Are the Foundations of Regional Scientific Advantage Fragile or Robust?
Evidence from U.S. Human Embryonic Stem Cell Policy, 2001-2007*

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Abstract

We investigate in this paper the impact of the August 2001 U.S. administration stem cell research policy on the geography of scientific advantage. The 2001 policy constitutes an interesting policy experiment, as its impact on the field was profound and its particular form was unanticipated in advance. The policy enabled the first U.S. federal funding for human embryonic stem cell (hESC) research; however, it precluded the use of federal funds for all but a narrow (and scientifically unpromising) set of pre-existing stem cell lines. We evaluate the specific impact of this policy on (a) the scientific advantage of U.S. stem cell researchers relative to the international community and (b) the consequences of this policy for the composition of follow-on research in the United States. A particular challenge in this research is in identifying a counterfactual estimate of the production of human embryonic stem cell research that would have occurred had the policy shock not been implemented. To address this issue, we develop multiple control samples, including a particularly novel sample based on the production of research in RNA Interference (RNAi), a scientific breakthrough in a closely related field in cell biology that occurred in the same year as human embryonic stem cell research (1998) and that, like HESC research, also pioneered in the United States. Our estimates suggest that the production of human embryonic stem cell research in the United States was approximately 35-40 percent lower following the policy shock than it would have been in the absence of the shock. On one hand, the results imply that nuanced changes in funding policy can have a substantive impact on the output of scientific research. On the other hand, however, the results also suggest that the policy shift did not lead to a wholesale erosion of U.S. scientific competitiveness in human stem cell research. Instead, the results are consistent with overall trends in the globalization of and convergence in scientific capabilities and suggest that the country-level institutions that support scientific production are relatively long-lived in their effectiveness, i.e., that they are more robust than fragile.

I. Introduction

The cumulative nature of knowledge is recognized as central to economic growth; however, the microeconomic and institutional foundations of cumulativeness are less well-understood (Mokyr 2002). Though "Open Science" is widely recognized to play a fundamental role in the production and diffusion of fundamental knowledge (Merton, 1973; Dasgupta and David, 1994; David 1998; Stephan, 1996), few formal analyses support our understanding of the impact of policies and practices on the rate and direction of scientific progress. The substance of science policy takes many forms, including choices about the level of (and restrictions on) public funding, rules governing access to scientific research materials and data, and policies regarding intellectual property rights for discoveries resulting from (publicly funded) scientific process. Along each of these dimensions, science policy may influence both the overall productivity and the direction of the scientific research enterprise. More subtly, science policy may have important *distributional* consequences: for example, while the establishment of "open access" research repositories may enhance accessibility and productivity for the *average* researcher, some researchers (e.g., those at leading institutions) may face a higher degree of scientific competition if key resources are made accessible to a wider set of researchers. Similarly, specific science policy interventions may enhance the impact of "important" discoveries while reducing attention to and/or diffusion of more minor findings.

In both straightforward and nuanced ways, public policies may have an impact on national and regional scientific advantage. In order for localized knowledge spillovers to be translated into scientific leadership, researchers in close proximity to an original discovery must be able to exploit that discovery more rapidly and more intensively than more distant researchers. Local researchers must be able to take scientific advantage of a discovery more quickly than competitive researchers are able to catch up. This paper exploits an exogenous shock to the process of step-by-step scientific discovery to assess the sensitivity of regional scientific agglomeration to a temporary revision in the knowledge production process. Specifically, this paper examines the impact of the Bush Administration's policy of limiting the scope of Federally funded human embryonic stem cell research to a set of already existing stem cell lines.

Over the past several years, research into the biological foundations of stem cells has been described by biologists as one of the most promising areas of scientific progress, and there have been rapid advances using both embryonic and non-embryonic stem cells, as well as human and non-human stem cell sources. Moreover, at least in the first few years after key discoveries in the 1990s, stem cell research has tended to be geographically localized, with a small number of locations and institutions accounting for a very large fraction of the overall discoveries. In August, 2001, the Bush Administration enacted a policy that placed a subtle but substantive restriction on the freedom of Federally funded researchers by limiting Federal funding with human embryonic stem cell lines to a small number of stem cell lines that had been developed prior to the date of the policy change. While researchers were free to seek private funding, or to use these specific stem cell lines, qualitative research suggests that the policy placed significant restrictions on academic researchers dependent on Federal funding, and that adapting to the policy required a period of adjustment and exploration. This unexpected delay in the scientific productivity of those at the scientific frontier provided an opportunity for less well-positioned researchers to catch up and for equally well-positioned researchers to forge ahead during this period of adjustment.

We have assembled a dataset of the citations to all publications through the end of 2007 which cite a set of 110 seminal stem cell articles published in the mid-to-late 1990s. While some of these publications are primarily focused on human embryonic stem cell research, others are linked to non-human or non-embryonic stem cell research. In addition to these stem cell research articles, we assemble sets of controls based on "normal science" and on another area of "hot science." Our "normal science" sample includes *Nearest Neighbor articles* (Furman and Stern, 2006), i.e., the three articles that immediately precede and follow each of the stem cell articles in the same year and issue of the journal in which the stem cell article was published. Using these articles as a comparison allows us to get a sense for the geography of stem cell research relative to a comparable sample of articles across scientific fields. Our "hot science" sample reflects research building on another significant discovery in cell biology, the understanding of RNAi. As was the case for the seminal research on human embryonic stem cells (hESC), the pioneering work in RNAi was published by US-

based researchers in 1998. As a consequence, the geography of RNAi research appears to constitute a reasonable comparison set for studying the geography of stem cell research.[1]

We consider the set of articles that cite the original articles in our treatment and controls groups as indicators of the nature and extent of follow-on research. (We refer to each of our original treatment and control articles as "root articles," and label the follow-on articles as "citing articles".) For each follow-on publication, we have information about the location and institutional affiliation of the researchers, as well as other publication and researcher characteristics. Our empirical examination focuses on two principal questions: First, we ask whether the geographic pattern of human embryonic stem cell research after the Bush stem cell policy decision differs significantly from the pattern of regional agglomeration/dispersion realized by research into non-human and/or non-embryonic stem cell lines. Second, we ask investigate the impact of the Bush administration policy on the nature of human embryonic research in the United States, examining, for example, whether the policy shifted the locus of research to different types of authors or institutions or whether it affected the extent and nature of collaboration.

Prior work on this subject has demonstrated differences in the extent of hESC research published by US and non-US authors in the years following the Bush administration policy decision (Owen-Smith & McCormick, 2005). Our approach makes a number of contributions relative to this state of knowledge. First, our analysis makes clear that that the interpretation of these data depends greatly on the inclusion of matched controls and on the ability to take advantage of nuanced details about the institutional affiliations of authors. Human embryonic stem cell research and RNAi research are substantively different from "normal science" during the sample period in the sense that research built on these initial discoveries at a greater rate than on discoveries published in similar journals at the same time.

With respect to the geography of scientific discovery, our analysis suggests that the impact of the Bush Administration Stem Cell policy was nuanced: In the years following the policy's enactment, our counterfactual analysis suggests that U.S.-based human embryonic stem cell research experienced a 35%-40% decrement, relative to such research outside the United States between 2001 and 2007. However, the negative impact of the policy on U.S.

[1] Andrew Fire and Craig Mello were awarded the 2006 Nobel Prize in Physiology/Medicine for this research.

research output appears to have been concentrated in the years 2001 to 2004; the data suggest recovery between 2005 and 2007. Further, our analysis suggests that the impact of the policy was greater among non-elite research institutions in the United States than it was among the most research-intensive U.S. universities. Indeed, by 2007, the negative impact of the policy on human embryonic stem cell research has virtually disappeared among elite U.S. universities.

While we should note a number of important caveats about the construction of the dataset, which suggest interpreting our results with caution, a few broader conclusions seem warranted. On one hand, the results imply that nuanced changes in funding policy can have a substantive impact on the output of scientific research. On the other hand, however, the results also suggest that the policy shift did not lead to a wholesale erosion of U.S. scientific competitiveness in human stem cell research. Instead, the results are consistent with overall trends in the globalization of and convergence in scientific capabilities and suggest that the country-level institutions that support scientific production are relatively long-lived in their effectiveness, i.e., that they are more robust than fragile.

II. Institutional Details

II.1. Introductory details[2]

The recent history of stem cell research involves a number of unexpected milestones. The first relates to the advances made by James Thomson and colleagues at the University of Wisconsin – Madison, who successfully isolated and cultured cells from the inner cell mass of human embryos (NIH, 2001). Thomson and associates published their work in 1998, developed the first embryonic stem cell lines, and obtained intellectual property rights pertaining to those lines (Murray, 2007). Related advances, using fetal gonadal tissue, were achieved by John Gearhart of Johns Hopkins University and with his associates that same year (NIH, 2001). These advances opened the way for others to engage on follow-on and related work, both by pioneering necessary techniques and by developing essential research materials.

[2] This section is quite preliminary. The details of this section follow quite closely on the Overview of Stem Cell research provided by the 2001 NIH report, "Stem Cells: Scientific Progress and Future Research Directions."

As was the case over the broader history of stem cell research, these advances occurred in the context of contentious ethical debates and complex policy considerations. A second crucial milestone relevant to the advance of knowledge in this area was the introduction in August 2001 of the Bush Administration human embryonic stem cells policy. While it was the first federal policy that enabled federal funds to be approved for research on certain human embryonic stem cell lines, the policy famously prohibited federal funding for human embryonic stem cells derived from lines that were not on the approved list. Both advocates and opponents of human embryonic stem cell research were, in a number of ways, surprised by the specifics of the policy, which appears to have been a compromise between ethical, political, and scientific considerations. We introduce useful background material on stem cells and on the history of stem cell research in order to set the stage for discussions about the history of stem cell research funding policy in the U.S.

II.2. What are stem cells?

"A stem cell is a special kind of cell that has a unique capacity to renew itself and to give rise to specialized cell types. Although most cells of the body, such as heart cells or skin cells, are committed to conduct a specific function, a stem cell is uncommitted and remains uncommitted, until it receives a signal to develop into a specialized cell. Their proliferative capacity combined with the ability to become specialized makes stem cells unique" (NIH, 2001, ES-1). The scientific and medical promise of stem cell research derives from their potential to develop multiple types of cells.

It is important to note the distinction between adult stem cells and embryonic stem cells. "An adult stem cell is an undifferentiated cell that is found in a differentiated (specialized) tissue in the adult, such as blood. It can yield the specialized cell types of the tissue from which it originated. In the body, it too, can renew itself. During the past decade, scientists discovered adult stem cells in tissues that were previously not thought to contain them, such as the brain" (NIH, 2001, ES-1). Embryonic stem cells "have the potential to develop almost all of the more than 200 different known cell types" (NIH, 2001, ES-1).

Although the scientific understanding of both adult and embryonic stem cells continues to evolve, the consensus among leading scientists in 2001 was that embryonic

stem cell held more promise as research tools because their greater ability to differentiate (i.e., their "pluripotency").

Prior to isolating human embryonic stem cells, researchers had devoted considerable effort to examining embryonic and adult stem cells in animal models. Mouse models are among the most often-used. Thomson and colleagues, as well as numerous others, have also made significant advances using cells derived from primates.

II.3. A brief history of Stem Cell Research

Current stem cell research is built from 19th and early 20th century advances in biology, in particular the observations that certain cells could produce other cells, most notably blood cells. The pace of stem cell research accelerated in the late 1960s with advances in animal based research on in-vitro fertilization techniques observations on the self-renewing properties of bone marrow cells. In the 1980s, some physicians and scientists began to extend successes with in-vitro fertilization techniques to humans, while others worked with animal-based embryonic and adult stem cells. Evans and Kaufman, and Martin isolate and culture mouse embryonic stem cells in 1981. By the mid-1990s, IVF techniques have diffused to some extent across the medical community. Working with primates, Thomson and colleagues succeed in isolating and maintaining embryonic stem cells *in vitro* in 1996. These discoveries laid the groundwork for their successes with human embryonic stem cells two years later.[3]

II.4. U.S. Policy History

Even in the decades prior to Thomson's development of hESC lines, there had been considerable variation across national and local governments in the nature and degree of support for research on human embryos. There has also been substantial variation within some governments, including that of the U.S., over time. The U.S. federal government has often imposed restriction on its support for research involving human embryos and other aspects of conception (Fletcher, 2000). Beginning in 1973, US government policy

[3] One important difference between the policy environments in the U.S. and foreign countries is the intellectual property regime. In general, IP rights with respect to stem cell lines are stronger in the United States. For example, the University of Wisconsin, through its technology transfer office (the Wisconsin Alumni Research Fund or WARF), has strong IP rights over the Thomson stem cell lines in the United States, although these cells may be circulated without such restrictions outside the United States.

prohibited federal research funding from supporting research on fetuses, embryos, tissues associated with either. These restrictions did not, however, impose bans on private sector or privately funded research. In the late 1980s, both the NIH and Congress became more sympathetic to the prospect of using government funding for research on human embryos. President Clinton initially supported the removal of the ban on federal funding, but reversed course early in his presidency. Congressional action in 1995 expressly prohibited the use of federal funding for the development of human embryos that would either be destroyed or employed in research. This limitation essentially precluded federal support for *in vitro* fertilization, which usually creates more embryos than are deployed. The policy environment became more supportive of the federal support for human embryonic stem cell research during the final years of the Clinton Administration. In August 2000, only a few months before the Bush vs. Gore presidential election, the NIH published guidelines enabling federal funding for research using existing cell lines and soliciting proposals for future research. Thus, the United States began 2001 amidst a contentious public debate and an evolving, uncertain policy environment in which the scientific community actively touted the prospective value of hESC research and remained hopeful but uncertain about the prospects for large-scale funding.

II.5. The 2001 Bush Administration Stem Cell policy

Soon after taking office, the Bush Administration initiated an official review of its policy options with respect to human embryonic stem cell research and placed a hold on the funding of proposals solicited by the NIH. As part of the administration review process, Tommy Thompson, the Secretary of Health and Human Services and former Governor of Wisconsin requested in February 2001, "that the National Institutes of Health prepare a summary report on the state of the science on stem cells … [which] provides the current information about the biology of stem cells derived from all sources— embryo, fetal tissue, and adult" (NIH, 2001, p. i). The NIH issued its report, "Stem Cells: Scientific Progress and Future Research Directions," in June 2001.

On August 2001 in an environment of substantial interest and speculation, President Bush introduced his administration's policy. The policy included three features that are notable for our current project: The policy (1) enabled federal funding for research on a set

of existing human embryonic cell lines, (2) prohibited federal funding for research on new human embryonic cell lines, and (3) placed no restrictions on the use of private, state, or local funds for hESC research purposes and no federal restrictions on the funding of human adult stem cell research or animal research on either adult or embryonic stem cells. This nuanced policy thus provided the first large-scale federal funding for research on human embryonic stem cell research while also ensuring that the U.S. federal government would not financially support the destruction of human embryos. The policy also formally opened the opportunity for interested non-federal actors to support hESC research efforts. Overall, the U.S. federal government allocated approximately $550 million to stem cell research in 2005; only $24 million of this, however, was devoted to human embryonic stem cell research (Beardsley, 2005). One important feature of the policy is its requirement that researchers cannot federal funding to any research that employs human embryonic cell lines outside of the narrow set approved in August 2001. Researchers who would like to conduct work on non-approved hESC lines and also receive federal support for research on approved lines must establish laboratories that are physically and organizational distinct from one another.

The U.S. Administration Stem Cell policy was altered in March 2009 when President Barack Obama issued an executive order overturning the ban on the use of federal funding for human embryonic stem cell research. The NIH authorized approximately $20 million in funding for human embryonic stem cell research in 2009 and approved the first set of new hESC lines in December 2009.

II.6. The U.S. policy in international context – comparisons with other countries

The policy enacted by the Bush Administration in 2001 was by no means the most restrictive of all national policies: At the time of the policy announcement, a number of European countries did not offer permission to scientists to derive stem cell lines, conduct research on existing lines, or research involving somatic cell nuclear transfer, including Austria, Ireland, and Italy. The policy environment in Germany was also restrictive: National policies allowed research on existing lines, but prohibited nuclear transfer and the derivation of new lines. At the same time, some countries supported stem cell research to a substantially greater degree. Leading stem cell research countries, including Israel, Singapore, Sweden, and the United Kingdom (as well as follower countries China, Japan,

and South Korea) allowed research on existing cells and nuclear transfer and also supported the derivation of new stem cell lines. A summary of national policies with respect to stem cell research in the year 2005 appears in Appendix Table 1.

III. Methods & Research Design: Identifying the Impact of a Nuanced Policy Shift On The Geography Of Scientific Advantage

III.1. An experimental approach to assessing the impact of science policy shocks

Our approach assessing the impact of the Bush Administration policy intervention exploits a number of features of the scientific system and the storage and ease of use of bibliometric data. It is premised on several assumptions. First, we believe that data on the production and citation of academic papers provide valuable (though imperfect) indicators of scientific progress. We rely on the seminal work of Merton (1973), Garfield (1955), and De Solla Price (1971) in articulating the importance of priority and publication in the system of scientific rewards and noting the importance of publications and citations in tracking the rate and direction of scientific progress.[4] We rely upon the fact that (a) academic papers are produced at a specific and measurable point in time and (b) the use by follow-on researchers of the knowledge articulated in those papers takes place over time and in a way that can be measured as well. We interpret citations to academic papers as evidence of the use of prior knowledge by follow-on researchers, although we acknowledge that these are noisy measures.

Our second assumption is that the degree to which future research "draws upon" (cites) a given article (and by whom and where and when) depends on institutional mechanisms, including intellectual property rights over the knowledge disclosed in the article, rules and institutional arrangements governing access to research resources, and national and local policies. Further, the opportunity to take advantage of a given research trajectory by researchers in any one location or institution depends on access to funding, materials, and support infrastructure to conduct that research in a timely manner (i.e., before

[4] We recognize that bibliometric analysis provides only a noisy indicator of scientific progress (see, e.g., Garfield (1979), Lindsey (1989), and Schubert and Braun (1993)): For a number of reasons, small differences in the citation rate of a single paper (particularly early in its publication history) are of limited value in distinguishing the importance of research or its use by the research community. We take care to minimize the impact of these limitations by drawing comparisons among large samples of publications, comparing across control samples, and assessing the impact of policy changes by drawing comparisons within articles across time.

others are able to exploit the opportunity). The impact of institutions and policy interventions on facilitating this process of step-by-step scientific discovery is a key challenge for science policy, and a central focus of science policy analysis (Aghion Dewatrapoint & Stein 2005; Mokyr 2002).

Our third and final assumption is that science policy interventions that change the institutional environment for scientific research will be reflected in changes in the rate and direction of scientific progress, which in turn is captured in citation patterns.[5]

From an experimental perspective, the econometrician would ideally observe a given piece of knowledge in distinct institutional or policy environments and compare the impact of that knowledge across regimes. To do so, our analytical framework relies on the fact that institutional changes or policy interventions may induce changes in the production of scientific articles or changes in citation behavior relative to baseline levels.[6] Moreover this natural experiment approach exploits the fact that the institutional environment changes over time in ways that do not impact the original "piece of knowledge" but which do impact the incentives and opportunities for follow-on researchers to exploit that piece of knowledge in their own research.

III.2. Evaluating the impact of the Bush Administration hESC policy shock

[5] Given these assumptions, it should be possible to observe and evaluation the impact of science policies on scientific progress. In reality, social scientists and policy analysts face a considerable challenge in assessing the extent to which any particular institution or policy influences the way in which the "knowledge stock" is created, maintained, and extended. In particular, it is empirically difficult to separate the influence of a particular institution or policy from the influence of the knowledge in which it is embedded, even though the two are conceptually distinct. Specifically, a selection effect may result from a correlation between the characteristics of institutional and policy regimes and the type of knowledge associated with them giving rise to a fundamental inference problem. Specifically, for a given piece of knowledge produced or diffused within a given institutional or policy environment, one cannot directly observe the counterfactual impact that knowledge would have had if the knowledge had been produced and diffused in an alternative institutional or policy setting. Moreover, even it if were possible to evaluate the average impact of a particular policy, ideally we would like to know how such an intervention impacted particular sub-populations of scientists and its impact on both high and low quality research/researchers.

[6] There are, of course, some important caveats to this approach. First, not all research is disclosed in the scientific literature; indeed, for-profit entities may decline to publish research results either to increase the costs of rivals' research (Rosenberg, 1990) or in the event that such results are disadvantageous for the firm. Second, a increases citations (relative to a baseline) may occur not because of the increased importance of a particular 'unit' of knowledge, but simply because of the ease of its availability relative to alternative pieces of knowledge or for other reasons (such as changes in author prominence or position) that do not reflect changes in the actual use of knowledge. Such problems would average out across the areas we study, unless these changes are closely correlated with the specific policy or institutional changes we study.

Because the outcome of the November 2000 was particularly uncertain and the specifics of the Bush Administration were also uncertain prior to its announcement in August 2001, we interpret the policy as a (plausibly) exogenous shock to the policy environment. We then examine the impact of this policy by comparing the rate and nature of human embryonic stem cell research with that of other types of stem cell research, other important research in cell biology, and a more loosely-matched control sample of related science.

Specifically, we investigate two central issues whether there is evidence that the Bush Administration policy had an impact on the geography of stem cell research – i.e., whether the enactment of the policy is associated with a shift the relative level of US vs. Non-US human embryonic stem cell research – accounting for trends in the progress of related science. In addition, we examine the distributional consequences of the policy, investigating whether the policy led to a shift in the nature of hESC research in the United States relative to other locations. For example, we are interested in (a) the extent to which the policy affects researchers at the highest status institutions differently from researchers at other institutions, (b) the extent to which the policy affects collaboration among researchers, and (c) whether the policy has a relatively different impact on research incumbents vs. entrants (which one could interpret as impact on the industrial organization of hESC research).

To do this, we employ an estimator that identifies the average differences in citations across the treated and control groups, and estimates the change in citations resulting from the change in the institutional or policy environment including article-specific fixed effects. Specifically, this baseline estimator is:

$$(1)\; CITES_{i,j,pubyear(j),t} = f(\varepsilon_{i,j,t}; \gamma_i + \beta_t + \delta_{t-pubyear} + \psi POST-SHOCK_{i,t})$$

where (γ_i) is a fixed effect for each article, β_t is a year effect, $\delta_{t\text{ - pubyear}}$ captures the age of the article, and POST-SHOCK is a dummy variable equal to one only for years after root article is affected by the Bush Administration policy shock (i.e., beginning in 2002). The coefficient on POST-SHOCK (ψ) indicates the marginal impact of the intervention on the set of treated articles. Thus, we test for the impact of policy interventions by calculating how

the citation rate for a scientific publication *changes* following such interventions, accounting for fixed differences in the citation rate across articles and relative to the non-parametric trend in citation rates for articles with similar characteristics.

By modifying (1) to allow for pre-deposit and post-deposit dynamics it is possible to estimate whether the impact of the policy changes with the time elapsed since policy intervention and to check for the presence of a pre-deposit time trend. The former is important to understand the dynamic consequences induced by the policy intervention – for example, whether the impact of the policy intervention occurs as a one-time change in the levels or diffusion of knowledge, whether it declines or returns to baseline over time, or whether the policy intervention induces continuously growing effects. The pre-deposit trend might provide evidence about the exogeneity of the policy intervention itself.

While the prior paragraphs focus on the impact of policy interventions or institutional changes on the overall count of citations to a given discovery, we are interested in how the policy shock affects the relative distribution of hESC research by institution type, the quality of journals in which follow-on research appears, and the extent and nature of collaborative research. To estimate the impact of policy interventions on each of these subpopulations, we can aggregate these individual citations into counts of the number of citations received by a given article in a given year by a given subpopulation of citers:

$$(2)\ CITES_{i,l,t} = f(\varepsilon_{i,j,t}; \gamma_i + \lambda_l + \beta_t + \delta_{t-pubyear} + \sum_{l=1,\ldots L} \psi_l \iota_l POST - SHOCK_{i,t})$$

In other words, ψ_l is the average impact of the treatment on sub-population *l*, conditional on a fixed effect for each article, and age and citation-year fixed effects.

To implement this approach we construct a dataset composed of scientific publications linked to four types of articles: (1) seminal human embryonic stem cell research articles, (2) seminal articles on all other types of stem cell research, (3) seminal RNAi articles, and (4) control articles matched to the sets described in (1) and (2). Because we observe citations to a scientific publication both before and after the policy shock (and because we are able to identify a counterfactual estimate of the citation rate that would have occurred had the shock *not* occurred), we can identify the causal impact of the Bush Administration policy shock on the pattern of citations to a scientific publication.

Of course, citations data takes the form of count data that are skewed to the right and over-dispersed relative to Poisson. As well, the rate of citation to a given piece of research will vary with the calendar year and with the time elapsed since initial publication. Therefore, except where noted, we employ a conditional negative binomial model with age and year fixed effects for citations produced per year for each scientific article in our dataset.[7,8] We experiment with a range of alternative specifications.

IV. Data

To implement the difference-in-differences framework we articulate above, we identify multiple series of treatment and control articles, and construct a database that includes bibliometric information on both the original articles and ("root articles") the follow-on articles that cite them ("citing articles").

Our sample of stem cell articles is comprised of the publications identified by the NIH report, "Stem Cells: Scientific Progress and Future Research Directions." This report was published in June 2001 and was an input into the Bush Administration policy-making process. The report was devoted to scientific facts relevant to the policy debate, but does not appear to be a political document. The report notes in its Preface, "NIH recognizes the compelling ethical and legal issues surrounding human pluripotent stem cell research. Because extensive discussions regarding these issues have been presented in various forums elsewhere, they are not part of this review of the state of the science. Also, the report does not make recommendations pertaining to the policies governing Federal funding of such research" (NIH, 2001, p. II). Most importantly, the document identifies 110 articles that reflect the seminal articles in stem cell research, including paper associated with embryonic and adult stem cells derived from both human and animal models. We consider these as our

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[7] Several subtle issues, including the incidental parameters problem, arise in incorporating multiple fixed effect vectors into a negative binomial specification. We have experimented with a range of alternative procedures and approaches, including the conditional negative binomial estimator suggested by Hausman, Hall, and Griliches [1984] and the fixed effects estimator suggested by Allison and Waterman [2002]. Our core results are based on the traditional conditional fixed effects estimator with bootstrapped standard errors; however, our qualitative findings are consistent across these different procedures.

[8] When using a conditional fixed effects estimator, one citation year and one age fixed effect are not separately identified (Hall et al, 2005). Since the main effect that we are interested in is separable from these effects, the precise specification we employ to overcome this identification issue does not at all affect our estimate of the impact of BRC deposit on citations. In our estimation, we identify differences relative to age = 0, and relative to publication in years after 1975 (though, due to data limitations, we actually impose a single regressor on the years 1975-1979).

root articles, and track patterns of forward citations received by these articles. Of these articles, 17 root articles are associated with pioneering work in human embryonic stem cell research. We consider these to be our primary treatment sample. We consider the remaining 93 NIH publications, which consist of embryonic and adult animal and human adult stem cell research articles, to be control articles. We recognize, however, that the U.S. policy shock may also affect the incentives and ability to contribute to work in these other areas of stem cell research.

Our second control sample consists of a set of seminal articles on RNA interference (RNAi), another area of cell biology, which, like human embryonic stem cell research, experienced a substantial breakthrough in 1998 pioneered by U.S.-based researchers. As our sample of RNAi root articles, we employ a list of seminal RNAi articles published by Ambion Inc., a company that manufactures and markets products related to RNAi-research. The list includes 56 articles, of which 52 were published prior to or during 2001 and 4 of which were published in 2002.[9] We consider this sample to be a particularly valuable control sample, as it represents a scientific breakthrough that (a) was achieved in essentially the same field and at the same time as hESC research, (b) was of similar (or, indeed, greater scientific importance – Andrew Fire & Craig Mello won the 2006 Nobel Prize for their 1998 work in RNAi), and (c) was also introduced in the United States.

Our third set of control articles are less well-matched with respect to scientific importance but are more precisely matched with respect to publication timing and journal. Specifically, our third control sample consists of "nearest neighbor articles," including each of the three articles that immediately precede and follow each of the root stem cell articles in the same year and issue of the journal in which the stem cell article was published (Furman and Stern, 2006). Thus, each stem cell article in our sample includes up to six nearest neighbor control articles.

V. Results

V.A. Sample Description

Our data includes 699 root articles, of which 17 are human embryonic stem cell root articles, 93 are other stem cell root articles, 56 are RNAi root articles, and the remainder are

[9] Our results are not sensitive to including or omitting the 4 RNAi articles published in 2002.

nearest neighbor articles. Of the hESC articles, nearly 50% include reprint authors (i.e., the author designated to receive article "reprints" from the journal) whose addresses indicate an affiliation with an institution in the United States, nearly 25% include an Israel-based reprint author; 11.7% of the papers include a reprint author from the UK, Canada, and the Asia-Pacific region.[10] They receive a mean of 22.1 citations per year, with a standard deviation of 41.8. The other stem cell articles have a similar geographic distribution, with 55% or reprint authors associated with an institution location in the United States. These articles receive, on average, a larger number of annual citations than the hESC sample (mean annual citations = 36.0; standard deviation = 48.0). Israel-based authors are not overrepresented among the other stem cell articles. Consistent with the belief that RNAi constitutes a significant advance in biology, the RNAi root sample receives even more citations than either of the stem cell samples (mean = 59.2; standard deviation = 84.4). Relative to the stem cell articles, the RNAi articles are more heavily US-based; more than 70% of RNAi root articles include US-based reprint authors. Of the remaining 533 nearest neighbor controls, 62% are US-based; the non-US sample is broadly distributed across countries. The Nearest Neighbor sample is the least well-cited of the controls, receiving, on average, fewer than 9 annual citations (s.d. = 15.1).

Across the sample of root articles, the overwhelming majority of reprint authors (66%) are based in universities and/or hospitals. Of these, we classify 14.0% of reprint authors as associated with "Top 25" universities, based on the Center for Measuring University Performance (Arizona State University) 2006 Annual Report of university research rankings and 20.2% to be associated with "Top 50" universities. Based on a definition that considers "top journals" to be journals that achieve an ISI Journal Citation Impact greater than 25, we find that citations to root articles published in top journals constitute 71.9% of the sample.

V.B. Publication Trends

Figure 1 depicts the number of citing articles by broad article type and year, not distinguishing by country-of-origin. There is an upward trend among each of the

[10] Another convention that we could use to determine the geographic location of authors is one based on the complete set of institutions and addresses listed in the ISI field "C1". We have begun to experiment with this field. Using this field enables a single paper to be associated with multiple countries-of-origin.

subsamples. With the exception of the hESC sample, the rate of follow-on publications accelerates noticably between 1998 and 2002 (or 2003, depending on the sub-sample). The raw number of Nearest Neighbor citations is greatest. This is not surprising, as the baseline number of Nearest Neighbor root articles is 400 more than that of any other sub-sample. Prior to 1999, the number of articles building on hESC and RNAi roots is relatively similar. Beginning in 2000, however, the extent of cumulative reserach in these two areas diverges appreciably, as citations to the RNAi roots rise from fewer than 1,000 in 2000 to more than 5,000 by 2004.

Figure 2 reports citing articles by publication type and year for US and non-US reprint authors. It includes four separate graphics, one for each of our samples. Each graphic reports the number of citations to a different root article sample by papers with either (a) any US-based author or (b) no US-based author. In each case, the number of overall citations rises, before falling in the final years of the sample. The fact that the overall number of citations declines in the final few years of each graphic is reflective of a typical citation pattern in which root articles receive the highest number of citations in the few years after their publication (Furman and Stern, 2006). The rate of obsolescence is of less interest in our analysis than the relative levels of US-based and non-US-based citations.

The top-most graphic in Figure 2 compares trends in citations to hESC root articles by US-based and non-US-based Reprint Authors. While the number of citations by each category is similar between 1998 and 2000, the counts diverge beginning in 2001. Specifically, while the growth rate of non-US-based citations continues after 2001 (until 2004), the relative number of US-based citations declines beginning in 2001, although there appears to be a modest recovery in 2004. These findings are consistent with those reported by Owen-Smith and McCormick (2005), who conclude based on a keyword approach to identifying hESC publications up until l2004 that the US share of hESC articles experienced a relative decline beginning in 2001. The US share of Other Stem Cell citing articles (i.e., articles citing "root" articles in areas of stem cell research other than hESC research) declines beginning in 2003, though not before. US-based citations to RNAi root articles and *nearest neighbor* root articles also experience a relative decline in the later years of the data, but do not experience a relative decline between 2001 and 2003.

Interpreting these trends requires care and more structured analysis. In light of the relatively stable US share of RNAi and Nearest Neighbor articles, the unambiguous relative decline of the US share of hESC articles and modest decline in other stem cell articles may suggest that the shock to US funding policy had an impact on the rate of follow-on stem cell research in the United States. The results appear to be far from unambiguous, however, as the relative decline in US hESC share begins in 2001, although the policy was not introduced until August of that year. These descriptive statistics suggest the importance of measuring hESC research output relative to a carefully matched comparison group. In addition, they highlight the importance of controlling for the impact of timing and root-article effects on follow-on research. In the regression analyses that follow, we attend to each of these issues.

V.C. Regression Results

Our empirical approach relies on a differences-in-differences analysis using matched control samples that attempts to isolate the impact of the U.S. policy shock on the rate and nature of follow-on research. This strategy requires observing research articles in two distinct policy environments, associated with a pre-shock and post-shock period. By comparing citation patterns *across article groups,* i.e., comparing citations associated with root hESC articles with those of other root stem cell articles, root RNAi articles, and root nearest neighbor articles, while controlling for article fixed effects, publication year effects, and calendar year effects, we can identify the marginal impact of the policy shock on the rate and nature of knowledge accumulation. OLS would be inappropriate for inference in this context, as our citation data are composed of highly skewed count data. We therefore employ a conditional fixed effects negative binomial specification throughout the analysis. Our regressions model the sensitivity of FORWARD CITATIONS to the policy shock, controlling for root article age fixed effects, calendar year fixed effects, and conditional article fixed effects. All models include block bootstrapped standard errors, clustered by article [MacKinnon, 2002]. We do not report the significance of tests of joint restrictions on the article fixed effects, as these are not computed in conditional fixed effects models. We report the coefficients in our results as incidence-rate ratios (IRRs), which are easily interpreted as percentage changes relative to a baseline (i.e. the null hypothesis of no effect

yields a coefficient of 1.00, while a coefficient equal to 1.50 implies a 50% boost to FORWARD CITATIONS.)

A pre-requisite for assessing the impact of the policy shock on hESC research is identifying the most thoughtfully-matched treatment and control samples on which to base our counterfactual analyses. To do this, we assess the differences in the number of citations received by the root articles in each sample received during the pre-shock period (1996-2000). We report the results in Table 2. Specifically, each column reports estimates of stacked Negative Binomial regressions, in which coefficients appear in the top line of each cell as incident rate ratios, bootstrapped standard errors clustered at the article level (but not adjusted to IRRs) appear in the lower line of each cell. Calendar year and article age fixed effects are included in the models but not reported. Because the data are stacked and each of the RHS variables is a dummy reflecting the sample with which each citing article is associated, the coefficients reported in each column reflect the average difference in annual citations between an article in the sample indicated by the dummy variable and the baseline (omitted) sample for which no dummy is estimated.

The results in (2-1) and (2-2) suggest that, prior to the policy shock, hESC, OSC, & RNAI root articles received a substantially higher number of annual citations in comparison to Nearest Neighbors articles. We interpret this as suggesting that these areas of "normal science" do not constitute an ideal control sample for counterfactual analysis. Columns (2-3) and (2-4) compare annual citation rates to hESC root articles with those of other Stem Cell root articles and RNAI articles, respectively. The results do not imply no statistically significant difference in citations received, suggesting that each of these areas of science was on a similar growth trajectory prior to the hESC policy shock. There are no statistically significant differences between hESC & RNAi citations prior to the policy shock. RNAi is both conceptually appealing as a control group and appears to be econometrically appropriate. Although there are no statistically significant differences in pre-Shock levels of citations to Other Stem Cells (OSC) and hESC stem cell articles, we ignore this sample in our future estimations, because of the possibility of that hESC researchers could respond to the policy shock by shifting their efforts, to some extent, into OSC research. As a consequence, the policy shock may jointly affect hESC and OSC research, although it is

unlikely to have an effect on RNAi research, since it is substantially more difficult for hESC researchers to shift into this area.

We present the results of our core analysis in Table 3. Columns (3-1) and (3-2) estimate the impact of the policy shock in the year 2001, the year of the shock, and in the average of the years following the shock (2001-2007). The columns differ in that the dependent variable in (3-1) considers citations to be US-based if any address in the address field is US-based, while (3-2) considers citations to be US-based only if the Reprint Author is US-based. In both equations, the coefficients on the variables HESC_2001 and HESC_POST_2001 describe the average difference in citations between HESC and RNAI articles in the years 2001 and 2001-2007, respectively, controlling for year, article age, and article-specific fixed effects. The magnitude and lack of statistical significance of these coefficients in both columns suggest that HESC and RNAI research grew at relatively similar rates during the post-shock period. The coefficients on HESC_2001_US and HESC_POST_2001_US indicate the increment (or decrement) to citations with any US address during the years 2001 and 2001-2007, respectively. The magnitudes and significance levels of these coefficients imply that, relative to HESC research outside the United States, the production of follow-on research with any US address declined following the shock. The impact of the shock appears to be most great in 2001, during which research output falls by more than 50%. In the years after the shock, the production of papers with any US-based author declines by 37%, while the production of papers with a US-based Reprint Author declines by 41%.

In order to better understand the dynamic impact of the shock, we decompose the impact of the shock by year of post-shock impact in (3-3) and (3-4). In these models, the coefficients on HESC_YEAR indicate the relative growth of HESC in comparison to RNAI during that year, while the coefficients on HESC_YEAR_US compare the output of HESC publications in that year in the US to HESC publications outside the US. These results suggest that the impact of the shock was most negative and severe in 2001, but that a recovery begins in 2004. By the end of the sample period, the negative impact of the policy on US-based HESC output has declined to less than 25%. The statistical significance of the difference has also declined, although some of this may be due to obsolescence and truncation.

While the econometric results are clear and are robust to a number of alternative specifications, the interpretation of these results is complex: There is an unambiguous decline in US-based HESC output relative to the rest-of-the-world, which begins in 2001 and continues to the end of our sample period in 2007. As the policy was not unveiled until August 2001 and the most severe decline in US HESC output occurred in the same year, the data do not support the interpretation that the enactment of the policy caused the decline. The data are, however, consistent with an interpretation in which changes beginning in 2001 (which could include scientist expectations regarding the policy shock, as well as a host of other factors), led to a relative decline in US HESC output. The incremental though not complete recovery in US HESC output over the sample period, particularly between 2004 and 2007, suggests a capacity for adaptation within the US HESC research community. There are a number of possibilities to explain this recovery. We investigate variation in the impact of the policy shock and a few potential explanations for the recovery in the analyses that follow.

Table 4 compares the impact of the policy shock across three types of institutions: (a) elite US universities, (b) all other US institutions, and (c) institutions outside the United States. We base our definition of elite universities on those classified as being in the "Top 25" by the Center for Measuring University Performance at Arizona State University's 2006 Annual Report of University Research Rankings. (Our results are also robust to using the "Top 50" as defined by the same report.) Articles are classified into these institutional categories based on the addresses of their Reprint Author. The coefficients on HESC_YEAR_&_US_TOP_25 (HESC_YEAR_&_US_NOT_TOP_25) reflect the year-specific difference in citations between HESC articles with reprint authors in the US Top 25 universities (in other US institutions) relative to the omitted category, papers by reprint authors outside the US. The results suggest that HESC output by elite US universities declines significantly in 2002 and 2003, but recovers nearly completely thereafter. By contract, HESC research output by US-based reprint authors in other institutions declines beginning in 2001, recovering somewhat, though not completely (either in magnitude or statistical significance) by the end of the study period. These results are consistent with interview-based evidence we have assembled, which suggests that the constraints applied by the Bush Administration policy were more likely to be binding for those institutions for

which federal funding was a relatively more important source of funding, whereas those institutions that found it easy to obtain private funding were less negatively impacted by the policy.

We further examine a mechanism by which US-based HESC researchers may responded to the policy shock in Table 5. Specifically, we compare follow on research across three collaboration-location types: (a) papers with only US authors, (b) papers with US and non-US authors (i.e., those with international collaboration), and (c) papers with no US authors. The results suggest that the output of papers with only US-based authors declined more significantly than those of the other types following the policy shock. The output of HESC papers involving collaboration between US and non-US authors declined significantly in the year of the policy shock (2001), but are unaffected by the policy shock thereafter. These results suggest a behavioral response by scientists to the policy shock, similar in spirit to that observed by Murray (2009). These are limited results, but they are consistent with an explanation in which researchers (possibly those at the more resource-constrained institutions) in the United States collaborate with scientists outside the United States who may have access to resources more difficult to obtain in the United States.

VI. Discussion

In this paper, we present preliminary analyses of the impact of the Bush Administration Policy regarding Human Embryonic Stem Cell research on the competitiveness of US Stem Cell science in relation to that of the rest of the world. Our results suggest a modest relative decline in US-based work that builds on seminal hESC research. The timing of the shift, however, suggests that the decline in US competitiveness may have begun before the 2001 policy was announced. A number of other points are worth mention here: First, the decline in US leadership is, to some extent, evident in the control samples as well as the hESC treatment sample. In the latter years of the data, the rate of research in non-hESC stem cell research in the US is lower than that of the rest of the world. This pattern also obtains in RNAi and in the Nearest Neighbor articles. These results are consistent evidence documenting the broad-based globalization of scientific and technical capabilities (Furman et al, 2002; Furman & Hayes, 2006; Hayes, 2008).

Considering the policy restrictions placed on hESC research in the United States and the policy support provided in a number of other countries, including South Korea, Singapore, and Israel, the bigger surprise in our results may be the robustness of the United States hESC research community to modest perturbations of the system. US researchers at elite institutions were able to overcome federal funding limitations, principally, as our qualitative research suggests (and preliminary evidence from funding data shows), as a result of their ability to fund their research efforts with private sources of funding. The volume of research generated by researchers at institutions outside the elite circle did decline; however, there is evidence of valuable adaptation by US researchers. In particular, US-based researchers appear able to overcome funding difficulties by collaborating with researchers outside the United States. Although our results evidence a modest relative decline in U.S. competitiveness, we thus interpret the overall findings as consistent with a picture in which the regional institutions that support scientific competitiveness are robust and relatively enduring. Overall, the impact of the Bush Administration funding restrictions may be of second-order importance relative to issues such as the extent of overall funding for the NIH (Stephan, 2008).

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Table #1 – Descriptive Statistics

	Mean	Std. Dev.
Characteristics of Root articles *(n=699)*		
Publication Year	1997.4	4.96
US author on paper	63.7%	0.48
Non-US author on paper	51.4%	0.69
University author on paper	73.1%	0.44
Top 25 university author on paper	25.0%	0.43
Mean # *Annual* Citations received	15.40	33.67
Characteristics of Citing articles *(n=101,927)*		
Collaboration	59.8%	0.49
Mean # addresses	2.26	1.56
US author on paper	50.3%	0.50
Non-US author on paper	58.2%	0.49
University author on paper	77.3%	0.42
Top 25 University author on paper	13.4%	0.34

Table 2: Choosing the Control Sample

Differences in citation levels between potential sample articles; data from 1996-2000 (pre-shock)
Stacked Negative Binomial Regressions; IRRs reported; SEs not bootstrapped (& not adjusted to IRRs)
DV = Citations Received

	(2-1)	**(2-2)**	**(2-3)**	**(2-4)**
	Sample = Nearest Neighbor , hESC, Other Stem Cell, & RNAI articles	**Sample = hESC & Nearest Neighbor only**	**Sample = hESC & Other Stem Cell articles only**	**Sample = hESC & RNAI articles only**
HESC dummy	**2.987**	**3.581**	0.651	0.633
	(1.148)* **	**(1.408)*** **	(0.282)	(0.359)
Other Stem Cells dummy	**3.151**			
	(0.491)* **			
RNAI dummy	**4.698**			
	(1.359)* **			
Observations	1823	1516	297	104
Number of rart_num	604	501	95	34
Log Likelihood	-4505.62	-3469.55	-920.14	-326.70

All models include year FEs and article age FEs, which are not reported.

*Standard errors in parentheses / * significant at 10%; ** significant at 5%; *** significant at 1%*

Table 3: Core Results – Comparing US hESC Output to Rest-of-World (1996-2007)

Sample = hESC & RNAI only
Stacked Negative Binomial Regressions; IRRs reported; SEs not bootstrapped (& not adjusted to IRRs)

	(3-1)	(3-2)	(3-3)	(3-4)
	DV = Cites with Any US address (or No US Address)	**DV = Cites with US Reprint Author (or Not US Reprint Author)**	**DV = Cites with Any US address (or No US Address)**	**DV = Cites with US Reprint Author (or Not US Reprint Author)**
HESC_2001	1.132	1.081		
	(0.203)	(0.190)		
HESC_POST_2001	1.104	1.079		
	(0.129)	(0.125)		
HESC_2001_US	**0.491**	**0.488**		
	(0.117)* **	**(0.118)*** **		
HESC_POST_2001_US	**0.631**	**0.589**		
	(0.046)* **	**(0.045)*** **		
HESC_1998_US			0.801	0.855
			(0.335)	(0.361)
HESC_1999_US			0.864	0.635
			(0.294)	(0.221)
HESC_2000_US			1.021	0.891
			(0.274)	(0.247)
HESC_2001_US			**0.493**	**0.491**
			(0.108)* **	**(0.113)*** **
HESC_2002_US			**0.521**	**0.425**
			(0.095)* **	**(0.084)*** **
HESC_2003_US			**0.434**	**0.402**
			(0.072)* **	**(0.072)*** **
HESC_2004_US			**0.686**	**0.667**
			(0.098)* **	**(0.102)*** **
HESC_2005_US			**0.761**	**0.737**
			(0.115)*	**(0.119)***
HESC_2006_US			**0.704**	**0.659**
			(0.110) **	**(0.111)** **
HESC_2007_US			**0.749**	0.793
			(0.123)*	(0.140)
HESC_1998			**1.914**	1.507
			(0.682)*	(0.520)
HESC_1999			**1.764**	1.591
			(0.598)*	(0.507)
HESC_2001			**1.730**	1.343
			(0.471) **	(0.348)
HESC_2002			1.381	1.144
			(0.368)	(0.287)
HESC_2003			**1.625**	1.275
			(0.439)*	(0.327)
HESC_2004			**1.655**	1.287
			(0.435)*	(0.323)
HESC_2005			**1.902**	1.480
			(0.523) **	(0.389)
HESC_2006			**2.106**	**1.653**
			(0.582)* **	**(0.432)***
HESC_2007			**1.982**	1.474
			(0.564) **	(0.406)
HESC_2000			1.072	0.905
			(0.321)	(0.259)
Observations	1124	1124	1124	1124
Number of articles	67	67	67	67
Log Likelihood	-3202.34	-3187.15	-3177.63	-3161.86

Models also include Year FEs, Stack-specific Year FEs, Stack FEs, Article Age FEs, and Article FEs, as well as estimates based on a trivial number of observations in 1996 and 1997, which we do not report.

*Standard errors in parentheses / * significant at 10%; ** significant at 5%; *** significant at 1%*

Table 4: MECHANISM #1 –IMPACT BY UNIVERSITY QUALITY

Sample = hESC & RNAI only

DV = Cites by US-Top-25-University-RP-authors; Cites by US-Not-Top-25-University-RP-authors; Cites by Non-US-RP-authors

Triple Stacked Negative Binomial Regressions; IRRs reported; SEs not bootstrapped (& not adjusted to IRRs)

	(4-1)	**(4-2)**
HESC 2001	1.127 (0.180)	
HESC post-2001	1.141 (0.119)	
HESC 2001 (Top 25 University RP author)	0.703 (0.210)	
HESC post-2001 (Top 25 University RP author)	**0.670** **(0.062)*** **	
HESC 2001 (US - Not Top 25 University RP author)	**0.412** **(0.103)*** **	
HESC post-2001 (US - Not Top 25 University RP author)	**0.537** **(0.041)*** **	
HESC_1998 & US Top-25		0.946 (0.562)
HESC_1999 & US Top-25		0.786 (0.324)
HESC_2000 & US Top-25		0.876 (0.293)
HESC_2001 & US Top-25		0.699 (0.198)
HESC_2002 & US Top-25		**0.408** **(0.103)*** **
HESC_2003 & US Top-25		**0.409** **(0.091)*** **
HESC_2004 & US Top-25		0.871 (0.162)
HESC_2005 & US Top-25		0.826 (0.165)
HESC_2006 & US Top-25		0.835 (0.165)
HESC_2007 & US Top-25		0.993 (0.214)
HESC_1998 & US Not Top 25		0.788 (0.349)
HESC_1999 & US Not Top 25		**0.540** **(0.197)*** *
HESC_2000 & US Not Top 25		0.909 (0.253)
HESC_2001 & US Not Top 25		**0.415** **(0.097)*** **
HESC_2002 & US Not Top 25		**0.429** **(0.085)*** **
HESC_2003 & US Not Top 25		**0.388** **(0.070)*** **
HESC_2004 & US Not Top 25		**0.575** **(0.088)*** **
HESC_2005 & US Not Top 25		**0.656** **(0.105)*** **
HESC_2006 & US Not Top 25		**0.570** **(0.096)*** **
HESC_2007 & US Not Top 25		**0.648** **(0.114)** **
HESC_1998		**1.512** **(0.506)**
HESC_1999		**1.766** **(0.537)***
HESC_2000		0.997 (0.276)

HESC_2001		**1.508** **(0.385)**
HESC_2002		**1.297** **(0.322)**
HESC_2003		**1.461** **(0.368)**
HESC_2004		**1.444** **(0.357)**
HESC_2005		**1.698** **(0.436)****
HESC_2006		**1.878** **(0.485)****
HESC_2007		**1.715** **(0.456)****
Observations	1686	1686
Number of articles	67	67
Log Likelihood	-4268.57	-4232.29

Models include unreported fixed effects for Year, Article Age, Article, Stack, and Stack-Year, as well as estimates based on a trivial number of observations in 1996 and 1997.

*Standard errors in parentheses / * significant at 10%; ** significant at 5%; *** significant at 1%*

Table 5: MECHANISM #2 –IMPACT ON COLLABORATION

Sample = hESC & RNAI only

DV = Cites by Papers with Only US addresses (stack #1); Cites by papers with US address & Non-US addresses (stack #2); Cites by Papers with No US addresses (stack #3)

Triple Stacked Negative Binomial Regressions; IRRs reported; SEs not bootstrapped (& not adjusted to IRRs)

	(5-1)	**(5-2)**
HESC 2001	1.126	
	(0.178)	
HESC POST 2001	1.163	
	(0.122)	
HESC 2001 US_ONLY	**0.570**	
	(0.123)* **	
HESC POST 2001 US_ONLY	**0.532**	
	(0.037)* **	
HESC_2001 & US-NON-US COLLAB	**0.265**	
	(0.117)* **	
HESC_POST 2001 & US-NON-US COLLAB	0.993	
	(0.094)	
HESC 1998 US-Only		0.744
		(0.308)
HESC 1999 US-Only		0.785
		(0.247)
HESC 2000 US-Only		0.976
		(0.242)
HESC 2001 US-Only		**0.578**
		(0.114)* **
HESC 2002 US-Only		**0.410**
		(0.073)* **
HESC 2003 US-Only		**0.350**
		(0.056)* **
HESC 2004 US-Only		**0.626**
		(0.084)* **
HESC 2005 US-Only		**0.681**
		(0.098)* **
HESC 2006 US-Only		**0.621**
		(0.093)* **
HESC 2007 US-Only		**0.639**
		(0.100)* **
HESC 1998 US-Non-US Collaboration		0.985
		(0.512)
HESC 1999 US-Non-US Collaboration		1.178
		(0.437)
HESC 2000 US-Non-US Collaboration		0.838
		(0.296)
HESC 2001 US-Non-US Collaboration		**0.242**
		(0.104)* **
HESC 2002 US-Non-US Collaboration		0.979
		(0.219)
HESC 2003 US-Non-US Collaboration		0.801
		(0.168)
HESC 2004 US-Non-US Collaboration		0.809
		(0.153)
HESC 2005 US-Non-US Collaboration		1.093
		(0.196)
HESC 2006 US-Non-US Collaboration		1.044
		(0.191)
HESC 2007 US-Non-US Collaboration		1.063
		(0.203)
HESC_1998		1.864
		(0.628)*
HESC_1999		1.856
		(0.588)*

HESC_2000		1.165
		(0.339)
HESC_2001		1.789
		(0.480)**
HESC_2002		1.522
		(0.406)
HESC_2003		1.793
		(0.483)**
HESC_2004		1.798
		(0.474)**
HESC_2005		2.034
		(0.556)***
HESC_2006		2.257
		(0.623)***
HESC_2007		2.167
		(0.609)***
Observations	1686	1686
Number of articles	67	67
Log Likelihood	-4221.59	-4186.15

Models include unreported fixed effects for Year, Article Age, Article, Stack, and Stack-Year, as well as estimates based on a trivial number of observations in 1996 and 1997.

*Standard errors in parentheses / * significant at 10%; ** significant at 5%; *** significant at 1%*

Figure #1 – Citing articles by year

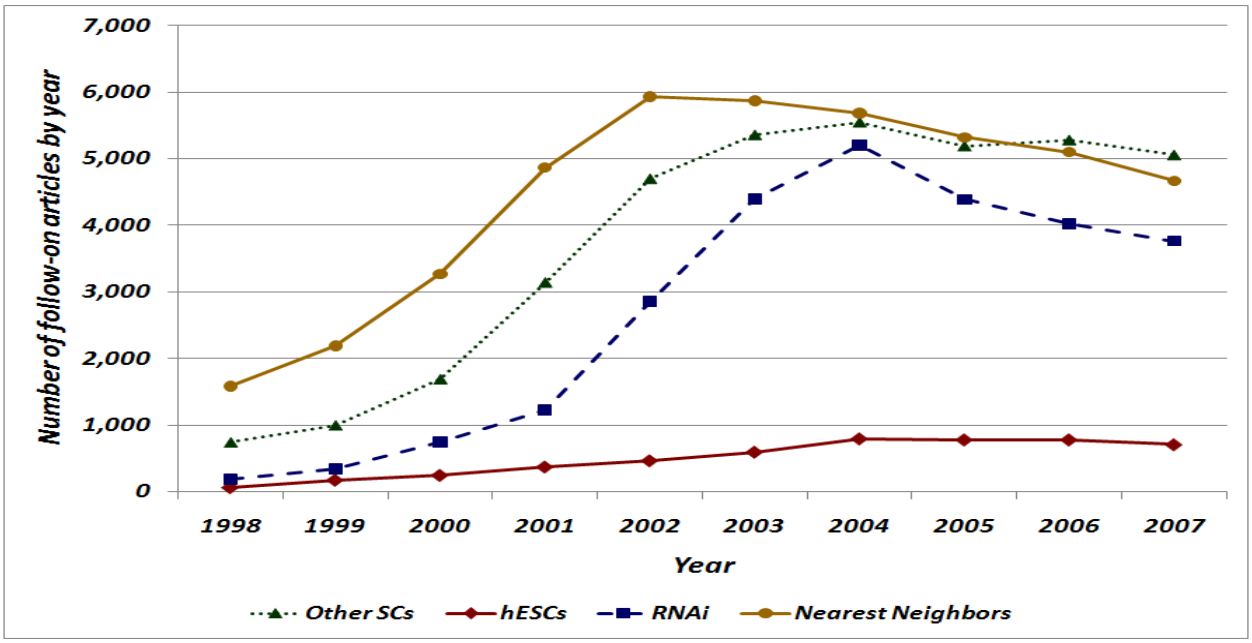
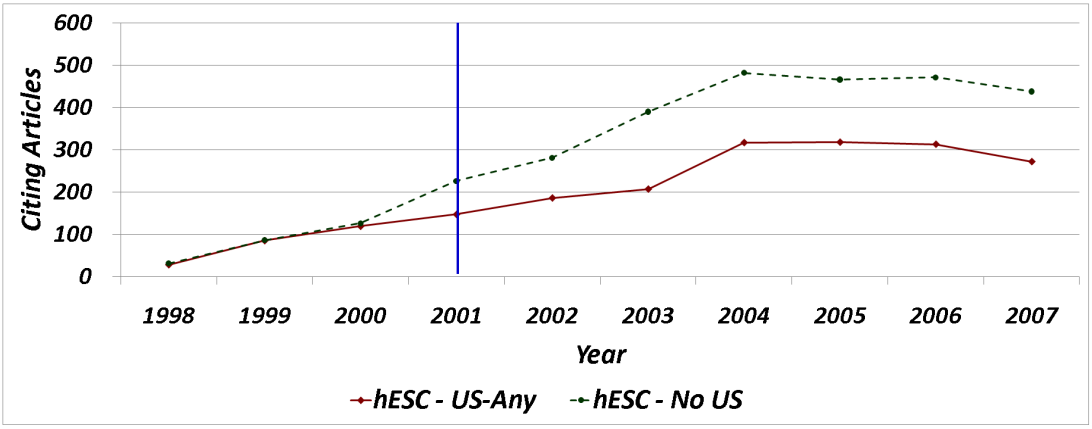
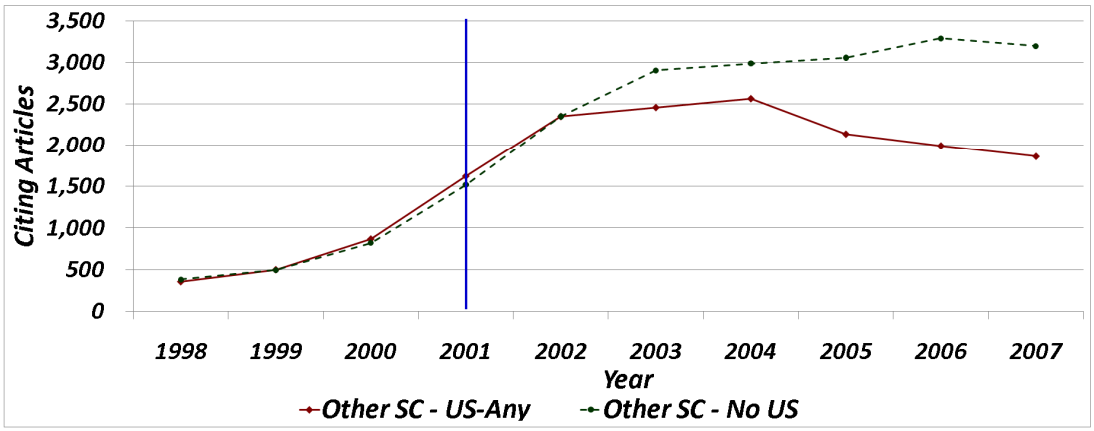
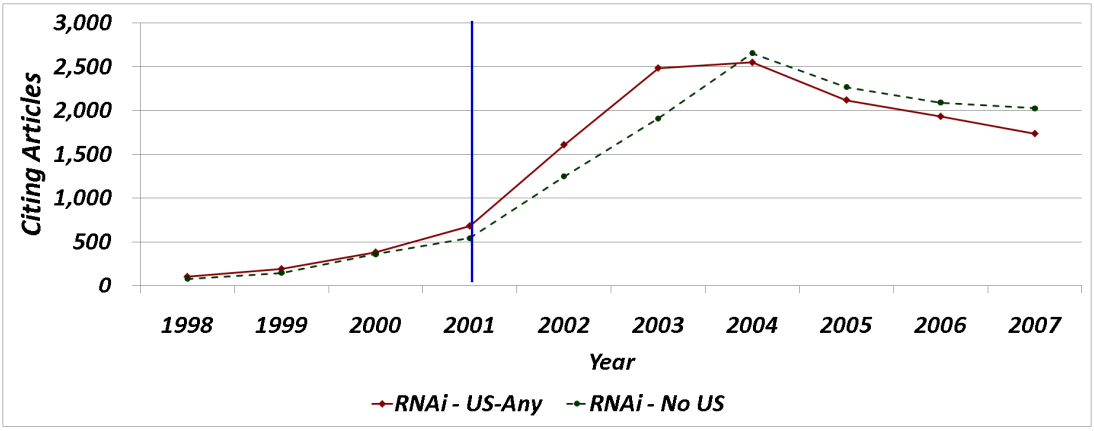
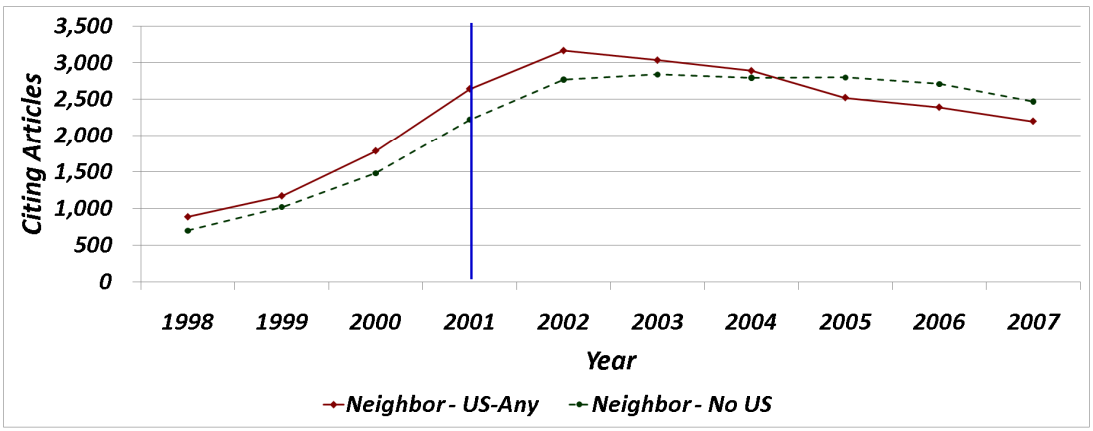


Figure #2 – Citing articles by publication type and year, US vs Non-US Reprint Authors









APPENDIX TABLE 1
US Stem Cell Research Policy in international comparison
(reproduced from Beardsley, 2005)

US

- Number of published hESC lines: 46
- Production of new lines: Legal, but prohibited with federal funds
- Therapeutic cloning: Legality varies from state to state
- Federal government funding: About $550m for all stem cell research ($24m for hESC)
- Private funding: About $200m
- Public funding at state level:
  California: $3bn over 10 years; New Jersey: $11.5m (another $380m proposed); Wisconsin: $375m proposed; Illinois: $1bn proposed; Connecticut: $20m proposed
- Federal government allows its funds to be used only on the 22 available hESC lines created before August 2001.

EU

- Production of new hESC lines: Permitted from unused IVF embryos where legal in member nations
- Therapeutic cloning: Prohibited
- Funding: $170m on stem cells over the past three years (only $650,000 for hESC research)
- Status in some member nations:
  - France: Creation of hESC lines from IVF embryos legal as of October 2004; public funding is $4m
  - Germany: Only work on hESC lines predating 2002 is legal; public funding is $4m
  - Finland: Permits research with IVF embryos; public funding is $5m
  - Italy: June 12 referendum will consider permitting IVF embryo research; public funding is $6m
  - ***EU will not increase funding for hESC projects despite a doubling of the total research budget.***

SWEDEN

- Number of published hESC lines: 8
- Production of new lines: Legal
- Therapeutic cloning: Legal as of April 2005
- Number of researchers: 400
- Government funding: $10m-$15m
- Private funding: Cellartis and NeuroNova, the two largest stem cell research companies in Sweden, contribute the bulk of the $35m spent annually there.
- Cellartis, the single largest source of defined hESC lines in the world, maintains more than 30--two of which are approved by the US National Institutes of Health.

UK

- Number of published hESC lines: 3
- Production of new lines: Legal
- Therapeutic cloning: Legal
- Government funding: About $80m
- Private funding: $15m-$20m:
  - The Wellcome Trust alone has spent $12m annually since 2002.
- First licence for human ES cell research was granted in 1996.
- The Human Fertilisation and Embryology Act of 1990 allows the UK to fund hESC research flexibly.
- UK's first licence for human cloning research granted in 2004. Its recipients announced in May 2005 the country's first cloned human embryo.

BRAZIL

- Production of new hESC lines: As of March, legal from IVF embryos at least 3 years old
- Therapeutic cloning: Banned
- Government funding: $4.5m annually planned, allocated by the Health Ministry and the Science and Technology Ministry

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SOUTH KOREA

- Number of published hESC lines: 29
- Production of new lines: Permitted with case approval from Ministry of Health
- Therapeutic cloning: Permitted with case approval from Ministry of Health
- Number of researchers: 300-400
- Government funding: About $10m
- Private funding: About $50m

SINGAPORE

- Number of published hESC lines: 1
- Production of new lines: Legal, if embryos are destroyed within 14 days
- Therapeutic cloning: Legal, as above
- Number of researchers: About 150, in industrial and academic settings
- Academic spending: About $10m, from public and private sources
- Industrial spending: About $10 million
- A pending government proposal would spend $60m over the next four years.

ISRAEL

- Number of published hESC lines: 1
- Production of new lines: Legal
- Therapeutic cloning: Legal
- Government spending: About $5m
- Private spending: $15m-$30m
- ***Israeli scientists led one of the research teams that first isolated hES cells. They were also the first to show that hES cells could be changed into heart cells, and to show that hES cells can integrate with tissues.***

CHINA

- Production of new hESC lines: Legal
- Therapeutic cloning: Legal
- Number of researchers: 300-400
- Public and private funding: About $40m
- The journal *Nature* reports that "China has probably the most liberal environment for embryo research in the world", with little public opposition to such studies. No laws govern stem cell research, but the recommendations of the Ministry of Health endorse it.

AUSTRALIA

- Number of published hESC lines: 1
- Production of new lines: Conditionally legal
- Therapeutic cloning: Banned
- Number of researchers: 200-250
- Government funding: The Australian Stem Cell Centre has $90m to spend through 2011.
