analysis benefits from the fact that the Cre-lox and Onco NIH agreements both occurred well after the initial development of these technologies; thus, for each mouse-article in our sample, we are able to observe citations both before and after the NIH agreements. Finally, as noted above, the precise timing and scope of the openness shock were largely unanticipated. Specifically, the NIH agreement could have been reached, in principle, at any point in time from the early 1990s through the present. Moreover, our main control group—Knock-out mice—is likely to have been drawn from a population of similar scientific quality and importance, differing only insofar as the patent over Knock-out technology was unenforced by the University of Utah.<sup>33</sup>

By measuring citations to Cre-lox and Onco mouse-articles before and after the sudden reduction in access costs, and by measuring the citations to mouse-articles that experienced no shift in access costs, we can identify the causal impact of the increase in openness stemming from the Cre-lox and Onco NIH agreements.<sup>34</sup>

### B. Regression Specifications

Our baseline regression takes the measure *Annual Citations<sub>jt</sub>* as its dependent variable, representing the number of citations to a given mouse-article *j* in calendar year *t*. On the right-hand side of the regression equation, we use *Post\_NIH<sub>jt</sub>* as our key treatment variable, equal to one for observation *jt* if the research stemming from mouse-article *j* was impacted by an NIH agreement in year *t*. We use the variable *NIH\_Window<sub>jt</sub>* in the same manner to capture the period between the signing of

<sup>32</sup> While these different technologies differ in the precise details of the specialized genetic manipulation they allow, with the exception of Spontaneous mice, they are broadly similar with regard to the scope of application and relevance to human disease. Moreover, all three technologies were patented and could have been subject to strict enforcement. Spontaneous mice differ to the extent that they were not subject to patents.

<sup>33</sup> We find support for this view in our analysis of pre-NIH-agreement trends in Section VB and Table 7. After controlling for mouse-article, age, and calendar-time fixed effects, we show that prior to their respective NIH agreement dates, the growth rates of citations to Cre-lox and Onco mice are statistically indistinguishable from those to Knock-out mice.

<sup>34</sup> Due to the targeted nature of our dataset, we are able to estimate the impact of changes in openness on a specific field of scientific research. By necessity, our results therefore reflect a partial-equilibrium effect: we cannot capture the impact of openness on fields outside of mouse genetics. Based on the significant start-up costs and specialized knowledge requirements of life science research, we expect general equilibrium effects to be quite small in the short run. However, we expect scientists to have greater research flexibility in the long run, and would need to account for the alternative research directions that would have been pursued under a counter-factual low-openness policy.

the NIH agreement and the point when it would have a chance to impact publication behavior.<sup>35</sup> Using a dataset of citations to mouse-articles impacted by the NIH agreement and mouse-articles that were unaffected, consider the following conditional fixed effects<sup>36</sup> negative binomial<sup>37</sup> estimator:

(1) *Annual Citations*<sub>jt</sub>

$$= f(\varepsilon_{jt}; \gamma_j + \beta_t + \delta_{t-PubYear} + \psi_0 NIH\_Window_{jt} + \psi_1 Post\_NIH_{jt}),$$

where  $\gamma_j$  is a mouse-article fixed effect (conditioned out in estimation),  $\beta_t$  is a calendar-year fixed effect, and  $\delta_{t-PubYear}$  is an age fixed effect calculated from the year in which mouse-article  $j$  was published. In our sample, these controls represent 2,171 mouse-article fixed effects, 22 age fixed effects, and 14 calendar-year fixed effects (1993–2006). Respectively, they account for the heterogeneity among the mouse-articles, the nonlinear evolution of citations over time elapsed from the initial publication of the mouse-article, and the potential for differences over time in citation rates. This specification also accounts for the incidental parameters problem (Hausman, Hall, and Griliches 1984), testing for the impact of the NIH agreements by estimating the *proportional change* in citation rate for mouse-articles in the treatment group in response to the NIH agreement, after accounting for the impact of our control variables, and relative to the untreated control groups. This specification is therefore based on a difference-in-differences estimator, with the key identifying assumption being that other than the NIH agreements we focus on, there are no time-varying factors other than age effects, which would have a differential effect on our treatment group relative to our control group.<sup>38</sup>

We then turn to evaluating the impact of the increase in openness on the composition of follow-on citations. Within each calendar year, for each mouse-article, we tabulate citations by key characteristics into two mutually exclusive types, and estimate the impact of the NIH agreement on each citation-year margin. For example, we predict that openness should increase the number of distinct researchers utilizing a given research mouse. To test this hypothesis, we estimate the differential impact of a shift in openness on the number of authors publishing follow-on research who have previously cited a particular mouse-article (*Old Authors*<sub>jt</sub>) relative to the number of researchers who have not previously cited that mouse-article (*New Authors*<sub>jt</sub>).

<sup>35</sup> Consistent with our description of life science research in Section II, the window period for Cre-lox mice covers 1998 and 1999, and the window period for Onco mice covers 1999 and 2000.

<sup>36</sup> In robustness tests, we have also estimated our main specifications using both random-effects and population-average negative binomial models. Our results across these alternative specifications remain consistent with the central findings we report in Section V and Tables 4, 5, and 6. In addition, we replicate Table 7 using a random-effects estimator, and report findings consistent with our fixed-effects estimates in Table A1 of the online Appendix.

<sup>37</sup> In addition to the more general negative binomial specification described here, we perform robustness tests by replicating our core analysis using a fixed-effects maximum-likelihood Poisson estimator. The results are consistent with our main findings in terms of both statistical and economic magnitude, and are reported in Table A2 of the online Appendix.

<sup>38</sup> We offer support for the validity of this assumption through robustness tests in Tables 7 and 8.

Specifically, we jointly estimate the following two equations:<sup>39</sup>

(2) *New Authors*<sub>jt</sub>

$$= f(\varepsilon_{jt,NEW}; \gamma_j + \beta_t + \delta_{t-pubyear}^{NEW} + \alpha^{NEW}t + \psi_0^{NEW}NIH\_Window_{jt} + \psi_1^{NEW}Post\_NIH_{jt})$$

*Old Authors*<sub>jt</sub>

$$= f(\varepsilon_{jt,OLD}; \gamma_j + \beta_t + \delta_{t-pubyear}^{OLD} + \psi_0^{OLD}NIH\_Window_{jt} + \psi_1^{OLD}Post\_NIH_{jt}),$$

where  $\gamma_j$  is a mouse-article fixed effect,  $\alpha^{NEW}$  parameterizes a linear calendar-time-trend difference between the two types of citations,  $\beta_t$  is a calendar-year fixed effect, and  $\delta^{NEW}$  and  $\delta^{OLD}$  are mouse-article age fixed effects as in the previous specification.<sup>40</sup> To evaluate whether the impact of the openness shock on follow-on citations is concentrated in citations by authors who had not previously cited a particular mouse-article, we test whether  $\Psi_1^{NEW} > \Psi_1^{OLD}$ . This specification includes several parametric restrictions, including setting the mouse-article fixed effects  $\gamma_j$  and calendar-time fixed effects  $\beta_t$  to be equal across the two equations, and imposing a linear functional form (parameterized by  $\alpha^{NEW}$ ) on the difference in the effect of calendar time across the two equations. We do allow for the mouse-article age fixed effects to vary freely across the two equations, as the evolution of citations in the time elapsed since publication may differ significantly for the two citation margins (almost by construction, most citations in the first few years after publication will be associated with *new* authors).

We use a similar approach to evaluate whether a boost in citations is associated with (a) new versus old institutions, (b) new versus old key words, and (c) new versus old journals. Finally, we explore the research response to the openness shocks by comparing citations to a given mouse-article in applied versus basic journals.

Our empirical framework allows us to examine whether citations to mouse-articles in the treatment and control groups have comparable *ex ante* growth rates prior to the shifts in openness. Specifically, we test this hypothesis in Table 7 by allowing for a linear calendar-time trend specific to the treatment group for each citation margin, and find no differences between our control and treatment groups in any specification. By taking advantage of variation in publication year across the mouse-articles in our sample, we are able to disentangle the treatment effect of the NIH agreements from age- or calendar-time-based differences in the citation trends of articles in the treatment group. At the same time, we conjecture that the treatment effect should actually increase with the time elapsed from the openness shock, due to the higher likelihood of new research lines being created from the original mouse-articles.

<sup>39</sup>We implement this joint estimation of two related equations because of the added flexibility in allowing some aspects of the control structure to vary across the two margins (e.g., age fixed effects) while imposing a common control structure for broad-based effects, such as a given mouse-article's underlying quality, as measured by its specific fixed effect. The two-equation approach allows our regressions to usefully reflect the details of the empirical setting in a fully transparent manner.

<sup>40</sup>Note that while the number of fixed effects for mouse-articles and calendar years remain unchanged at 2,171 and 14, respectively, these specifications double the number of age fixed effects to 44, covering ages from 1 to 22 years for both the "new" and "old" margins.

We therefore include a specification that separately estimates the short-term and long-term impacts of the NIH agreements. Lastly, we can also test for any potential increase in citations to the treatment group in the periods immediately preceding the NIH agreements, as a way to verify whether the timing of the openness shock was indeed unanticipated by follow-on researchers. Specifically, we explore this possibility by testing for a pre-NIH treatment period in the years immediately prior to the signing of the NIH agreements.

#### IV. Data and Variables

##### A. Data and Sampling

The data for this study are drawn from the entire population of research mice catalogued by the Mouse Genome Informatics (MGI) database. MGI consists of over 13,000 unique mice, each of which can be linked to a publication in the scientific literature describing its initial disclosure, thereby establishing a population of mouse-articles. Within this large population, we focus only on mouse-articles published between 1987 and 1998 (the date of the first NIH agreement). As outlined in Section II, we sample all mouse-articles for the four major genetic engineering technologies defined by MGI: Cre-lox (28), Onco (102), Knock-out (1895), and Spontaneous (146). Our sample thus includes 2,171 novel mice, each linked to a unique mouse-article.

We use PubMed and Thomson ISI Web of Science to collect detailed bibliometric information on all subsequent forward citations in academic journals through 2006. Each of these 432,083 citations includes information on last author, reprint author, institutional addresses, key words, and journal characteristics (including journal name, journal impact factor, and a score for basic-ness). Citations are then aggregated into 22,265 citation-year observations by combining all the citations received by a given mouse-article in any particular year; this citation-year structure serves as the basis for our analysis, producing an unbalanced panel where the average mouse-article is tracked for just over 10 citation-years.<sup>41</sup>

To capture the *composition* of follow-on research, we code citation characteristics into a set of mutually exclusive categorical variables. To illustrate the construction of these variables, take the case of new key words. For each citation, ISI Web of Science provides a series of key words (referred to as Key Words Plus). We first take the list of all key words in the set of citations a particular mouse-article receives in a given year, and remove duplicates to obtain a list of unique key words associated with that citation-year observation. We then categorize a given key word to be new if it has never been used in citations to that particular mouse-article in any prior year, and code as old all key words that have appeared in citations in prior years. This

<sup>41</sup> Note that our “youngest” mouse-articles are published in 1998; for these mouse-articles, we track citation-years from 1999 through 2006 for a total of eight years of observation. At the other extreme, approximately 10 percent of our mouse-articles were published in 1992 or earlier; we track these for the entire length of our 1993–2006 citation sample period, resulting in 14 years of observation.



construction allows us to capture changes in the research landscape over time. We generate four new/old categorical variables:

- New/Old Last Author: defined as new if the last author has never appeared as a last author before in a citation to the mouse-article in prior years; old otherwise.<sup>42</sup>
- New/Old Institution: defined as new if an address in the institution list has never appeared in an address list of citations to the mouse-article in prior years; old otherwise.
- New/Old Key Words: defined as new if a key word has never before appeared in the key word list of citations to the mouse-article; old otherwise.
- New/Old Journal: defined as new if the journal of the citation has never appeared before in the citations to the mouse-article; old otherwise.

We also categorize citations according to whether they are published in basic or applied journals.<sup>43</sup> This allows us to evaluate whether the two openness shifts in our study lead to follow-on research focused primarily on applied experiments moving toward commercialization, or on basic experiments aimed at expanding the base of scientific knowledge.

The categorical measures described above reflect various ways in which openness can have an impact on subsequent innovations. Using the two-equation framework described in Section III, they allow us to test the hypothesis that lower access costs lead to more diverse lines of research, pursued by a more diverse range of scientists. We also investigate whether openness is associated with more basic or applied follow-on research.<sup>44</sup>

## B. Variables and Summary Statistics

Table 1 provides variable names and definitions and Table 2 reports summary statistics. The dependent variable in our initial set of regressions is  $Annual\ Citations_{jt}$ , which measures the total number of citations received by mouse-article  $j$  in year  $t$ . The average of  $Annual\ Citations_{jt}$  is 19.41 (with a minimum of 0 and maximum of 336), highlighting the overall importance of mouse genetics research in this period. We observe citation-years from 1993 through 2006; because our sample

<sup>42</sup>In our analysis, we focus exclusively on *last* authors. The conventions of research in the life sciences are such that the last author is both the “lab owner” and also the principal investigator, or PI (van Dijk, Manor, and Carey 2014). This is the person who typically applies for major grants, and is the driver of the lab’s research agenda, while also serving as the primary academic advisor to graduate students and post-doctoral researchers in the lab. In addition, PIs tend to be more strongly associated with a specific field of research, and have longer research careers than other authors.

<sup>43</sup>Our Basic/Applied Journal definition is based on work by Lim (2004), who created the measure by building on a classification scheme developed by CHI Research, Inc. According to Lim, CHI awards each journal a score from zero to four. For the biomedical sciences, levels one through four correspond to clinical observation, clinical mix, clinical investigation, and basic science. It is worth noting that according to this measure, multidisciplinary journals are classified as basic.

<sup>44</sup>It is worth noting that we do not examine the impact of openness on the academic/industry citation margin. The NIH agreements were directed specifically to public sector researchers and 97.5 percent of all citations have at least one of their authors affiliated with a public institution.

TABLE 1—VARIABLES AND DEFINITIONS

Variable	Definition	Source
<i>Mouse-article characteristics</i>		
Publication year	Year in which mouse-article $j$ is published	PubMed
Number of authors	Count of the number of authors of mouse-article $j$	PubMed
Total citations	Number of citations to mouse-article $j$ from its publication date through 2006	SCI
<i>Citation-year characteristics</i>		
Annual citations	Count of all citations to mouse-article $j$ in year $t$	SCI
High quality annual citations	Count of citations to mouse-article $j$ in year $t$ where the journal of the citation is a top-50 journal based on impact-factor rankings.	ISI
Citation year	Year in which citations are received	SCI
<i>Citation-year margin characteristics</i>		
Basic citations	Count of citations to mouse-article $j$ in year $t$ where the journal of the citation is a basic-research journal	CHIBasic
Applied citations	Count of citations to mouse-article $j$ in year $t$ where the journal of the citation is an applied-research journal	CHIBasic
New X	Count of unique values of characteristic X of citations to mouse-article $j$ in year $t$ which are “new” and have not appeared in the citations to mouse-article $j$ in prior years.	
Old X	Count of unique values of characteristic X of citations to mouse-article $j$ in year $t$ which are NOT “new” and have appeared in the citations to mouse-article $j$ in prior years.	
X = Last author	Last author listed on the citation	PubMed
X = Institution	Institutional addresses listed on the citation	PubMed
X = Key word	Key words listed on the citation	ISI
X = Journal	Journal listed on the citation	PubMed
<i>Openness shock characteristics</i>		
Post-NIH	Dummy variable equal to 1 if article $j$ is associated with an openness agreement (Cre-lox, Onco) which is in effect in year $t$ .	MGI
NIH-window	Dummy variable equal to 1 if article $j$ is associated with an openness agreement (Cre-lox, Onco) which is in its initial period in year $t$ .	MGI
<i>Mouse technology characteristics</i>		
Earliest year	The publication year of the earliest mouse-article in the MGI database associated GM technology $k$ .	MGI
Total mice created (1983 onward)	The total number of mice listed in the MGI database, with mouse-articles published from 1983 onward, associated with GM technology $k$ .	MGI
<i>Mouse creation characteristics</i>		
Annual mouse creation	The number of mouse-articles published in year $t$ which introduce mice created using GM technology $k$ .	MGI
New creation journals	Count of unique journals publishing mouse-articles of GM technology $k$ in year $t$ , which are “new” and have not published mouse-articles for GM technology $k$ in prior years.	PubMed
Old creation journals	Count of unique journals publishing mouse-articles of GM technology $k$ in year $t$ , which are NOT “new” and have published mouse-articles for GM technology $k$ in prior years.	PubMed

TABLE 2—SUMMARY STATISTICS

Variable	Observations	Mean	SD	Min.	Max.
<i>Mouse-article characteristics (N = 2,171 mouse-articles)</i>					
Publication year	2,171	1995.58	2.34	1987	1998
Number of authors	2,171	7.11	3.48	1	34
Total forward citations	2,171	210.8	230.4	1	2543
<i>Citation-year characteristics (N = 22,265 citation-year observations)</i>					
Citation year	22,265	2001.19	3.26	1993	2006
Annual citations	22,265	19.41	21.67	0	336
High quality annual citations	22,265	4.31	5.87	0	71
<i>Citation-year margin characteristics (N = 22,265 citation-year observations)</i>					
Basic citations	22,265	9.18	11.24	0	151
Applied citations	22,265	7.45	10.78	0	157
New last-authors	22,265	11.71	13.48	0	243
Old last-authors	22,265	3.94	5.35	0	58
New institutions	22,265	17.54	17.83	0	287
Old institutions	22,265	10.21	13.66	0	135
New key words	22,265	74.88	67.28	0	794
Old key words	22,265	55.37	61.12	0	620
New journals	22,265	7.91	7.84	0	94
Old journals	22,265	6.17	7.61	0	81
<i>Openness agreement characteristics (N = 22,265 citation-year observations)</i>					
Post-NIH	22,265	0.036	0.187	0	1
NIH-window	22,265	0.011	0.105	0	1
Post-Cre-lox	22,265	0.009	0.093	0	1
Cre-lox-window	22,265	0.002	0.045	0	1
Post-Onco	22,265	0.027	0.164	0	1
Onco-window	22,265	0.009	0.095	0	1
<i>Mouse creation characteristics (N = 78 technology-year observations)</i>					
Annual mouse creation	78	108.19	171.59	0	875
New creation journals	78	6.99	5.81	0	24
Old creation journals	78	16.13	18.13	0	75

is an unbalanced panel and includes mouse-articles published as late as 1998, the average of *Citation Year<sub>it</sub>* is 2001. We also create an alternative dependent variable, *High Quality Citations<sub>it</sub>*, with mean equal to 4.3, which captures citations published in a top-50 scientific journal. We then construct a series of dependent variables based on the key categorical margins of interest:<sup>45</sup>

- *New Last Authors<sub>it</sub>* and *Old Last Authors<sub>it</sub>*, with mean values equal to 11.7 and 3.9, respectively.

<sup>45</sup>Note that the sum of the two means for a given annual citation margin need not add up to the mean annual citation count. First, due to data-matching issues we cannot always identify 100 percent of citations as belonging to one or the other margin; this leads to a sum lower than the mean annual citation count. Second, new/old margins focus on the count of unique instances of the characteristic in question; for example, if there are multiple citations from a particular journal to a mouse-article in a given year, we only count the first such citation. This also leads to a sum lower than the mean annual citation count. Finally, for the counts of institutions and key words, each citation contains multiple entries for these fields, leading to counts higher than the mean annual citation count. For example, in the case of key words, the sum of the margin means is just over 120, indicating that the average citation is associated with between six and seven key words.

- *New Institutions<sub>jt</sub>* and *Old Institutions<sub>jt</sub>*, with mean values equal to 17.5 and 10.2, respectively.
- *New Keywords<sub>jt</sub>* and *Old Keywords<sub>jt</sub>*, with mean values equal to 74.9 and 55.4, respectively.
- *New Journals<sub>jt</sub>* and *Old Journals<sub>jt</sub>*, with mean values equal to 7.9 and 6.2, respectively.
- *Basic Citations<sub>jt</sub>* and *Applied Citations<sub>jt</sub>*, with mean values equal to 9.2 and 7.4, respectively.

Next, we define two measures that will be used to estimate the impact of the NIH agreements. We divide the period after the NIH agreement signing into two sub-periods because the sudden increase in openness would likely take time to influence follow-on research. Specifically, we define a window period and a treatment period to allow a reasonable lag (two years) for the NIH agreement to impact observed citation patterns.<sup>46</sup> *NIH\_Window<sub>jt</sub>* (mean equal to 0.011) is a dummy variable equal to one for articles impacted by an NIH agreement during the year when that agreement was signed and during the following year (1998/1999 for Cre-lox mouse-articles, 1999/2000 for Onco mouse-articles). Our key treatment variable, *Post\_NIH<sub>jt</sub>* (mean equal to 0.036), is a dummy variable equal to one for all articles impacted by the NIH agreements in years after the window period ended. Using the same approach, we also define separate treatment variables for the two NIH agreements: *Cre-lox\_Window<sub>jt</sub>*, *Post\_Cre-lox<sub>jt</sub>*, *Onco\_Window<sub>jt</sub>*, and *Post\_Onco<sub>jt</sub>*. Finally, to examine the short-term versus long-term impact of the NIH agreements, we also define a treatment variable, *Post\_NIH, Short-Term<sub>jt</sub>*, equal to one for the first three years after the window period for affected mouse-articles, and a separate measure, *Post\_NIH, Long-Term<sub>jt</sub>*, equal to one for the fourth year and onward after the end of the window period.

We highlight our disaggregated summary statistics by the type of mouse technology in Table 3. The most salient point to note is that compared to the overall sample mean of 18, the *Annual Citations<sub>jt</sub>* for Cre-lox and Onco mice are 15 and 12, respectively. By contrast, the Spontaneous mice in our control group have a lower mean of 4, and the Knock-out mice have mean *Annual Citations<sub>jt</sub>* of over 21. This is consistent with the assumption of comparability between the treatment and control groups. Moreover, the mean publication year and mean number of authors across the four mouse technologies are similar.

## V. Results

We now turn to our estimates of the causal impact of the NIH agreements on follow-on scientific research. We begin with the dimension on which much of the literature has focused: the impact of the openness shock on the overall flow of citations

<sup>46</sup> Both of our NIH agreements specify a start date of July 1, in 1998 for Cre-lox and in 1999 for Onco. In practice, implementation occurred closer to the August–September timeframe for both agreements; thus, our window periods reflect an approximately 18-month transition period. This choice is based on a combination of anecdotal evidence of the usual length of time to publication for life science research and the desire to avoid the challenges of using a mid-year break point, in light of the different publication schedules of the various journals in our sample.

TABLE 3—SUMMARY STATISTICS BY MOUSE TECHNOLOGY

Variable	Mouse technology			
	Cre-lox	Onco	Knock-out	Spontaneous
<i>Mouse-article characteristics (N = 2,171 mouse-articles)</i>				
Number of mouse articles	28	102	1,895	146
Publication year	1996.7	1993.4	1995.8	1993.5
Number of authors	5.3	6.0	7.4	5.1
Total citations	144.4	167.8	226.3	52.7
<i>Citation-year characteristics (N = 22,265 citation-year observations)</i>				
Annual citations	14.72	12.30	21.29	3.96
<i>Mouse technology characteristics (N = 4 technologies)</i>				
Earliest year	1992	1983	1989	1915
Total mice created (1983 onward)	1,159	401	5,980	911
<i>Mouse creation characteristics (N = 78 technology-year observations)</i>				
Annual mouse creation	28.43	50.22	351.47	37.96
New creation journals	5.00	5.61	13.41	4.92
Old creation journals	7.29	14.78	37.77	7.25

(Table 4). We then move to the core of our analysis, focusing on the impact of the NIH agreements on the composition of citations (Tables 5 to 9) and on the subsequent production of new research mice (Table 10). In addition to the regression tables, we offer a visual representation of our findings in Figures 1–4. By adopting a difference-in-differences approach, we are able to infer the relationship between openness and academic freedom. In all regression tables, we report coefficient estimates and their corresponding incidence-rate ratios (IRRs). We discuss our results in terms of IRRs because they are easily interpreted as percentage changes relative to a baseline (i.e., the null hypothesis of no effect yields a coefficient of 1.0). Also, all of our specifications report block-bootstrapped standard errors clustered by mouse-article (MacKinnon 2002).

#### A. Impact of Openness on the Level of Follow-On Research

We begin the presentation of our results with Figure 1, which tracks the citation rates to the mouse-articles in our sample, aggregated by technology. Specifically, Figure 1 looks at citation rates averaged over all mouse-articles in each technology published no later than 1996. It then tracks annual citation rates for this fixed set of mouse-articles in an event-study format, with each technology's citation rate tracked relative to the year of its openness shock, and normalized to 100 percent at year zero. Note that we set the shock for our control groups to 1999, to correspond to the larger of our two treatment groups, namely, our set of Onco mice. All four technologies experience a decline in citation rates during this period, primarily due to the rising age of the fixed sample of mice in each technology. However, the Cre-lox and Onco openness shocks seem to mitigate this decline, particularly in the case of Cre-lox mice. The patterns in Figure 1 suggest that greater openness is associated with greater quantities of innovation when taking averages over our technology



TABLE 4—IMPACT OF OPENNESS ON FOLLOW-ON RESEARCH FLOWS

	Dep. var. = Annual citations [Incidence rate ratios reported in square brackets] Estimated coefficients in second line (Block bootstrapped SEs reported in parentheses)				
	OLS	Negative binomial			
	(4-1) Baseline model, DV = log Annual citations	(4-2) Baseline model	(4-3) Baseline model with treatment effect dynamics	(4-4) Treatment effects by Cre-lox and Onco	(4-5) Baseline model, citations from high quality journals only <sup>d</sup>
Post-NIH	[1.229]*** 0.206 (0.052)	[1.302]*** 0.264 (0.062)			[1.409]*** 0.343 (0.080)
Post-NIH, Short-term <sup>b</sup>			[1.220]*** 0.199 (0.064)		
Post-NIH, Long-term <sup>c</sup>			[1.429]*** 0.357 (0.074)		
Post-Cre-lox				[1.467]*** 0.383 (0.115)	
Post-Onco				[1.267]*** 0.236 (0.060)	
<i>Control variables</i>					
NIH-window <sup>a</sup>	[1.132]** 0.124 (0.049)	[1.146]** 0.136 (0.065)	[1.149]** 0.139 (0.058)	—	[0.954] −0.047 (0.092)
Cre-lox-window <sup>a</sup>	—	—	—	[1.069] 0.067 (0.089)	—
Onco-window <sup>a</sup>	—	—	—	[1.188]*** 0.172 (0.043)	—
Age FEs	Yes	Yes	Yes	Yes	Yes
Year FEs	Yes	Yes	Yes	Yes	Yes
Article FEs	Yes	Yes	Yes	Yes	Yes
log-likelihood	—	−55,919.8	−55,906.1	−55,912.4	−34,112.8
Observations	22,265	22,265	22,265	22,265	21,574

Notes: Tests of differences between coefficients:  
(4-2):  $\beta(\text{post-NIH}) - \beta(\text{NIH-window})$ :  
Estimate = 0.129; SE = 0.033; Pr > |z| < 0.001  
(4-3):  $\beta(\text{post-NIH, long-term}) - \beta(\text{post-NIH, short-term})$ :  
Estimate = 0.158; SE = 0.040; Pr > |z| < 0.001  
<sup>a</sup>Window is defined as the year of the NIH agreement and the following year (Cre-lox: 1998/1999; Onco: 1999/2000)  
<sup>b</sup>Short-term is defined as the three years following the window after the NIH agreement (Cre-lox: 2000–2002; Onco: 2001–2003).  
<sup>c</sup>Long-term is defined as the years following the window and the short-term period after the NIH agreement (Cre-lox: 2003 onward; Onco: 2004 onward).  
<sup>d</sup>For this regression we use a modified dependent variable that captures only those annual citations that appear in a subset of high quality journals, as ranked by ISI impact factor.  
\*\*\*Significant at the 1 percent level. \*\*Significant at the 5 percent level. \*Significant at the 10 percent level.

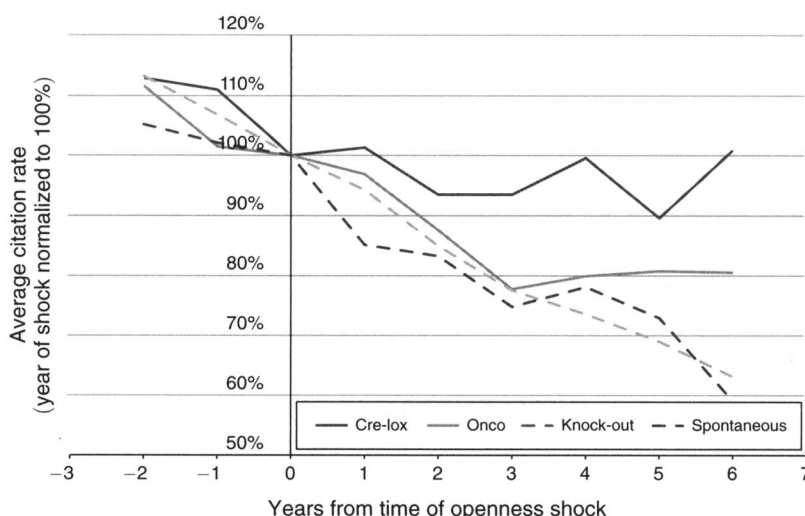


FIGURE 1. AVERAGE CITATION RATES BY MOUSE TECHNOLOGY, NORMALIZED RELATIVE TO YEAR OF OPENNESS SHOCK

categories. To evaluate the magnitude and statistical significance of this effect, we take advantage of the regression framework described in Section III to analyze the impact of openness on individual mouse-articles.

Our regression results begin in Table 4 with a set of conditional fixed effect specifications focusing on the impact of our openness shocks on the quantity of citations to the mouse-articles in our sample. The first column, (4-1), reports a conditional fixed effect OLS specification using the natural log of *Annual Citations<sub>it</sub>* as the dependent variable. The remaining columns, (4-2) to (4-5), report results from conditional fixed effect negative binomial specifications, using the raw count of *Annual Citations<sub>it</sub>* as the dependent variable.<sup>47</sup> All specifications also include the full set of article, age, and calendar-year fixed effects. In (4-1) and (4-2), we include both the *NIH\_Window<sub>it</sub>* and the *Post\_NIH<sub>it</sub>* regressors. The OLS specification in the first column serves as a point of comparison, and shows that the OLS and negative binomial results are similar in terms of both economic and statistical significance. Focusing on regression (4-2), the results are striking: after accounting for the window period, mouse articles impacted by an NIH agreement experience a 30 percent increase in their annual citation rate. As illustrated in (4-3), the impact of the NIH agreements is increasing over time: while the increase in citations in the 3 years after the window period is equal to 22 percent, the coefficient on *Post\_NIH, Long-Term<sub>it</sub>* is estimated at 43 percent, suggesting that the permanent effect is nearly twice as large. Not simply a reflection of publication lags, the results in (4-3) suggest the presence of a positive and permanent increase in the use of genetically engineered

<sup>47</sup> While a log-linear OLS model like the one used in specification (4-1) can be a useful guide in preliminary analyses of count data, it suffers from problems with zero-count outcomes, over-dispersion, and retransformation bias; consequently, we turn to the negative binomial specification (NB2 MLE), which adequately addresses these issues and offers consistent coefficient estimates in our empirical setting (Cameron and Trivedi 2013).

mice, which have been shifted to a higher level of openness. In (4-4), we estimate separate coefficients for the Cre-lox and Onco NIH agreements: both are statistically significant although the magnitude of the boost to citations associated with the Cre-lox agreement is larger (47 percent for citations to Cre-lox mouse-articles compared to 27 percent for citations to Onco mouse-articles). Finally, in (4-5), we undertake a robustness check by focusing on citations in high impact journals. We find a 41 percent boost in such citations, suggesting that the impact of the openness shift is concentrated in research that is published in the most prestigious and demanding journals.

The results in Table 4 provide strong support for the hypothesis that positive shocks to openness foster follow-on research. These findings reinforce previous studies of the impact of openness and accessibility, such as Furman and Stern (2011) and Murray and Stern (2007). Furthermore, our results are consistent with a multistaged view of innovation whereby an increase in openness does not simply lead to a temporary increase in follow-on research, but also has an increasing impact over time. Finally, though we hold off on this discussion until Table 7, we can show that the estimated impact of the NIH agreements is not simply due to a different time trend for the treatment and control groups. Taken together, these results highlight the sensitivity of follow-on researchers to the degree of openness of critical research inputs.

### B. Impact of Openness on Follow-On Exploration

Tables 5 and 6, along with Figures 2 and 3, present our main evidence that greater openness results in greater academic exploration, spawning a more diverse array of research lines and encouraging the participation of new researchers. In Table 5, our key comparison is between researchers listed as the last author (senior scientist) who have (or have not) been previously listed on a citation to the mouse-article of interest, as captured in our measures *New Authors<sub>it</sub>* and *Old Authors<sub>it</sub>*. In specifications (5-1a) and (5-1b) we estimate whether the marginal impact of *Post\_NIH<sub>it</sub>* is different for new versus old last authors. While there is only an insignificant 13 percent increase in citations by old authors, the increase by new authors is estimated to be more than 38 percent (and highly significant). Moreover, these two coefficients are significantly different from each other.<sup>48</sup> We then estimate a separate coefficient for the short-term versus long-term impact of the NIH agreements on new versus old authors (5-2a and 5-2b). The increase in citations by new authors is greater than the increase in citations for old authors in both the short- and long-term (with the difference between the two coefficients being significant at the 1 percent level). Strikingly, the estimate of the long-term increase in new author citations is above 50 percent. Next, when we separately estimate the impact of the Cre-lox and Onco agreements on new versus old authors, (5-3a and 5-3b) we find that the estimated boost for new authors is statistically significant for each agreement compared to

<sup>48</sup> Importantly, this difference in coefficients between new and old authors remains significant across our robustness tests, including our random-effects and ML Poisson specifications. Further details are available in the online Appendix.

TABLE 5—IMPACT OF OPENNESS ON CITATIONS BY NEW VERSUS OLD “LAST AUTHORS”  
AND NEW VERSUS OLD INSTITUTIONS

Stacked negative binomial [Incidence rate ratios reported in square brackets] Estimated coefficients in second line (Block bootstrapped SEs reported in parentheses)								
	(5-1a) DV= New authors	(5-1b) DV= Old authors	(5-2a) DV= New authors	(5-2b) DV= Old authors	(5-3a) DV= New authors	(5-3b) DV= Old authors	(5-4a) DV= New institutions	(5-4b) DV= Old institutions
Post-NIH	[1.379]*** 0.321 (0.065)	[1.135] 0.127 (0.088)					[1.269]*** 0.238 (0.052)	[1.127]* 0.120 (0.066)
Post-NIH, Short-term			[1.276]*** 0.244 (0.062)	[1.064] 0.062 (0.078)				
Post-NIH, Long-term			[1.537]*** 0.430 (0.071)	[1.224]*** 0.202 (0.073)				
Post-Cre-lox					[1.649]** 0.500 (0.203)	[1.189] 0.173 (0.211)		
Post-Onco					[1.305]*** 0.266 (0.076)	[1.160] 0.148 (0.108)		
<i>Control variables</i>								
Window FEs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Age FEs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Year FEs		Yes <sup>a</sup>		Yes <sup>a</sup>		Yes <sup>a</sup>		Yes <sup>a</sup>
Article FEs		Yes		Yes		Yes		Yes
log-likelihood		-86,889.3		-86,874.1		-86,877.2		-114,094.0
Observations		42,802		42,802		42,802		42,830

Notes: Tests of differences between coefficients:  
(5-1):  $\beta(\text{post-NIH effect on new authors}) - \beta(\text{post-NIH effect on old authors})$ :  
Estimate = 0.194; SE = 0.042; Pr > |z| < 0.001  
(5-2):  $\beta(\text{post-NIH, short-term effect on new authors}) - \beta(\text{post-NIH, short-term effect on old authors})$ :  
Estimate = 0.181; SE = 0.047; Pr > |z| < 0.001  
 $\beta(\text{post-NIH, long-term effect on new authors}) - \beta(\text{post-NIH, long-term effect on old authors})$ :  
Estimate = 0.227; SE = 0.042; Pr > |z| < 0.001  
(5-3):  $\beta(\text{post-Cre-lox effect on new authors}) - \beta(\text{post-Cre-lox effect on old authors})$ :  
Estimate = 0.327; SE = 0.064; Pr > |z| < 0.001  
 $\beta(\text{post-Onco effect on new authors}) - \beta(\text{post-Onco effect on old authors})$ :  
Estimate = 0.118; SE = 0.054; Pr > |z| = 0.029  
(5-4):  $\beta(\text{post-NIH effect on new institutions}) - \beta(\text{post-NIH effect on old institutions})$ :  
Estimate = 0.118; SE = 0.035; Pr > |z| = 0.001  
<sup>a</sup>Calendar-year fixed effects include a set of indicator variables common to both margins in a given regression, and a linear difference variable that allows for a constant difference in growth rates between the two margins.  
\*\*\*Significant at the 1 percent level.  
\*\*Significant at the 5 percent level.  
\*Significant at the 10 percent level.

a much smaller and statistically insignificant increase in citations by old authors. Moreover, we find that the difference between the new versus old coefficients is significant for each agreement at the 5 percent level.

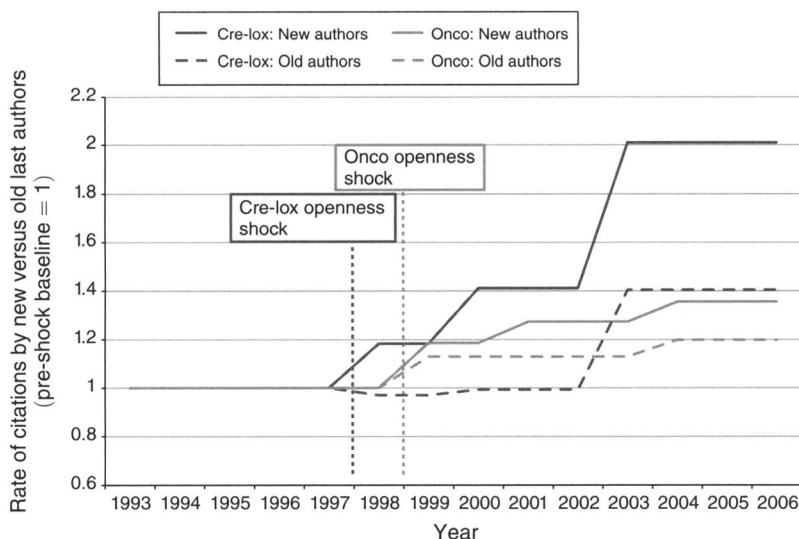


FIGURE 2. IMPACT OF OPENNESS ON RATES OF CITATIONS BY NEW VERSUS OLD “LAST AUTHORS”

Finally, in (5-4a) and (5-4b), we turn to an alternative measure of the diversity of researchers as captured by their institutional affiliation. Similar to the results for new versus old authors, the boost in citations associated with the NIH agreements is concentrated in citations from institutions that had not previously cited that mouse article (27 percent, versus 13 percent for old institutions). Overall, the results in Table 5 provide direct evidence that the shift in openness associated with the NIH agreements expanded the diversity of researchers drawing on a particular line of research.

Figure 2 presents the above effects graphically. Specifically, we plot the evolution of citations by new and old “last authors” for Cre-lox and Onco mouse-articles, relative to their pre-shock baselines. As in the regressions, we find that citations by new authors increase much more strongly than those by old authors, and that this gap is greater in the long run than in the short run. The result holds for both openness shocks, though the impact for Cre-lox mouse-articles is stronger, as they were more difficult to obtain prior to their respective NIH agreement.

In Table 6, we turn to the related prediction that openness enhances the diversity of research lines (particularly in an academic research environment where scientists are free to choose their own research direction). We capture the degree of diversity by using the key words that categorize each citation (recall that key words are chosen by the archiving service rather than the researchers). In (6-1a) and (6-1b), we compare the impact of the NIH agreements on *New Key Words<sub>jt</sub>* and *Old Key Words<sub>jt</sub>*, respectively. While there is a small and statistically insignificant decline in the number of old key words, there is a significant 26 percent increase in the number of citations with new key words. Moreover, these coefficients are statistically significantly different from each other. This is not just a short-term effect: the analysis of impact dynamics in (6-2a) and (6-2b) indicates that there is an even larger 41 percent increase in the number of new key works in the long term, relative



TABLE 6—IMPACT OF OPENNESS ON CITATIONS WITH NEW VERSUS OLD KEY WORDS

	Stacked negative binomial [Incidence rate ratios reported in square brackets] Estimated coefficients in second line (Block bootstrapped SEs reported in parentheses)							
	(6-1a) DV=New key words	(6-1b) DV=Old key words	(6-2a) DV= New key words	(6-2b) DV= Old key words	(6-3a) DV=New key words	(6-3b) DV=Old key words	(6-4a) DV=New journals	(6-4b) DV=Old journals
Post-NIH	[1.260]*** 0.231 (0.070)	[0.925] −0.078 (0.075)					[1.381]*** 0.323 (0.076)	[1.201]** 0.183 (0.084)
Post-NIH, Short-term			[1.178]*** 0.164 (0.061)	[0.882]* −0.126 (0.066)				
Post-NIH, Long-term			[1.405]*** 0.340 (0.070)	[0.989] −0.011 (0.071)				
Post-Cre-lox					[1.399]* 0.336 (0.202)	[0.879] −0.129 (0.194)		
Post-Onco					[1.208]*** 0.189 (0.062)	[0.955] −0.046 (0.076)		
<i>Control variables</i>								
Window FEs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Age FEs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Year FEs	Yes <sup>a</sup>		Yes <sup>a</sup>		Yes <sup>a</sup>		Yes <sup>a</sup>	
Article FEs	Yes		Yes		Yes		Yes	
log-likelihood	−179,179.1		−179,162.5		−179,146.0		−88,007.3	
Observations	44,488		44,488		44,488		42,830	

Notes: Tests of differences between coefficients:  
(6-1):  $\beta(\text{post-NIH effect on new key words}) - \beta(\text{post-NIH effect on old key words})$ :  
Estimate = 0.310; SE = 0.038; Pr > |z| < 0.001  
(6-2):  $\beta(\text{post-NIH, short-term effect on new key words}) - \beta(\text{post-NIH, short-term effect on old key words})$ :  
Estimate = 0.290; SE = 0.038; Pr > |z| < 0.001  
 $\beta(\text{post-NIH, long-term effect on new key words}) - \beta(\text{post-NIH, long-term effect on old key words})$ :  
Estimate = 0.351; SE = 0.035; Pr > |z| < 0.001  
(6-3):  $\beta(\text{post-Cre-lox effect on new key words}) - \beta(\text{post-Cre-lox effect on old key words})$ :  
Estimate = 0.466; SE = 0.059; Pr > |z| < 0.001  
 $\beta(\text{post-Onco effect on new key words}) - \beta(\text{post-Onco effect on old key words})$ :  
Estimate = 0.235; SE = 0.039; Pr > |z| < 0.001  
(6-4):  $\beta(\text{post-NIH effect on new journals}) - \beta(\text{post-NIH effect on old journals})$ :  
Estimate = 0.140; SE = 0.043; Pr > |z| = 0.001

<sup>a</sup>Calendar-year fixed effects include a set of indicator variables common to both margins in a given regression, and a linear difference variable that allows for a constant difference in growth rates between the two margins.  
\*\*\*Significant at the 1 percent level.  
\*\*Significant at the 5 percent level.  
\*Significant at the 10 percent level.

to an insignificant decrease to old key words in the long term; moreover, the difference between this 41 percent increase and the 18 percent increase to new key words in the short term is statistically significant at the 1 percent level.<sup>49</sup> When we decompose the openness changes into the Cre-lox and Onco agreements (in specifications 6-3a and 6-3b), we continue to find a quantitatively and statistically significant difference between the new and old key words coefficients. Both the Cre-lox and Onco agreements are associated with a significant boost in new key words (40 percent and 21 percent, respectively) and a small and insignificant decline in old key words.

Finally, as in our analysis of the diversity of citing researchers in Table 5, we use an alternative measure to test the robustness of our findings on research diversity. In (6-4a) and (6-4b), we compare the citation margins between *New Journals<sub>it</sub>* and *Old Journals<sub>it</sub>*, where a “new” journal is one that has never before published an article citing the original mouse-paper article in question. We find that being in the post-NIH period leads to a 38 percent increase (significant at the 1 percent level) in citations from new journals and only a 20 percent increase in citations from old journals (significant at the 5 percent level). As with earlier specifications in Table 6, the impact of openness on the “New” margin is significantly larger than the impact on the “Old” margin, with all differences between coefficients reflecting *p*-values smaller than 0.01.

In Figure 3, we present the key word results in a graphical format. As in Figure 2, we plot citations containing new and old key words for both Cre-lox and Onco mice, relative to their pre-shock baselines. For Cre-lox mice, we see a small short-term drop in all key words, followed by a return to pre-shock levels for old key words and a strong increase in new key words. For Onco mice, we also see a drop in old key words followed by a slow return to pre-shock levels, while new key words experience an immediate and permanent increase. For both technologies, there is a strong shift away from old and toward new key words following the openness shocks.

### C. Robustness Tests for Results on Citations, Authors, and Key Words

In our analysis so far, our difference-in-differences estimators have been based on the implicit assumption that the citation-age profile is similar for the treatment and control groups. In Table 7, we test this assumption directly by re-estimating each of the key equations for overall citations, new versus old authors, and new versus old key words, allowing for a linear time trend specific to the treatment group for each citation margin.<sup>50</sup> Since the treatment effect itself is predicted to increase in the time elapsed since the agreement, we separately allow for a post-NIH-agreement calendar-time trend. The results reinforce our overall findings. We find that the point estimates for the NIH agreements remain positive, although smaller and below

<sup>49</sup>This difference remains significant under robustness test specifications, including random-effects and ML Poisson estimators. Further details are available in the online Appendix.

<sup>50</sup>Our difference-in-differences analysis may be susceptible to first-order linear differences in growth trends between the treatment and control groups (i.e., a growing “gap” between the treatment and control group that begins to arise prior to the treatment). We test for this possibility directly through the inclusion of a separate linear trend that allows for a differential pattern for the treatment and control group. As shown in Table 7, our results are robust. As well, in alternative specifications, we test for nonlinear differences in growth patterns between the treatment and control groups, and continue to find no meaningful difference between them in the pretreatment period.

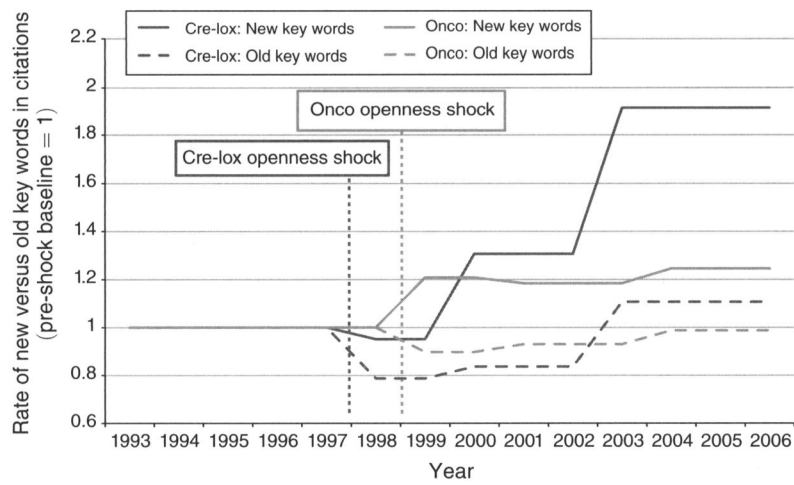


FIGURE 3. IMPACT OF OPENNESS ON RATES OF NEW VERSUS OLD KEY WORDS IN CITATIONS

traditional significance levels, presumably because they now capture the impact of the openness shock only for the first year after the window period. More importantly, there is a significant impact of the treatment over time for overall citations, new authors, and new key words. While we also find increases over time for old authors and old key words, these coefficients are smaller, and when combined with the baseline post-NIH effect, lead to a significant difference between the new and old margins. Finally, and most crucially, across all specifications, the treatment group age trend is both statistically and economically indistinguishable from zero. This indicates that after controlling for article-level fixed effects, there is no difference in preshock citation patterns between our treatment and control groups. In other words, there is no evidence of a significant increase in citations prior to the NIH agreements that might raise concerns about the endogeneity of the timing of the agreement.

In Table 8, we examine the direct impact of the openness shocks on the control groups in our study. Specifically, we independently estimate the deviation from pre-shock trends for both the treatment groups (Onco and Cre-lox) and the control groups (Knock-Out and Spontaneous). This approach allows us to decompose the difference-in-differences effects of the results in Tables 4 to 7, and determine the extent to which our results reflect changes in the use of mice in the treatment groups. Because we are estimating the impact of openness shocks for all mice in our dataset, we cannot include calendar-year fixed effects; instead, we use unconstrained fourth-order polynomials to estimate citation trends over the sample, with independent trends for the “new” and “old” margins in our two-equation specifications. As in previous regressions, we also include full sets of age and mouse-article fixed effects, as well as the traditional openness shock variables: the  $NIH\_Window_{jt}$  and  $Post\_NIH_{jt}$  regressors. The new regressors in this table are similar in construction to those linked with the NIH openness shocks, but are instead applied to the control mice in our dataset. Specifically, we introduce a “Placebo Shock” coinciding with the Onco openness shock of 1999, and affecting only our control groups: Knock-out and Spontaneous mice. For these mice, the regressor  $Placebo\_Window_{jt}$  is equal to

TABLE 7—ROBUSTNESS TESTS FOR A PRE-SHOCK TREATMENT TREND FOR RESULTS ON OVERALL CITATIONS, NEW VERSUS OLD AUTHORS, AND NEW VERSUS OLD KEY WORDS

	[Incidence rate ratios reported in square brackets] Estimated coefficients in second line (Block bootstrapped SEs reported in parentheses)				
	Negative binomial	Stacked negative binomial			
	(7-1) DV= Annual citations with treatment trends	(7-2a) DV= New authors with treatment trends	(7-2b) DV= Old authors with treatment trends	(7-3a) DV= New key words with treatment trends	(7-3b) DV= Old key words with treatment trends
Post-NIH	[1.145]* 0.135 (0.078)	[1.117] 0.111 (0.091)	[1.034] 0.033 (0.078)	[1.127] 0.120 (0.096)	[0.854] −0.157 (0.108)
Treatment group age trend per year	[1.003] 0.003 (0.015)	[1.014] 0.014 (0.018)	[1.000] −0.000 (0.020)	[1.001] 0.001 (0.020)	[0.997] −0.003 (0.024)
Post-NIH change in trend per year	[1.050]*** 0.049 (0.017)	[1.052]** 0.051 (0.025)	[1.046]* 0.045 (0.025)	[1.053]** 0.052 (0.024)	[1.045]* 0.044 (0.026)
<i>Control variables</i>					
NIH-Window	[1.114]** 0.108 (0.047)	[1.079] 0.076 (0.062)	[1.091] 0.087 (0.071)	[1.120]* 0.182 (0.068)	[0.939] −0.063 (0.102)
Age FEs	Yes	Yes	Yes	Yes	Yes
Year FEs	Yes	Yes <sup>a</sup>		Yes <sup>a</sup>	
Article FEs	Yes	Yes		Yes	
log-likelihood	−55,899.5	−86,859.4		−179,152.1	
Observations	22,265	42,802		44,488	

Notes: Tests of differences between coefficients:  
(7-2):  $\beta(\text{post-NIH effect on new authors}) - \beta(\text{post-NIH effect on old authors})$ :  
Estimate = **0.078**; SE = **0.077**; Pr > |z| = **0.312**  
(7-3):  $\beta(\text{post-NIH effect on new key words}) - \beta(\text{post-NIH effect on old key words})$ :  
Estimate = **0.277**; SE = **0.053**; Pr > |z| < **0.001**  
<sup>a</sup> Calendar-year fixed effects include a set of indicator variables common to both margins in a given regression, and a linear difference variable that allows for a constant difference in growth rates between the two margins.  
\*\*\*Significant at the 1 percent level.  
\*\*Significant at the 5 percent level.  
\*Significant at the 10 percent level.

one in 1999 and 2000, and  $Post\_Placebo_{it}$  is equal to one from 2001 onward. For the mice in our treatment groups, these regressors are set to zero throughout the sample period.

We begin the analysis with specification (8-1), which adds the above regressors to the analysis of citation rates in Table 4. In the original analysis, we found that the openness shocks led to a 30 percent increase in citations to treated mouse-articles relative to controls. When we estimate the impact on treatment and control groups separately, we find that the NIH shocks were responsible for approximately three-quarters of the total effect, or an increase of just over 22 percent. By contrast, the impact of the shock on control mice, relative to baseline trends, was a modest reduction of 6 percent. Both effects are statistically significant, and indicate that the

TABLE 8—TESTS FOR IMPACT OF OPENNESS ON CONTROL MICE, FOR RESULTS ON OVERALL CITATIONS, NEW VERSUS OLD AUTHORS, AND NEW VERSUS OLD KEY WORDS

	[Incidence rate ratios reported in square brackets] Estimated coefficients in second line (Block bootstrapped SEs reported in parentheses)				
	Negative binomial	Stacked negative binomial			
	(8-1) DV= Annual citations with placebo effects	(8-2a) DV= New authors with placebo effects	(8-2b) DV= Old authors with placebo effects	(8-3a) DV= New key words with placebo effects	(8-3b) DV= Old key words with placebo effects
Post-NIH (impact on treatment groups)	[1.223]*** 0.202 (0.065)	[1.328]*** 0.284 (0.064)	[0.694]*** −0.364 (0.081)	[1.146]** 0.137 (0.067)	[0.882]* −0.125 (0.074)
Post-placebo (impact on control groups)	[0.936]*** −0.066 (0.020)	[0.956]** −0.044 (0.021)	[0.620]*** −0.478 (0.036)	[0.903]*** −0.102 (0.027)	[0.951]** −0.050 (0.023)
<i>Control variables</i>					
NIH-window	[1.134]** 0.126 (0.055)	[1.180]*** 0.166 (0.054)	[0.808]*** −0.212 (0.064)	[1.086] 0.083 (0.071)	[0.836]*** −0.178 (0.069)
Placebo-window	[0.987] −0.013 (0.014)	[1.002] 0.002 (0.013)	[0.814]*** −0.205 (0.025)	[0.975] −0.025 (0.017)	[0.978] −0.022 (0.015)
Age FEs	Yes	Yes	Yes	Yes	Yes
Year controls	Yes <sup>a</sup>		Yes <sup>a</sup>		Yes <sup>a</sup>
Article FEs	Yes		Yes		Yes
log-likelihood	−55,926.8		−86,541.0		−179,174.6
Observations	22,265		42,802		44,488

Notes: Tests of differences between coefficients:  
(8-1):  $\beta(\text{post-NIH}) - \beta(\text{post-placebo})$ :  
Estimate = 0.269; SE = 0.065; Pr > |z| < 0.001  
(8-2):  $\beta(\text{post-NIH effect on new authors}) - \beta(\text{post-placebo effect on new authors})$ :  
Estimate = 0.328; SE = 0.063; Pr > |z| < 0.001  
(8-2):  $\beta(\text{post-NIH effect on old authors}) - \beta(\text{post-placebo effect on old authors})$ :  
Estimate = 0.113; SE = 0.079; Pr > |z| = 0.155  
(8-3):  $\beta(\text{post-NIH effect on new key words}) - \beta(\text{post-placebo effect on new key words})$ :  
Estimate = 0.239; SE = 0.068; Pr > |z| < 0.001  
(8-3):  $\beta(\text{post-NIH effect on old key words}) - \beta(\text{post-placebo effect on old key words})$ :  
Estimate = −0.076; SE = 0.076; Pr > |z| = 0.322  
<sup>a</sup>Calendar-year controls are based on a polynomial time trend up to the fourth power, with separate trend estimates for each of the two margins in the stacked regressions.  
\*\*\*Significant at the 1 percent level.  
\*\*Significant at the 5 percent level.  
\*Significant at the 10 percent level.

bulk of the difference-in-differences findings in Table 4 are driven by changes in citations to the mice directly experiencing changes in openness.

Moving to our core results, we examine the differential impact of the NIH openness shocks on new and old authors in specifications (8-2a) and (8-2b). Comparing the impact of openness on the “Old Authors” margin, we find no significant



difference between the treatment and control groups, represented by  $Post\_NIH_{jt}$  and  $Post\_Placebo_{jt}$  regressors, respectively. This implies that researchers with established access to GM mice experienced similar outcomes, regardless of pre-shock openness regime. By contrast, citations along the “New Authors” margin show a much greater sensitivity to the NIH openness shock, particularly when compared to the shift experienced by the control groups. Specifically, the post-NIH period is associated with a 33 percent increase in citations by new last-authors for our treatment groups, compared to a modest 4 percent decrease for the control groups. Unlike the “Old Authors” margin, this difference is highly significant, and the overall pattern of results indicates that the flow of authors toward newly available GM mice is a secular increase, with no major reduction in new researchers using mice in our control groups

Finally, we repeat the above analysis along the margins of new and old “Key Words,” in specifications (8-3a) and (8-3b). Again, we find no significant difference between the treatment and control groups in terms of the old key words margin, with both experiencing a moderate decrease in citation rates. By contrast, for new key words, we find a significant difference between the impact of the post-NIH shock on treatment mice, and the effect on control mice. Specifically, the post-NIH period is associated with a 15 percent increase in the rate of new key words appearing in citations to our treatment groups, while the control groups experienced a 10 percent decrease in new key words. As in the previous specifications, we therefore find that the bulk of the difference-in-differences result is driven by the impact of the openness shocks on our treatment groups along the new-key-words margin.

When interpreting the stacked regressions in Table 8, it is important to remember that the “old” margins will have a mechanical negative tendency as a result of fluctuations reflecting the rapidly changing nature of the field of mouse genomics during our sample period. Such effects would normally be fully absorbed by our calendar-year fixed effects in our standard regressions, but are evident in Table 8 because of the need to use a polynomial time trend when estimating the impact of the NIH agreements on both the treatment and control groups. Further, our results on the “new” margins indicate that any substitution of researchers or research topics from the control to the treatment group is only a minor contributor to our main findings.<sup>51</sup> For example, in specification 8-2a, we find only a 4 percent decline in the flow of new researchers into our control groups, relative to a 32.8 percent increase in their flow to the treatment group. Thus, Table 8 offers insight into a rapidly changing scientific field, and is consistent with the view that the NIH agreements had a strong influence on our treatment group without significantly affecting our control mice.<sup>52</sup>

<sup>51</sup>In additional robustness tests, reported in Table A4 of the online Appendix, we specifically identify “new” last authors substituting into our treatment group mice after having been active in our control group. We separate these “new to technology, old to sample” authors from those “new” authors who are coming from other mice within the treatment group, and those that are entirely new to the sample. Along with our usual measure of “old” last authors, these four margins are analyzed jointly in Table A4, where we find that the NIH agreements had the strongest impact on the “new to sample” subgroup. Combining this with the fact that authors switching from one technology to another represent less than 3 percent of new-last-author observations, we conclude that substitution is at most only a minor contributor to the pattern of our results.

<sup>52</sup>In addition to the robustness tests and placebo regressions reported in Tables 7 and 8, we have run a number of additional specifications to examine our results in greater detail. Notably, we have tested for differences prior to the NIH openness shocks using “pre-window” effects, and have analyzed the impact of the openness shocks

### D. Impact of Openness on Basic and Applied Follow-On Research

In Table 9, we turn to the effects of openness shocks on the distribution of research along the development spectrum, ranging from early-stage basic science to later-stage applications of the preceding innovations. We do so by examining the marginal impact of the openness shocks on the production of research in basic versus applied research journals. In (9-1a) and (9-1b), we find that the *Basic Citations<sub>it</sub>* dependent variable increases by 26 percent during the post-NIH-agreement period; at the same time, *Applied Citations<sub>it</sub>* experience a 30 percent increase during that period (both significant at the 1 percent level). This suggests that the overall impact of the NIH agreements involves both basic and applied citations. We then disentangle the separate impacts of the Cre-lox and Onco agreements.<sup>53</sup> In (9-2a) and (9-2b), we evaluate the differential impact of these two NIH agreements on basic versus applied citations. We find that the impact of the Cre-lox agreement is concentrated in basic citations, whereas the Onco shock has a significant effect only on applied citations. Specifically, the Cre-lox agreement leads to a 120 percent increase in basic citations (significant at the 1 percent level) but no change in applied citations, whereas the Onco agreement leads to a 57 percent increase in applied citations but has no significant impact on basic citations. This difference in citation composition stands in contrast to our previous results, where the Cre-lox and Onco openness shocks were consistent in their direction of impact, if not in their magnitude. As a potential topic for future research, one might explain these divergent impacts based on the difference between the two technologies in the pre-openness period. For Cre-lox mice, not only were there stringent reach-through rights, but there was also very limited access to the mice due to ex ante enforcement by DuPont. In contrast, Onco mice were made available in the pre-openness period through the Jackson Laboratory. Thus, the Onco agreement's primary effect was to reduce reach-through rights to follow-on research, while the Cre-lox agreement had a significant impact on access costs in addition to reducing reach-through rights. Our findings therefore suggest that when direct access to research inputs is already secured (as was the case for Onco mice), an agreement that shifts the balance of IP rights toward follow-on innovators induces more applied research.

### E. Impact of Openness on the Creation of New Genetically Modified Mice

Finally, we analyze the impact of the Cre-lox and Onco openness shocks on the rate of creation of genetically modified mice. Our empirical approach begins with the full set of mice in the MGI database (approximately 13,000). For each mouse

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on researchers outside the United States. In both cases, our findings are consistent with the pattern of our core results: there is no evidence of "pre-window" differences between treatment and control groups; similarly, foreign researchers exhibit no significant difference between the window and short-term post-NIH periods, but do exhibit an increase in the long-term period.

<sup>53</sup> Both Onco mice and Cre-lox mice could be used in basic research—studying mechanisms of action in diseases, and disease progression. Similarly, they could both be used in applied work, such as the testing of new drug compounds. While the Cre-lox technology was more versatile, and could be used to create GM mice pertaining to a broader range of diseases, these could be used in basic or applied research in the same way that Onco mice could be. This would lead to a difference in overall levels, but have no impact on the distribution of types of uses.

TABLE 9—IMPACT OF OPENNESS ON CITATIONS IN BASIC VERSUS APPLIED JOURNALS

	Stacked negative binomial [Incidence rate ratios reported in square brackets] Estimated coefficients in second line (Block bootstrapped SEs reported in parentheses)			
	(9-1a) DV= Basic journal citations	(9-1b) DV= Applied journal citations	(9-2a) DV= Basic journal citations	(9-2b) DV= Applied journal citations
Post-NIH	[1.262]*** 0.233 (0.066)	[1.301]*** 0.263 (0.061)		
Post-Cre-lox			[2.212]*** 0.794 (0.126)	[1.073] 0.070 (0.105)
Post-Onco			[1.076] 0.073 (0.062)	[1.565]*** 0.448 (0.075)
<i>Control variables</i>				
Window FEs	Yes	Yes	Yes	Yes
Age FEs	Yes	Yes	Yes	Yes
Year FEs		Yes <sup>a</sup>		Yes <sup>a</sup>
Article FEs		Yes		Yes
log-likelihood		−105,989.0		−105,894.7
Observations		44,530		44,530

Notes: Tests of differences between coefficients:  
(9-1):  $\beta(\text{post-NIH effect on basic journal citations}) - \beta(\text{post-NIH effect on applied journal citations})$ :  
*Estimate* = **−0.030**; *SE* = **0.072**; *Pr* > |*z*| = **0.676**  
(9-2):  $\beta(\text{post-Cre-lox effect on basic journal citations}) - \beta(\text{post-Cre-lox effect on applied journal citations})$ :  
*Estimate* = **0.724**; *SE* = **0.122**; *Pr* > |*z*| < **0.001**  
 $\beta(\text{post-Onco effect on basic journal citations}) - \beta(\text{post-Onco effect on applied journal citations})$ :  
*Estimate* = **−0.375**; *SE* = **0.086**; *Pr* > |*z*| < **0.001**  
<sup>a</sup>Calendar-year fixed effects include a set of indicator variables common to both margins in a given regression, and a linear difference variable that allows for a constant difference in growth rates between the two margins.  
\*\*\*Significant at the 1 percent level.  
\*\*Significant at the 5 percent level.  
\*Significant at the 10 percent level.

and its associated mouse-article, we obtain information regarding the technology used in its creation, and the journal in which the article was published. We focus on mice created since 1983, using one of the four technologies present in our citation analysis. Figure 4 describes the creation of mice by technology category, from 1990 through 2006, in order to provide a visual representation of any potential impact of the NIH agreements on mouse creation. A standard incentive story might predict a reduction in the creation of Cre-lox and Onco mice, relative to the control technologies, following the corresponding NIH agreements. However, the graph does not exhibit any marked change in creation rates around the time of the two agreements (1998 and 1999, respectively).

Next, we perform a difference-in-differences regression similar to those in our citation analysis. Specifically, our baseline regression takes the measure *Annual Mouse Creation<sub>kt</sub>* as its dependent variable, representing the number

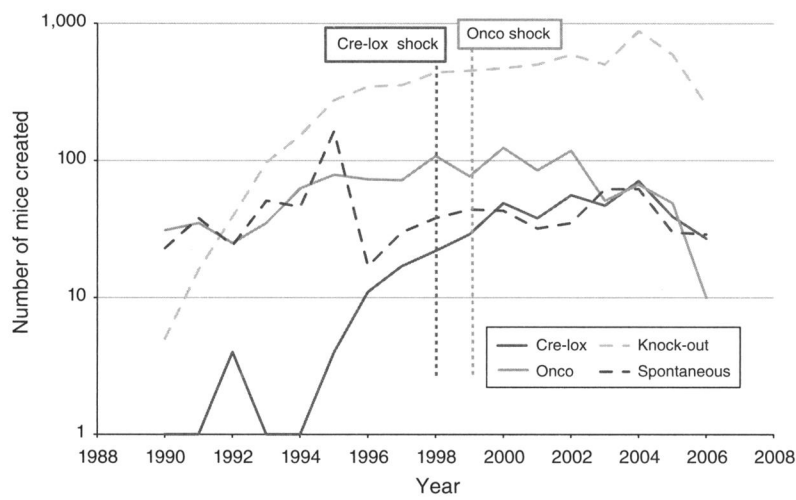


FIGURE 4. MOUSE CREATION BY TECHNOLOGY

of mouse-articles published to a given technology  $k$  in a given calendar year  $t$ . Our key regressors are now technology-specific indicator variables for the years impacted by our treatment groups’ respective NIH agreements  $Cre-lox\_Window_{kt}$ ,  $Post\_Cre-lox_{kt}$ ,  $Onco\_Window_{kt}$ , and  $Post\_Onco_{kt}$ . We also include controls for calendar-year, age, and technology-specific effects. Similar to our earlier specifications, we include a technology fixed effect (conditioned out in the context of our conditional fixed effect negative binomial estimator), calendar-year fixed effects, and a cubic polynomial in the age of the technology. Finally, because of the much older age of the Spontaneous technology, we estimate age effects separately for the Spontaneous group. This results in the following specification:

$$\begin{aligned} AnnualMouseCreation_{kt} = & f(\varepsilon_{kt}; \gamma_k + \beta_t + g(t - EarliestYear_k) \\ & + 1(k = Spontaneous) \cdot h(t - EarliestYear_k) \\ & + \varphi_1 Cre-lox\_Window_{kt} + \varphi_2 Post\_Cre-lox_{kt} \\ & + \varphi_3 Onco\_Window_{kt} + \varphi_4 Post\_Onco_{kt}). \end{aligned}$$

Using the above framework, we first estimate how the overall mouse-creation rates for our treatment technologies change in response to their corresponding NIH agreements, accounting for fixed differences across technologies and relative to the trend in creation rates for the non-treated control groups. Our results are shown in the first two columns of Table 10. In specification (10-1), we use the four technologies studied in our citation analysis. Rather than finding a decrease, the estimates indicate a 45 percent increase in mouse creation after the NIH agreements for Cre-lox mice, and an even larger 62 percent increase for Onco mice. However, only the Onco technology estimate is statistically significant; further, these findings are quite sensitive

TABLE 10—IMPACT OF OPENNESS ON OVERALL MOUSE CREATION AND MOUSE CREATION IN NEW VERSUS OLD JOURNALS

	[Incidence rate ratios reported in square brackets] Estimated coefficients in second line (Block bootstrapped SEs reported in parentheses)					
	Negative binomial		Stacked negative binomial			
	(10-1) DV= Annual mouse creation	(10-2) DV= Annual mouse creation	(10-3a) DV= New creation journals	(10-3b) DV= Old creation journals	(10-4a) DV= New creation journals	(10-4b) DV= Old creation journals
Post-Cre-lox	[1.452] 0.373 (0.312)	[2.915] 1.070 (0.728)	[1.952] 0.669 (0.899)	[1.458] 0.377 (0.658)	[1.774] 0.573* (0.333)	[1.326] 0.282 (0.241)
Post-Onco	[1.624]*** 0.485 (0.011)	[1.202] 0.184 (0.436)	[2.826]*** 1.039 (0.105)	[1.182]* 0.167 (0.086)	[1.745] 0.557 (0.374)	[0.876] −0.132 (0.312)
<i>Control variables</i>						
Cre-lox-window	[1.525] 0.422 (0.268)	[4.208]** 1.437 (0.693)	[3.939]** 1.371 (0.611)	[0.860] −0.151 (0.377)	[3.582]*** 1.276 (0.217)	[0.824] −0.193 (0.137)
Onco-window	[1.502]*** 0.407 (0.152)	[1.196] 0.179 (0.358)	[1.562]*** 0.446 (0.080)	[0.992] −0.008 (0.038)	[1.160] 0.148 (0.251)	[0.824] −0.193 (0.206)
Age controls	Yes <sup>a</sup>	Yes <sup>a</sup>	Yes <sup>a</sup>	Yes <sup>a</sup>	Yes <sup>a</sup>	Yes <sup>a</sup>
Year FEs	Yes	Yes		Yes <sup>b</sup>		Yes <sup>b</sup>
Technology FEs	Yes	Yes		Yes		Yes
log-likelihood	−287.58	−554.96	−263.46		−527.42	
Number of technologies	4	8	4		8	
Observations	78	136	156		272	

Notes: Tests of differences between coefficients:

(10-3):  $\beta(\text{Cre-lox-window effect on new creation journals}) - \beta(\text{Cre-lox-window effect on old creation journals})$ :

*Estimate* = 1.522; *SE* = 0.234;  $\text{Pr} > |z| < 0.001$

$\beta(\text{post-Cre-lox effect on new creation journals}) - \beta(\text{post-Cre-lox effect on old creation journals})$ :

*Estimate* = 0.292; *SE* = 0.241;  $\text{Pr} > |z| = 0.225$

$\beta(\text{Onco-window effect on new creation journals}) - \beta(\text{Onco-window effect on old creation journals})$ :

*Estimate* = 0.454; *SE* = 0.117;  $\text{Pr} > |z| < 0.001$

$\beta(\text{post-Onco effect on new creation journals}) - \beta(\text{post-Onco effect on old creation journals})$ :

*Estimate* = 0.872; *SE* = 0.191;  $\text{Pr} > |z| < 0.001$

(10-4):  $\beta(\text{Cre-lox-window effect on new creation journals}) - \beta(\text{Cre-lox-window effect on old creation journals})$ :

*Estimate* = 1.469; *SE* = 0.215;  $\text{Pr} > |z| < 0.001$

$\beta(\text{post-Cre-lox effect on new creation journals}) - \beta(\text{post-Cre-lox effect on old creation journals})$ :

*Estimate* = 0.291; *SE* = 0.164;  $\text{Pr} > |z| = 0.076$

$\beta(\text{Onco-window effect on new creation journals}) - \beta(\text{Onco-window effect on old creation journals})$ :

*Estimate* = 0.341; *SE* = 0.164;  $\text{Pr} > |z| = 0.038$

$\beta(\text{post-Onco effect on new creation journals}) - \beta(\text{post-Onco effect on old creation journals})$ :

*Estimate* = 0.689; *SE* = 0.279;  $\text{Pr} > |z| = 0.013$

<sup>a</sup>Age controls include a cubic polynomial in the age of the technology, with a separate age trend for the much older spontaneous technology. Note that there are separate effects for the two margins in stacked regressions.

<sup>b</sup>Calendar-year fixed effects include a set of indicator variables common to both margins in a given regression, and a linear difference variable that allows for a constant difference in growth rates between the two margins.

\*\*\*Significant at the 1 percent level.

\*\*Significant at the 5 percent level.

\*Significant at the 10 percent level.



to the choice of control group. In (10-2), we expand the control group to include all major genetic modification categories in the MGI database, adding the following four technologies: Targeted (reporter), Targeted (knock-in), Targeted (Floxed/Frt), and Genetrapped mice.<sup>54</sup> In this specification, while the point estimates continue to indicate increasing rates of mouse creation following the openness shocks, neither of our treatment effect estimates are statistically significant. Further, while the Cre-lox effect increases in strength in (10-2), the Onco estimate is smaller than in (10-1). However, both (10-1) and (10-2) offer an important take-away: *increased openness did not lead to a reduction in the overall creation of new research mice*. This stands in contrast to the traditional hypothesis that increased openness on existing research mice should discourage the development of new mice. Instead, consistent with our emphasis on exploration in the process of innovation, a more open environment had either a neutral or a slight positive impact on the creation of new mouse varieties.

Finally, we consider the impact of the openness shocks on the diversity of mice creation. To this effect, we divide the set of mice created through a particular technology in a given year from each citation year into two mutually exclusive types: those published in journals that had previously published mice associated with that same technology (“Old Creation Journals”), and those which have not previously published any such mice (“New Creation Journals”). Our specifications here are simply a two-equation version of the specifications employed in (10-1); we estimate the impact of each of the NIH agreements on new mice published in old versus new journals, accounting for fixed differences across each technology type, calendar year effects, and including time trends as above. The results are reported in (10-3) and (10-4), with the former specification focusing on the mouse technologies from our citation analysis, and the latter including the wider set of control groups. In (10-3), we find economically and statistically significant (positive) differences between the number of “new journals” and “old journals” in which new mouse-articles are published for the window periods of both Cre-lox and Onco mice, and for the post-NIH period for Onco mice. Moving to the expanded control group in (10-4) we find significant differences for both window and post-NIH periods for both of our treatment technologies. Importantly, for both specifications, we find only positive point estimates for all New-Creation-Journal margins, and for all differences between new and old creation journals.

Overall, the results in Table 10 show no evidence of a reduction in the creation of genetically modified mice following the NIH agreements, but do indicate an increase in the diversity of mouse creation, as reflected by the new journals in which mouse-articles are published. Under the traditional linear view of sequential innovation, new research lines can only result from the introduction of new tools (in this case, new mice), and greater openness reduces the incentives for their creation. By contrast, our findings are more consistent with a setting where new lines can also

<sup>54</sup> These additional technologies are reasonably comparable from the perspective of mouse creation, and are useful in expanding the number of available observations. By contrast, they are not as significant in the context of follow-on research in the field of mouse genomics, and would not have offered an effective control group for our results in earlier tables.

result from cross-fertilization with existing lines by scientists engaging in exploratory research, and where this cross-fertilization is itself facilitated by openness.

## VI. Conclusion

In this paper, we argued that greater openness of early-stage research leads to an increase in the diversity and the exploratory nature of follow-on innovation. Decreasing costs of access to preexisting innovations has a differentially stronger impact on speculative research, increasing the likelihood of establishing entirely new research directions. This increase in the scope of follow-on research can provide additional incentives for new early-stage projects, offsetting the potential drawbacks of reduced reach-through rights. Further, academic research can be motivated by the desire for recognition and citation within the academic community, in addition to the incentives provided by intellectual property. We tested our hypotheses by examining a natural experiment in openness within the academic community: NIH agreements during the late 1990s that reduced IP restrictions for academics and increased the openness of key types of genetically engineered mice and the research tools associated with their production. Our empirical results suggest that the NIH agreements had a profound and long-lasting impact on follow-on research. Moreover, we found that these openness shocks not only increased the overall flow of research using specific engineered research mice, but also expanded both the diversity of researchers working on particular research lines, and the diversity of the research lines being pursued. Finally, we found that increased openness did not result in a reduction in the flow of new mouse creation. Our results therefore highlight a key limitation in the current literature on intellectual property and innovation: the impediments intellectual property restrictions may place on the diversity of follow-on research, particularly in the case of academic researchers seeking to explore the potential uses of multi-purpose research tools.

The analysis developed in this paper could be extended in several interesting directions. One avenue would be to reassess the Bayh-Dole Act based on our findings. Indeed, our results highlight one of the possible dangers of excessive IP enforcement: namely, if IP is used to restrict openness at very early stages of a research line, then it may stifle exploratory projects that are necessary for diverse follow-on innovation. Importantly, an attempt to use IP protections to ensure strong incentives for early-stage research may prove counterproductive, as the lack of exploration may severely limit both the scope and total value of follow-on research stemming from the initial innovation. We expect these results will hold and the lessons have salience for the range of fields where an underlying set of tools are critical in the development of both marketable products and new fundamental innovations, i.e., Pasteur's Quadrant (Stokes 1997). In addition to its implications for academic researchers working in these fields, our analysis suggests that more attention should be paid by economists to recent corporate attempts to generate new sources of profit through building on the openness of knowledge production by others. Tapscott and Williams (2008) explain how IBM has recovered from competition with Microsoft by engaging in the openness promoted by the Linux community. By contrast, the experience of DuPont and other

companies that continued to enforce patents while also attempting to engage with the open scientific community was less successful (Huang and Murray 2008). This pattern suggests the need for a systematic analysis of the forces and trade-offs at work in an economic environment where both proprietary-technology and open technology-firms compete with each other and cooperate with open communities, setting the stage for future research.

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