**Academic Entrepreneurship and State Science Policy: Lessons from State Support for Stem Cell Research**

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Final Report

This project had led, thus far, to the development of four academic papers. The first of these was published in *Nature Biotechnology* and the second was published in *Cell Stem Cell*. The third paper has recently been submitted to a peer-reviewed journal, while the fourth is currently being revised in preparation for submission to a peer-reviewed journal later in the year. In addition, this project led to the development of a new website (www.stemcellstates.net) that provides public access to information on state stem cell grants awarded between 2005 and 2009.

Copies of the two published papers and working drafts of the two other papers are attached to this report.

informed debate regarding stem cell tourism and for protecting potentially vulnerable individuals.

*Note: Supplementary information is available on the Nature Biotechnology website.*

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All authors contributed to this work. T.C., C.R. and A.Z. conceived the research concept. C.R. collected the data. C.R. and A.Z. coordinated the coding of the data. A.Z. and T.C. prepared the draft manuscript and M.N. helped with interpretation and with theoretical analysis. All authors discussed the results and implications and commented on the manuscript at all stages.

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1. Qui, J. *Nat. Biotechnol.* **27**, 790–792 (2009)
2. Lindvall, O. & Hyun, I. *Science* **324**, 1664–1665 (2009).
3. Lau, D. *et al. Cell Stem Cell* **3**, 591–594 (2008).
4. Regenberg, A., Hutchinson, L., Schanker, B. & Matthews, D. *Stem Cells* **27**, 2312–2319 (2009).
5. Ryan, K., Sanders, A., Wang, D. & Levine, A. *Regenerative Med.* **5**, 27–33 (2010).
6. Amariglio, N. *et al. PLoS Med* **6**, e1000029 (2009).
7. http://www.isscr.org/clinical_trans/pdfs/ISSCRGLClinicalTrans.pdf
8. MacReady, N. *Lancet Oncol.* **10**, 317–318 (2009).
9. Kiatpongsan, S. & Sipp, D. *Nat. Rep. Stem Cells* published online 3 December, 2008, doi:10.1038/stemcells.2008.151 (2008).
10. Zarzeczny, A. & Caulfield, T. *Am. J. Bioeth.* **10**, 1–13 (2010).
11. Iyengar, S. & Kinder, D. *News that Matters: Television and American Public Opinion*. (University of Chicago Press, Chicago, IL, USA, 1987).
12. Nisbet, M.C. & Mooney, C. *Science*, **316**, 56 (2007).
13. Creasy, G. & Scott, C. *Nat. Biotechnol.* **27**, 21–22 (2009).

# Tracking and assessing the rise of state-funded stem cell research

**To the Editor:**

The editorial in your October issue[1] highlights the legal challenges to new guidelines issued by the US National Institutes of Health (NIH) in July 2009 for the federal funding of human embryonic stem cell (hESC) research. In the eight-year period preceding these most recent NIH guidelines, only a small number of cell lines could be studied with federal funds. During this time, six states—California, Connecticut, Illinois, Maryland, New Jersey and New York—took on a role typically played by the NIH and created funding programs specifically designed to support stem cell research, including hESC research. These are not the first state programs to fund scientific research but their commitment to basic research is atypical, as most state science and technology programs have focused on science closer to commercialization[2]. Although the state stem cell programs differ, they each share at least two goals: advancing promising science, including research not eligible for federal funding during the Bush Administration, and returning economic benefits to their state.

In this article, we report an initial attempt to track and assess the impact of these state funding programs. Existing work on state stem cell policy has focused on identifying policy differences between various jurisdictions[3,4], assessing the impact of state decisions to support or restrict hESC science[5–7] and examining the role of states in governing controversial science[8,9]. The analysis reported here extends this literature though use of a novel data set of the grants these states have awarded. These data provide insight into how states have prioritized their funding, including the extent to which they have supported hESC research generally and hESC research not eligible for federal funding during the Bush Administration more specifically, as well as the extent to which these states have drawn new scientists into the field. The underlying data have been publicly released on a new website (http://www.stemcellstates.net) designed to facilitate additional analysis of state-funded stem cell science and improve public awareness of these programs. Given ongoing legal uncertainties surrounding federal funding of hESC research and the likelihood that voters, at least in California, will be asked to approve additional state stem cell funding in the future, understanding and evaluating the effects of state-funded stem cell research is both timely and useful.

The database that forms the basis for the analysis described here contains the title, principal investigator, institution, abstract and amount for each grant awarded by the agency overseeing stem cell research funding in these six states (**Supplementary Methods**). In all, between December 2005 when New Jersey awarded the first state stem cell grants and the end of 2009, the six stem cell states awarded nearly 750 grants totaling just over $1.25 billion. The scale of these programs varies substantially, ranging from the roughly $15 million awarded by Illinois and New Jersey to the $1.02 billion awarded by California. On a *per capita* basis, funding awarded through the end of 2009 ranges from just over $1 in Illinois to nearly $28 in California (**Table 1**).

States funding stem cell research can choose to support several different activities, ranging from investigator-initiated research grants to new facilities to workforce development. To investigate how states prioritized these various types of funding, each grant was classified by its primary purpose (**Supplementary Methods**). Research grants and support for scientific infrastructure were the two largest categories, accounting for more than 90% of all state stem cell funding (**Table 1**). The infrastructure category was dominated by the $271 million California awarded for the construction of 12 major stem cell research facilities, although several other states also dedicated a substantial portion of their funding to infrastructure, such as shared equipment or core laboratories. In contrast to supporting basic investigator-initiated research, spending money on infrastructure is a classic state economic development approach, but, in these cases, spending was motivated, at least in part, by the need to create separate laboratories to facilitate research on unapproved hESC lines.

The restrictions on federal funding for hESC research instituted by former President George W. Bush were an important rationale behind the adoption of most state stem cell programs, yet it is not clear to what extent state programs focused on hESC research generally or hESC research not eligible for federal funding more specifically. To address these questions, each research grant awarded through the end of 2009 was analyzed to assess if funded research used hESCs and, if applicable, appeared ineligible for federal funding under the Bush Administration rules (**Supplementary Methods**). The percentage of grants that supported hESC

**Table 1 The scale and prioritization of state stem cell funding programs[a]**

| | State program | | | | | |
|---|---|---|---|---|---|---|
| **Grants and funding** | **California** | **Connecticut** | **Illinois** | **Maryland** | **New Jersey** | **New York** |
| Year first grants awarded | 2006 | 2006 | 2006 | 2007 | 2005 | 2008 |
| Total funding pledged/time period | $3 billlion/ 10 years | $100 million/ 10 years | N/A | N/A | N/A | $600 million/ 11 years |
| Number of grants awarded | 329 | 69 | 17 | 140 | 35 | 158 |
| Funding awarded ($ millions) | 1,024 | 40 | 15 | 54 | 15 | 121 |
| Funding *per capita*[b]($) | 28 | 11 | 1 | 10 | 2 | 6 |
| **Research prioritization[c]** | | | | | | |
| Percentage of funding for research | 58% | 76% | 100% | 93% | 64% | 61% |
| Percentage of funding for infrastructure | 31% | 24% | 0% | 0% | 36% | 34% |
| Percentage of grants for hESC research | 75% | 97% | 35% | 42% | 21% | 21% |
| Percentage of grants clearly not NIH eligible | 18% | 16% | 12% | 3% | 6% | 0% |
| **NIH funding status of state grant recipients[d]** | | | | | | |
| Percentage of state PIs without NIH stem cell funding | 42% | 61% | 65% | 71% | 61% | 49% |
| Percentage of state hESC PIs without NIH hESC funding | 77% | 91% | 67% | 79% | 100% | 66% |

[a]Includes grants awarded through the end of 2009. [b]Per capita funding based on state population from US Census Bureau 2009 Population Estimates. [c]hESC prioritization analysis includes only grants with a primary purpose of research. [d]NIH funding was examined from FY2005 to present. PIs, principal investigators.



research varied substantially among these states (**Table 1**). Large majorities of the research grants awarded in Connecticut and California supported studies involving hESCs, whereas only a minority of grants supported hESC research in the other states. These disparities likely reflect differences in the types of stem cell scientists present in these states as well as priorities of the various state funding bodies.

Only a subset of grants for hESC research supported science that was clearly ineligible for NIH funding during the Bush Administration. California and Connecticut focused the most on this sort of research—which typically involved the derivation of new hESC lines or the use of newer unapproved cell lines—but even in these states fewer than a fifth of grants went to clearly ineligible research. Many scientists indicated plans to use existing hESC lines but did not specify which lines they planned to use. Given evidence that a handful of approved cell lines account for a large proportion of the hESC lines actually distributed to scientists and an even larger share of published literature[10], most of these projects probably used approved hESC lines. In some cases, however, scientists may have chosen to use ineligible cell lines but not clearly indicated these plans. Thus, the share of grants reported here as clearly ineligible for NIH funding should be viewed as a lower bound on the amount of research each state funded that was ineligible for federal funding.

Several factors could explain the relatively small share of grants that went toward clearly ineligible research. Some scientists who wished to pursue this research may have been unable to access the raw materials or acquire the intellectual property rights required to do so. Alternatively, these findings could simply reflect scientific interest. The discovery of induced pluripotent stem cells[11] may, for instance, have reduced scientific interest in the derivation of new hESC lines. Finally, these findings may reflect a preference on the part of scientists to use well-established and well-studied hESC lines. This last explanation may be particularly relevant for new scientists entering the field of hESC research, as using recognized cell lines may give their initial research efforts greater credibility.

In addition to supporting research not eligible for federal funding, focused state programs might serve to draw new scientists into the field of stem cell research. To evaluate this potential impact, the recent NIH funding portfolio of each scientist receiving a state stem cell grant with a primary purpose of research was examined (**Supplementary Methods**). Although most scientists had received NIH funding, a substantial number (ranging from 42% in California to 71% in Maryland) had not received NIH funding for stem cell research (**Table 1**). Similar, but more pronounced, results are observed when the NIH funding portfolio of scientists receiving state funding for hESC research is examined, as only a small minority of these scientists also had NIH grants supporting hESC research. Given the importance of NIH funding for biomedical research in the United States, these results suggest that the existence of state funding programs for stem cell research has drawn many new scientists into the field of stem cell research, or at least encouraged scientists to consider how stem cell research could complement their existing research programs.

These data also permit a more nuanced comparison between state stem cell funding and NIH stem cell funding than has previously been available (**Fig. 1**). Total state funding for all types of stem cell research has risen rapidly since grants were first awarded in 2005, but states still spend less than half of what the NIH spends each year on stem cell research. The situation is different for hESC research, as state funding for hESC research grants first exceeded comparable NIH funding in 2007 and equaled or exceeded it in 2008 and 2009.

Considered together, these data and analyses indicate that state funding for stem cell research has grown into a substantial enterprise that has provided funding on a scale comparable to the NIH. Although states vary in the degree to which they have focused on hESC research, as a whole, state funding for hESC research has been substantial, exceeding, in cumulative terms, NIH funding for this research between 2005 and 2009. Most state hESC funding appears to have supported research also eligible for federal funding during the Bush Administration. This finding is surprising, given the explicit intent of several state programs to preferentially support science not eligible for federal funding, but likely reflects the nature of the grant proposals state agencies received, particularly given the number of grants states awarded to scientists relatively new to the field of hESC research.

In the light of the recent change in federal stem cell policy and the ongoing economic downturn, the future of state

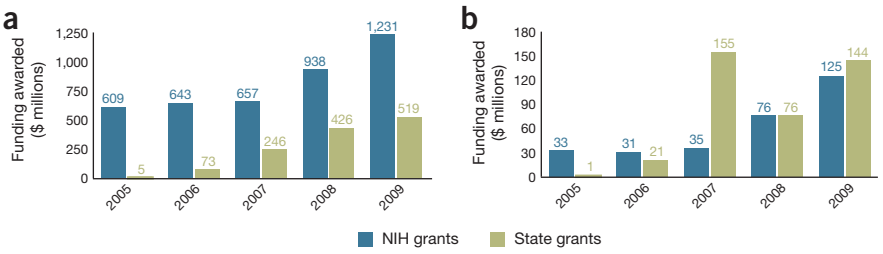


**Figure 1** Comparing state and NIH stem cell funding. (**a**) Total amount of all NIH stem cell grants and all stem cell grants awarded by the six states. (**b**) Total amount of all NIH and state hESC research grants. Only grants with a primary purpose of research are included. State funding is by calendar year. NIH funding is by fiscal year.

stem cell programs, as well as similar state programs supporting other areas of science, is uncertain. The analysis here suggests that state stem cell funding programs are sufficiently large and established that simply ending the programs, at least in the absence of substantial investment in the field by other funding sources, could have deleterious effects. Such action would fail to capitalize on the initial efforts of scientists who have been drawn to the field of stem cell research by state programs and leave many stem cell scientists suddenly searching for funding to continue their research.

Large-scale state funding for basic research is a relatively new phenomenon, and many questions remain about the impact of these programs on the development of scientific fields and the careers of scientists. The influence of state funding programs on the distribution of research publications, the acquisition of future external funding, the creation of new companies and the translation of basic research into medical practice, for instance, are important unanswered questions. Similarly, comparing state funding programs with federal funding programs as well as foundations could offer new insight into the relative priorities of different funding bodies and the extent to which their funding portfolios overlap or are distinct. We hope the analysis presented here and the public release of the underlying database will inspire additional analysis of state science funding programs generally and state-funded stem cell science in particular.

*Note: Supplementary information is available on the Nature Biotechnology website.*

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1. Anonymous. *Nat. Biotechnol.* **28**, 987 (2010).
2. Plosila, W.H. *Econ. Dev. Q.* **18**, 113–126 (2004).
3. Stayn, S. *BNA Med. Law Pol. Rep.* **5**, 718–725 (2006).
4. Lomax, G. & Stayn, S. *BNA Med. Law Pol. Rep.* **7**, 695–698 (2008).
5. Levine, A.D. *Public Adm. Rev.* **68**, 681–694 (2008).
6. Levine, A.D. *Nat. Biotechnol.* **24**, 865–866 (2006).
7. McCormick, J.B., Owen-Smith, J. & Scott, C.T. *Cell Stem Cell* **4**, 107–110 (2009).
8. Fossett, J.W., Ouellette, A.R., Philpott, S., Magnus, D. & Mcgee, G. *Hastings Cent. Rep.* **37**, 24–35 (2007).
9. Mintrom, M. *Publius* **39**, 606–631 (2009).
10. Scott, C.T., McCormick, J.B. & Owen-Smith, J. *Nat. Biotechnol.* **27**, 696–697 (2009).
11. Takahashi, K. & Yamanaka, S. *Cell* **126**, 663–676 (2006).

# Towards a knowledge-based Human Protein Atlas

**To the Editor:**

We report on the launch of version 7 of the Human Protein Atlas with subcellular localization data and expression data for all major human tissues and organs. A milestone has been achieved with the inclusion of expression data for >50% of the human protein-coding genes. The main new feature of the release is an attempt towards a knowledge-based portal, including an annotated protein expression feature for protein targets analyzed with two or more antibodies, and the establishment of the main subcellular localization of protein targets.

In 2005, the first version of the Human Protein Atlas (http://www.proteinatlas.org/) was released with protein profile data based on immunohistochemistry on tissue microarrays covering 48 different human tissues and organs, including kidney, liver, heart, brain and pancreas[1]. The first version included data from 718 antibodies corresponding to 650 human protein-coding genes. High-resolution images were published along with annotation of the presence or absence of a particular protein target in all represented tissues. The 2005 Human Protein Atlas also contained information regarding protein profiles from 20 different types of human cancer, including breast, colorectal, lung and prostate cancer. The data in the portal were made available freely both for academia and industry without restrictions or password protection. In 2007, the portal was extended to also include subcellular profiling data[2] using immunofluorescence-based confocal microscopy in three human cancer cell lines of different (glial, mesenchymal and epithelial) origin. More data have been added to the portal every year since the first release[3] and version 6, launched in March 2010, contained 11,274 antibodies corresponding to 8,489 protein-coding genes. This entire effort depends heavily on the availability of good quality antibodies, and recently a community-based portal, Antibodypedia (http://www.antibodypedia.org/), has been launched to allow antibodies from different providers to be listed and compared[4,5], although the main source of information so far comes from the providers' own validation data, not by independent third-party users. At present, the Antibodypedia contains close to 100,000 antibodies, corresponding to >70% of the protein-coding genes in humans.

An important objective has now been reached with the inclusion of 10,118 protein-coding genes corresponding to >50% of the 19,559 human entries as defined by UniProt, including only entries with evidence at protein

Cell Stem Cell
Forum

# Policy Uncertainty and the Conduct of Stem Cell Research

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A survey of U.S. stem cell scientists shows that uncertainty following the legal challenge to the Obama Administration's hESC research policy has negative scientific and economic impacts and affects a range of stem cell scientists, not just those working with hESCs. The international implications of these results are also discussed.

One consequence of the ethical controversy inspired by human embryonic stem cell (hESC) research has been an atypically uncertain policy environment. For stem cell scientists in the United States and, in particular, those scientists working with hESCs, frequent policy changes have made the years since these cells were first derived (Thomson et al., 1998) something of a roller coaster. Similar challenges have faced stem cell scientists around the world, as numerous countries in Europe, South America, and Asia, as well as the European Union as a whole, have engaged in protracted debates over stem cell policy (see Gottweis et al., 2009 for a discussion of global stem cell policy debates).

In the United States, scientists have faced several hESC policy changes (reviewed in Gottweis, 2010). First, following a legal review, the Clinton Administration adopted a policy in August 2000 that permitted federal funding of hESC research, but not the derivation of new hESC lines (65 Fed. Reg. 51,975). Before any grants could be funded, however, the Bush Administration put this policy on hold and President Bush announced a new policy in August 2001 limiting federal funding to research using hESC lines derived prior to the date of his speech. Although this policy remained in place for nearly eight years, uncertainty persisted. Congress, for instance, twice passed legislation to overturn the temporal restrictions central to the policy, yet President Bush vetoed both these bills.

During the Bush Administration, stem cell policy was frequently addressed at the state level with some states supporting stem cell research and others restricting it, creating one of the many heterogeneous "policy patchworks" that have become typical of the field, even on an international scale (Caulfield et al., 2009). Supportive state policies aimed to provide a workaround for scientists affected by federal funding restrictions, yet even these programs were plagued by uncertainty, as legal challenges and state budget problems hindered their implementation. California's stem cell program, for instance, was delayed for nearly 2 and a half years by litigation, causing difficulties for scientists considering starting new stem cell projects or moving to new institutions. California's funding is now flowing and the state has awarded more than $1 billion, yet the future of this program remains uncertain as the end of its 10 year term approaches (see Karmali et al., 2010 for a recent review of state stem cell funding).

More recently, at the federal level, the Obama Administration adopted a new stem cell research policy in July 2009 (74 Fed. Reg. 32,170), only to throw the field into chaos when scientists realized the limited number of hESC lines that had been eligible for federal funding during the Bush Administration were no longer on the approved list and needed to be reevaluated. Key hESC lines, including the two most heavily studied lines, have since been added to the registry, but not before months of uncertainty during which some scientists were placed in the awkward position of choosing to delay projects until their preferred cell lines were approved or switching to other lines and facing the delays associated with reoptimizing experimental protocols.

A legal challenge filed following the promulgation of the Obama Administration's policy adds additional uncertainty to the field. This challenge claims that the Obama Administration's policy violates the Dickey-Wicker Amendment, a rider added to the Department of Health and Human Services appropriations bill each year since fiscal year 1996. This lawsuit received minimal attention from the scientific community until August 23, 2010 when U.S. District Court Judge Royce Lamberth granted the plaintiffs' request for a preliminary injunction barring implementation of the Obama Administration's policy pending the outcome of the court case. This ruling led the NIH to suspend funding and review of pending hESC research proposals as well as evaluation of new hESC lines (see Gottweis, 2010 for a general discussion, U.S. NIH Notice NOT-OD-10-126 for details). The Obama Administration appealed and on September 9, 2010 the U.S. Court of Appeals for the District of Columbia enjoined the preliminary injunction, allowing the NIH to resume funding hESC research while the case proceeded. Both the ultimate outcome of this case and the length of time before the outcome is known are uncertain, placing some scientists in the situation of checking the news each day to determine the legal status of their research (Harmon, 2010).

Although the ultimate outcome of the litigation will depend on statutory interpretation of the Dickey-Wicker Amendment, much of the legal wrangling thus far has focused on the issue of potential harm to stem cell scientists associated with these policy changes. In his ruling announcing the injunction, Judge Lamberth concluded that the plaintiffs—two adult stem cell scientists—would "suffer irreparable injury in the absence of the

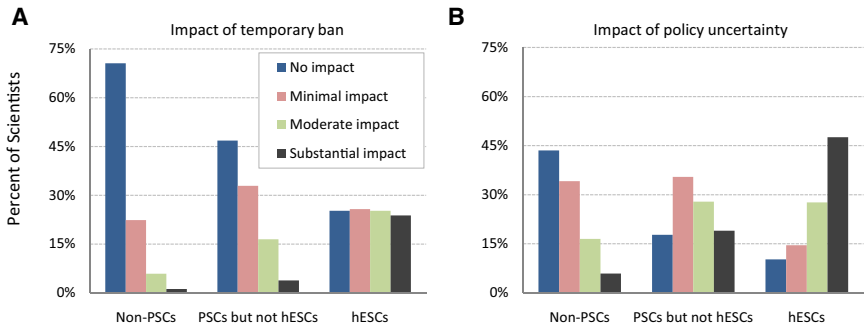


**Figure 1. Impact of the Temporary Funding Ban and Ongoing Policy Uncertainty by Type of Stem Cells Used**

Stem cell scientists' views of the impact of the temporary ban on federal funding on their research (A) and the impact of the ongoing policy uncertainty on their future research plans (B) are shown, grouped by the type of stem cells scientists use in their research. n = 370 respondents (85 who use only nonpluripotent stem cells [Non-PSCs], 79 who use pluripotent stem cells but not hESCs [PSCs but not hESCs], and 206 who use hESCs). Respondents were provided with a brief description of the ongoing legal proceedings and then asked about the impact of the temporary funding ban on their research and ongoing policy uncertainty on their research plans. Chi-square testing found that differences among these groups were statistically significant (ban: chi-statistic = 75.1, df = 6, p = $3.6e^{-14}$; policy uncertainty: chi-statistic = 91.7, df = 6, p = $1.3e^{-17}$). See Table S1 for text of the survey questions.

injunction'' due to increased competition for limited federal research funding, while the ruling ''would not seriously harm ESC researchers because the injunction would simply preserve the status quo and would not interfere with their ability to obtain private funding for their research'' (U.S. District Court for the District of Columbia). In its appeal, the Obama Administration disagreed, arguing that the harm to the plaintiffs was speculative and ''cannot outweigh the disruption or ruin of research into promising treatments for the most debilitating illnesses and injuries'' caused by the preliminary injunction (U.S. Court of Appeals for the D.C. Circuit).

Despite this ongoing legal debate in the United States and the prevalence of policy uncertainty in this field around the world, relatively few empirical studies address these issues. In order to begin to fill this gap, this Forum reports responses from 370 individuals who participated in a survey of U.S. stem cell scientists in November 2010 and assesses the reported impact of the preliminary injunction and ongoing uncertainty about the future of federal funding for hESC research on their work (see Supplemental Information available online for details of survey design and analysis strategies employed). These data show that both Judge Lamberth's ruling and the ongoing uncertainty have had a substantial impact on stem cell scientists and illustrate that this impact extends beyond hESC scientists to affect, often negatively, a larger group of stem cell scientists.

Scientists reported the impact of the temporary funding ban and ongoing policy uncertainty on a four-point scale ranging from no impact to substantial impact and scientists who indicated that they experienced an impact were asked to briefly explain the impact (see Table S1 for the text of the survey questions). Figure 1 shows the responses for these questions for three groups: (1) Scientists who use hESCs in their research; (2) scientists who do not use hESCS but do use human induced pluripotent stem cells (IPSCs), nonhuman embryonic stem cells, or non-human IPSCs in their research; and (3) scientists who use only nonpluripotent stem cells in their research. Scientists working with hESCs were most likely to report being impacted by the temporary ban. Approximately 75% of these scientists reported an impact and 24% reported a substantial impact. In addition, 41% of stem cell scientists not working with hESCs reported that the temporary ban impacted their research, and 13% of these respondents indicated this impact was either moderate or substantial. Notably, among the 50 non-hESC scientists who indicated they were impacted by the ban and answered a free-text question describing this impact, negative impacts were much more common than the positive impact envisioned by Judge Lamberth in his ruling. In total, 45 of these non-hESC scientist respondents described negative impacts (e.g., hindered collaborations, blocked review of funding applications, and challenges recruiting), two described positive impacts (enhanced attractiveness and fundability of non-hESC research), and three could not be classified as clearly positive or negative.

The impact of ongoing policy uncertainty on stem cell scientists' research plans was more substantial than the impact of the temporary funding ban. Just under half of the hESC scientists who participated in the survey indicated that this uncertainty has a substantial impact on their research plans and another 28% of these scientists said this uncertainty has a moderate impact. In addition, 47% of scientists who worked with pluripotent stem cells, but not hESCs, and 22% of scientists working only with nonpluripotent stem cells also indicated that this uncertainty has either a moderate or substantial impact on their research plans.

To better understand the nature of these impacts, the responses of the 235 scientists who provided a free-text description of the impact of policy uncertainty on their research plans were analyzed (see Supplemental Information for details). Table 1 shows the ten most frequent impacts mentioned by these respondents (see Table S2 for example responses for each impact). Many of these reported impacts affected the type or quality of science that these scientists conducted, by, for instance, changing the types of stem cells they used in their research. The single most common impact—mentioned by 50 respondents—was delaying plans to begin hESC research or start a new hESC research project. Over 80% of the respondents reporting this impact did not currently work with hESCs but were considering transitioning their research to use these cells. In addition, 34 scientists identified transitioning away from or reducing reliance on hESCs as an impact of the ongoing uncertainty. Not all of these scientists specified the type of research to which they were transitioning, but 13 indicated that they were shifting their research to human IPSCs or nonhuman embryonic stem cells, even if, as might be the case, these were less appropriate tools for their specific research questions.

**Table 1. Impacts of Ongoing Policy Uncertainty on Stem Cell Scientists' Future Research Plans**

| Impact | Number of Respondents | Percent of Impacts |
|---|---|---|
| Delay plans to begin hESC research or new hESC project | 50 | 18% |
| Impede ongoing research | 44 | 16% |
| Limit future funding options | 37 | 13% |
| Transition away from or reduce reliance on hESCs | 34 | 12% |
| Disrupt long-term planning (e.g., hiring decisions) | 24 | 9% |
| Adopt suboptimal research designs | 19 | 7% |
| Delay or abandon NIH proposals | 14 | 5% |
| Alter NIH proposals to avoid hESC research | 11 | 4% |
| Consider relocation | 9 | 3% |
| Disrupt collaborations | 9 | 3% |

The ten most common impacts reported by stem cell scientists are shown, based on qualitative analysis of free-text responses describing the impact of ongoing policy uncertainty on scientists' research plans. See Table S2 for example responses for each impact.

Forty-four scientists indicated that policy uncertainty was impeding ongoing research. This impact took several forms, including increased cost and administrative burden associated with returning to the Bush Administration practice of segregating federally and nonfederally funded hESC research or conducting research in duplicate with both hESCs and IPSCs. Also notable, given the ongoing economic downturn and the inclusion of research funding as part of the financial stimulus plan, were economic impacts noted by some scientists. In particular, 24 scientists indicated that the ongoing policy uncertainty made it difficult to engage in long-term planning, such as decisions to hire postdoctoral researchers, graduate students, and research technicians. In addition, a small number of stem cell scientists indicated that the ongoing uncertainty was leading them to consider relocating to more favorable research environments. Similar to the impact of the temporary ban discussed above, there was little evidence that non-hESC scientists found this uncertainty beneficial. Only 4 of the 87 responding non-hESC scientists who provided a free-text description of the impact described it as beneficial to their research through increased prominence or funding opportunities. In contrast, 6 of these non-hESC scientists described a negative impact on their research through, for example, increased competition (presumably from hESC scientists moving to non-hESC work) or spillover effects between various types of stem cell research. In addition, numerous non-hESC scientists described other negative impacts, such as hindered collaborations and changes to their future research plans. These results indicate that policy uncertainty surrounding hESC research in the United States has both negative scientific and economic impacts and affects scientists working with all types of stem cells.

The results reported here provide one of the first systematic estimates of the impact of the short-lived preliminary injunction and ongoing policy uncertainty on the conduct of stem cell research in the United States. The results conflict with Judge Lamberth's assertion that his preliminary injunction would have little impact and suggest that rather than simply preserving the status quo, this injunction substantively changed the playing field for many hESC scientists in the United States as well as a lesser number of stem cell scientists working with other cell types. In addition, these results indicate the broad impact of ongoing policy uncertainty on the research plans of stem cell scientists. These results suggest that, regardless of the ultimate outcome of the ongoing legal proceedings, Judge Lamberth's ruling has already been a substantial victory for opponents of hESC research. The ruling increased the policy uncertainty in the field at a time when many scientists believed President Obama's policy offered respite from a lengthy period of restricted funding and has encouraged scientists to reconsider plans to use hESCs in their research or accelerated plans to transition away from these cells. More surprisingly, these results also suggest that the ruling and ongoing policy uncertainty have negatively affected non-hESC stem cell research, a finding that likely runs counter to the plaintiffs' hopes.

While this analysis focused on stem cell scientists in the United States, presumably the scientists most affected by the ongoing litigation, the nature of some of the impacts reported—notably the disruption of collaborative research projects—suggests that this particular case of policy uncertainty might also be affecting stem cell scientists around the world. Policy heterogeneity has previously been identified as a concern that could hinder collaborative stem cell research (Mathews et al., 2006), and this analysis suggests that policy uncertainty—essentially a form of policy heterogeneity over time—should also be considered a potential barrier to collaboration. Policy uncertainty may also hinder academic/industry collaborations and limit access to venture funding, hindering commercialization of hESC-based technologies (Harvey, 2009). Although the current U.S. situation, where a lawsuit threatens the legality of all federal hESC funding, is a particularly dramatic case, scientific uncertainty can arise in other situations, and this analysis also highlights the types of impacts policymakers around the world should consider when crafting stem cell policies.

In addition to arguing for a reassessment of the concept of harm to stem cell scientists in the ongoing legal proceedings, these findings suggest more broadly that lawmakers, both in the United States and around the world, aiming to support stem cell research should strive for policies that, to the extent possible, reduce uncertainty facing stem cell scientists. In the United States, passing legislation to provide a clear legal basis for the federal funding of hESC research, thus pre-empting the ongoing legal proceedings and reducing the field's reliance on executive action, would meet these goals. For individual U.S. states as well as other jurisdictions around the world developing stem cell funding policies, adopting long-term programs rather than relying on yearly authorizations would seem a wise strategy. Given the divisiveness of the debate over hESC research and the

history of policymaking in other morally charged areas, however, such policy certainty will likely prove difficult to achieve and some degree of uncertainty may be unavoidable. For this reason, hESC scientists should prepare to face continued policy fluctuations, legal challenges, and other hurdles to their research in the future.

## SUPPLEMENTAL INFORMATION

Supplemental Information includes two tables and Supplemental Experimental Procedures and can be found with this article online at doi:10.1016/j.stem.2011.01.002.

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## REFERENCES

Caulfield, T., Zarzeczny, A., McCormick, J., Bubela, T., Critchley, C., Einsiedel, E., Galipeau, J., Harmon, S., Huynh, M., Hyun, I., et al. (2009). Stem Cell Rev. *5*, 82–88.

Gottweis, H. (2010). Cell Stem Cell *7*, 555–558.

Gottweis, H., Salter, B., and Waldby, C. (2009). The Global Politics of Human Embryonic Stem Cell Science: Regenerative Medicine in Transition (Basingstoke: New York, Palgrave Macmillan).

Harmon, A. (2010). Stem Cells in Court, Scientists Fear for Careers. In New York Times, pp. A14.

Harvey, O. (2009). Politics & Policy *37*, 51–71.

Karmali, R.N., Jones, N.M., and Levine, A.D. (2010). Nat. Biotechnol. *28*, 1246–1248.

Mathews, D.J., Donovan, P., Harris, J., Lovell-Badge, R., Savulescu, J., and Faden, R. (2006). Science *313*, 921–922.

Thomson, J.A., Itskovitz-Eldor, J., Shapiro, S.S., Waknitz, M.A., Swiergiel, J.J., Marshall, V.S., and Jones, J.M. (1998). Science *282*, 1145–1147.

U.S. Court of Appeals for the D.C. Circuit. No. 10-5287. Defendants' Emergency Motion to Stay Preliminary Injunction Pending Appeal and Request for Immediate Administrative Stay. Document 1264671.

U.S. District Court for the District of Columbia. Civ. No. 1:09-cv-1575 (RCL). Memorandum Opinion. Document 44.

# Accessing Human Embryonic Stem Cell Lines and Other Controversial Research Tools

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# Accessing Human Embryonic Stem Cell Lines and Other Controversial Research Tools

Scientists' ability to acquire data and research materials and build upon previous discoveries is critical to the advancement of knowledge. Historically, norms of scientific behavior have supported this requisite sharing, yet concerns have emerged that sharing of research materials is in decline for several reasons, including increasing commercial pressures on scientists as well as competitive and strategic behavior by individual scientists. These concerns are particularly acute when scientists are attempting to acquire upstream research tools crucial to numerous experiments or even the development of an entire field, as is the case for human embryonic stem cell (hESC) research.

The promise of hESC science for basic research, drug discovery, and cell-based therapies depends on a wide range of scientists acquiring existing hESC lines or deriving their own lines – in short, gaining access to the field's key research tool. Access to hESC lines is complicated by an intellectual property environment that features several broad patents, which claim essentially all hESC lines and are assigned to the Wisconsin Alumni Research Foundation (WARF), as well as a heterogeneous patchwork of patents claiming techniques related to hESC research, such as culture conditions and differentiation approaches [1]. Access is also complicated by the ethical controversy associated with the derivation and use of hESC lines, the political salience of the field, and the commercial potential of regenerative medicine (of which hESC research is one component). Responding to this environment, the Hinxton Group, an interdisciplinary group of scholars, recently called for new information and data sharing hubs to facilitate stem cell research, echoing and amplifying concerns voiced in the years since hESCs were first derived[2].

Despite these concerns, only anecdotal reports indicate that stem cell scientists are having difficulty accessing the raw materials they need to conduct their research. A recent study identified access and utility as two key factors influencing stem cell scientists' choices of which cell lines to study, but did not document whether scientists had difficulties acquiring their research materials[3]. Another study, which focused on the commercialization of stem cell research in Canada, found relatively few material sharing issues, with less

than 10% of principal investigators reporting that they had ever been refused a license to a patented technology they needed for their research [4]. Material sharing concerns have been identified in biomedical research more generally with 19% of a broad group of biomedical scientists reporting that their last request for materials was rejected [5].

This study reports data from a recent survey of stem cell scientists in the United States to assess the importance of access concerns in the development of hESC science and evaluate the impact of ethical controversy on research material sharing practices (see Supplementary Methods for details). A total of 205 of the 388 respondents reported using hESCs in their work and each of these was queried about the specific hESC lines they used and their experiences acquiring these lines (see Supplementary Table 1 for text of key survey questions). Difficulty acquiring hESC lines was common among these scientists. In all 38% of these scientists reported facing an excessive delay acquiring at least one hESC line and 28% reported that they were unable to acquire a hESC line that they wanted to study. These results indicate that concerns about scientists' access to hESC lines are not misplaced and that both delays in acquiring and an inability to acquire certain hESC lines have likely hindered the development of hESC science in the United States. In addition, because these survey questions were conditional on respondents conducting hESC research, scientists that avoided hESCs entirely due to data access issues were excluded, raising the possibility that these results underestimate the magnitude of the problem.

Scientists who reported problems acquiring a hESC line were asked to briefly explain the difficulty they experienced. Not all respondents chose to complete this free-text question, but the answers of the hESC scientists who did provides insight into the specific access issues these scientists faced (see Supplementary Methods for details of the analysis). Among 31 respondents who faced excessive delays acquiring a hESC line but ultimately acquired the line, delays were most frequently caused by difficulties associated with negotiating and executing the material transfer agreement (MTA) (n=17, 55%). The second most common cause for delay was internal approval for hESC research, typically from oversight committees,

such as Institutional Review Boards or Embryonic Stem Cell Research Oversight Committees (n=5, 16%). Among 37 respondents who were unable to acquire at least one hESC line they wanted to use in their research, the most common problem was failure to successfully execute a MTA (n = 12, 32%). The second most common problem was failure to acquire institutional approval to study a specific cell line (n=10, 27%). Institutions rejected cell lines for several reasons, including concerns over their provenance as well oversight issues associated with studying non-NIH approved hESC lines. A third common problem was deriving labs or facilities that were unwilling to share a line or even respond to requests for lines (n=7, 19%).

WARF, with prodding from the NIH and others, has taken steps to simplify the process of acquiring hESC lines[6]. This raises the possibility that many of the respondents reporting difficulties acquiring hESC lines were early adopters who sought to acquire hESC lines before these changes. To test this possibility, respondents who had been working with stem cells more than five years were compared with those who joined the field more recently. Results were similar for both groups of scientists (Excessive delay: 31% of scientists with less than five years in field vs. 40% of scientists with five or more years, Unable to acquire cell line: 33% vs. 25%, not significant), suggesting access issues were not limited to a brief period of time.

More than a thousand hESC lines have been derived in the brief history of this field. For this reason, the rejection of a single request for a hESC line does not necessarily end a research program, as the scientist can attempt to acquire cell lines from another source. Each hESC line is unique, however, and some may be better than others for certain lines of research. In addition, as scientists develop and refine differentiation protocols or develop approaches to use hESC-derived cells to test drug candidates for efficacy or toxicity, there are sound scientific reasons to prefer studies comparing multiple hESC lines rather than relying on a single cell line. One potential consequence of the difficulties scientists face acquiring hESC lines may be a reliance on a relatively small number of lines, raising risks that research results are cell-line specific rather than broadly applicable. Previous studies have found that a small number of cell lines have been distributed from cell banks and reported in published research and conference presentations much more frequently

than others [7-8], but prior work has not examined the cell lines individual scientists have available in their labs and, consequently, their ability to conduct comparative hESC research or replicate their research on multiple lines. To address this issue, each hESC scientist participating in the survey was asked to indicate all the hESC lines they used in their research.

The most commonly used hESC lines were H1 and H9 – two of the initial lines derived by Jamie Thomson at the University of Wisconsin in the late 1990s[9]. These lines were used by 79% and 68% of the hESC scientist respondents, respectively. The third most common cell line was H7, another Wisconsin line, used by 26% of respondents. Although scientists reported using more than 100 other lines, no lines other than these three were used by more than 11% of respondents. To assess scientists' ability to conduct comparative hESC research, the total number of cell lines each scientist reported using was examined (see Figure 1). The most common number was two, reported by a third of the respondents, followed by three and one, reported by 22% and 21%, respectively. In cumulative terms, more than half of respondents reported using two or fewer hESC lines in their research and more than three quarters reported using three or fewer hESC lines in their research.

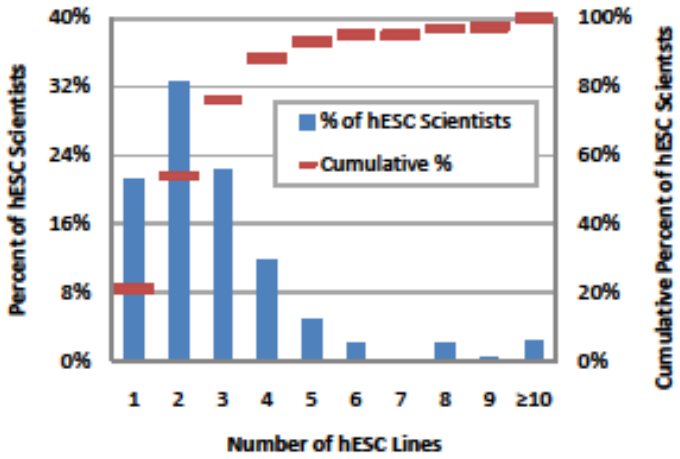


**Figure 1 – Number of Human Embryonic Stem Cell Lines Used by Individual Stem Cell Scientists.** Vertical bars show the percent of scientists using the specified number of hESC lines in their research. Red lines show the cumulative percentage of scientists using the specified number of hESC lines or fewer in their research.

Access issues are only one of several factors affecting scientists' choices regarding which cell lines or how many cell lines to use. Other considerations, such as the suitability of a cell line for a specific research project, the extent of published literature on a cell line, and the preferences of a scientist's colleagues or collaborators, also affect these choices. To address this issue, each hESC respondent was asked to list the major reasons they chose to use the particular hESC lines they used in their research. Reasons related to availability were the most common, listed by 51% of the 130 respondents who completed this free-text question. Other common reasons included scientific considerations (35%), such as growth or differentiation characteristics, and a preference for well-characterized cell lines (29%). Policy considerations, such as federal funding eligibility, were listed by 18% of the hESC scientists who responded to this question. These results illustrate that the ability of many hESC scientists in the United States to conduct comparative studies is limited and suggest that access issues are one of several factors responsible for this situation.

This analysis lends empirical support to previously anecdotal concerns over hESC scientists' ability to acquire key research tools. The prevalence of delays and, in particular, the inability of more than a quarter of hESC scientist respondents to acquire a desired cell line, suggests that ongoing efforts to simplify the process of accessing hESC intellectual property and acquiring hESC lines should be continued and, if possible, accelerated [2, 10]. Stem cell scientists were unable to access cell lines for a variety of reasons, including challenges negotiating and executing MTAs as well as outright rejections of their requests by other scientists or firms. Both scientists facing delays acquiring cell lines and those unable to acquire lines reported challenges navigating the internal bureaucracy of their institutions. Among these internal hurdles were issues associated with establishing the provenance of individual hESC lines as well as concerns about acceptable policies to avoid comingling of federally and non-federally funded hESC research. Some additional bureaucratic challenges may be inevitable in an ethically contentious and politically sensitive field, such as hESC research, but policymakers should explore steps to mitigate these issues, such as encouraging a greater reliance by individual institutions on third-party provenance verification and providing clearer

guidance on the issue of hESC research not eligible for federal funding. The role played by ethical and policy controversy associated with hESC science in hindering scientists' access to research tools suggests that similar challenges may face scientists in other ethically contentious fields.

Most of the hESC scientists surveyed had access to only one or two hESC lines, limiting their ability to conduct comparative work or replicate their results on multiple cell lines. Although access issues are only one of several factors creating this situation, funding agencies may want to consider prioritizing research using multiple diverse hESC lines to improve the reliability of research results and promote efficient advancement of hESC science.

The results reported here focused on access to hESC lines in the United States. Given the heterogeneity of the international intellectual property landscape for stem cell research and varying commercial pressures, the extent to which these findings generalize to stem cell scientists outside the United States remains an important unanswered question. A second important question is the extent to which access issues will affect research using induced pluripotent stem (IPS) cells both in the United States and around the world. Although the patent landscape is still emerging in this area, access to intellectual property appears likely to be an ongoing concern [11]. IPS cells raise less ethical controversy, however, providing hope that institutional bureaucracy will prove less of a barrier in this field than it has for hESC science.

## References


1. Bergman, K. & Graff, G.D. *Nature Biotechnology* **25**, 419-424 (2007).
2. Mathews, D.J., Graff, G.D., Saha, K. & Winickoff, D.E. *Science* **331**, 725-727 (2011).
3. Scott, C.T., McCormick, J.B., Derouen, M.C. & Owen-Smith, J. *Cell* **145**, 820-826 (2011).
4. Caulfield, T., Ogbogu, U., Murdoch, C. & Einsiedel, E. *Regenerative Medicine* **3**, 483-496 (2008).
5. Walsh, J.P., Cho, C. & Cohen, W.M. *Science* **309**, 2002-2003 (2005).
6. Golden, J.M. *Journal of Law, Medicine and Ethics* **38**, 314-331 (2010).
7. Scott, C.T., McCormick, J.B. & Owen-Smith, J. *Nature Biotechnology* **27**, 696-697 (2009).
8. Scott, C.T., McCormick, J.B., Derouen, M.C. & Owen-Smith, J. *Nature Methods* **7**, 866-867 (2010).
9. Thomson, J.A. et al. *Science* **282**, 1145-1147 (1998).
10. Winickoff, D.E., Saha, K. & Graff, G.D. *Yale Journal of Health Policy, Law, and Ethics* **9**, 52-127 (2009).
11. Simon, B.M., Murdoch, C.E. & Scott, C.T. *Nature Biotechnology* **28**, 557-559 (2010).
12. Karmali, R.N., Jones, N.M. & Levine, A.D. *Nature Biotechnology* **28**, 1246-1248 (2010).

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**Supplementary Information**

**Materials and Methods**

**Survey description**

Data were acquired for this analysis through a survey of stem cell scientists in the United States. This survey was administered in November 2010 to stem cell scientists working at academic and non-profit medical research institutions in the United States using a web-based survey tool. The survey was pre-tested on a group of stem cell scientists at Georgia Tech, and, following revisions, sent to a larger sample of 1,525 stem cell scientists. This list of stem cell scientists was derived primarily from two sources: the member directory of the International Society for Stem Cell Research (ISSCR) and a list of recipients of state stem cell grants, developed as part of a related project [12]. Scientists working with both adult and embryonic stem cells were included in the sample. Both mailing and email addresses were available for 1,313 stem cell scientists. Only email addresses were available for the remaining 217 scientists. Each potential participant for which a postal mail address was available was sent an introductory letter in late October 2010. Approximately, one week later, each potential participant was contacted by email and invited to complete the survey. Two reminders were sent to potential participants who had not completed the survey at roughly one-week intervals.

A total of 120 scientists in the original sample could not be reached due to incorrect contact information, yielding a final sample size of 1,410. A total of 438 respondents started the survey, yielding an overall response rate of approximately 31%. The survey began with an informed consent process and continued with a screening question designed to ensure that all respondents were active stem cell researchers. A total of 23 respondents did not meet this screening criterion and did not complete the remainder of the survey. In addition, a total of 27 respondents started the survey but stopped before completing the initial demographics section and are excluded from this analysis.

This left a total of 388 respondents and their responses form the basis of the analysis reported here. The actual number of responses varied by question, as item non-response was permitted. Sixty-six percent of respondents were principal investigators and 26% were either post-doctoral researchers or advanced graduate students. Respondents came from 32 different states and their distribution among these states closely paralleled the distribution of academic biomedical research in the United States, as measured by the NIH's fiscal year 2009 extramural budget.

Survey questions relevant to the analysis reported here are shown in Supplementary Table 1. Questions are presented in the order they were asked in the survey. Questions about the specific cell lines that scientists used and the reasons they used these lines were asked before questions about access issues to avoid priming respondents to think about access considerations when explaining why they worked with certain cell lines.

The survey protocol was approved by the Georgia Tech Institutional Review Board for Human Subjects Research.

**Analysis**

Analysis of scientists' free-text responses explaining why they chose specific cell lines or describing the difficulty they had acquiring a hESC line proceeded in an inductive manner using a modified grounded

theory approach. A careful reading of the responses was used to develop an initial set of codes that represented the various types of explanations that respondents provided and this set of codes was revised through an iterative and comparative process. A total of 130 respondents provided a free-text response describing their reasons for using specific hESC lines and these responses were each assigned one or more of six distinct codes (including an "other" code). A total of 31 respondents who experienced an excessive delay acquiring a hESC line but ultimately were able to acquire the line provided a free-text response describing the delay. These responses were assigned one or more of five distinct codes (including an "other" code). A total of 37 respondents who were unable to acquire at least one hESC line provided a free-text response describing the difficulties they faced. These responses were assigned one or more of five distinct codes (including an "other" code). For each of the three analyses, some answers included multiple reasons and received multiple codes.

| **Section** | **Question Text** |
|---|---|
| Cell Line Usage | Which human embryonic stem cell lines do you use in your research? (Check all that apply)<br>□ H1 (WiCell) □ BG02 (BresaGen) □ HUES1 (Harvard)<br>□ H7 (WiCell) □ HES-2 (ESI) □ HUES7 (Harvard)<br>□ H9 (WiCell) □ HES-3 (ESI) □ HUES9 (Harvard)<br>□ BG01 (BresaGen) □ HSF-6 (UCSF)<br>□ Other(s) (Please list _____)<br><br>What are the major reasons you use these particular lines?<br>Blank field for text entry |
| Cell Line Access | When acquiring human embryonic stem cell lines for your research, have you ever<br>Experienced an excessive delay acquiring a cell line you wanted to study?<br>○ Yes<br>○ No<br>Been unable to acquire a cell line you wanted to study?<br>○ Yes<br>○ No<br><br>[If the respondent chose "Yes" for either of the previous two questions, the following question was asked]<br><br>Please briefly describe the difficulty you experienced acquiring this cell line.<br>Blank field for text entry |

**Supplementary Table 1 – Text of key survey questions.** The complete text and answer choices for the survey questions that formed the basis of the analysis shown are shown. Survey processing commands are shown in []. Additional survey questions not analyzed here are omitted.

**PRELIMINARY DRAFT – not for circulation**

# Academic Entrepreneurship and State Stem Cell Policy

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**PRELIMINARY DRAFT – not for circulation**

# Academic Entrepreneurship and State Stem Cell Policy

## Introduction

During most of the last decade, human embryonic stem cell (hESC) research in the United States has been regulated by an atypically heterogeneous policy environment, sometimes termed a "regulatory patchwork" (Knowles, 2004). This environment emerged following the August 2001 decision of President Bush to limit federal research funding for this controversial, but potentially promising, field to a small number of hESC lines derived prior to the date of his announcement (Bush, 2001). Despite substantial debate, this policy remained essentially unchanged for the duration of George W. Bush's presidency. Following his election, President Obama announced a new policy in early 2009. This policy permits federal funding for research on a wider range of hESC lines, although some practices, such as the derivation of new hESC lines are still restricted. A lawsuit challenging the legality of the Obama Administration's guidelines was filed in 2009 and substantial uncertainty over the future of federal funding continues to persist as this lawsuit works its way through the courts.

In the years following the announcement of the Bush Administration's federal funding restrictions, numerous states adopted policies designed to support hESC research and stem cell research more broadly, while other states have taken steps to explicitly restrict research in this field. Some, but not all, of the supportive states, have taken the unusual step of providing state funding to support stem cell research. New Jersey became the first state to commit state funding to this field in early 2004. California followed New Jersey with a large commitment of $3 billion over ten years and, because of scale of its program, now dominates the policy landscape. Since the approval of California's program by state voters in November 2004, Connecticut, Maryland, New York and Illinois have also committed varying amounts of state funding to stem cell research. All told, six states have pledged approximately $3.75 billion to support this field

over the next decade. Thus far, these states have awarded in excess of $1 billion with additional funding slated for the next few years (Karmali et al., 2010).

These state policies have many goals. They hope to counteract restrictions on federal funding for hESC research and accelerate potentially life-saving research. In addition, state policymakers hope that state-specific research support will yield localized economic benefits. These economic development goals are visible in the economic impact assessments (Baker and Deal, 2004; Seneca and Irving, 2005) that supporters of these stem cell policies commissioned and used to help sell the programs to undecided voters and legislators. These reports enumerate a range of potential economic benefits, including reduced health care costs, the recruitment of scientists and biotechnology firms and the return of licensing revenue to the state.

Because funding investigator-initiated basic research has largely been a federal responsibility in the United States, states seeking to support stem cell research had to develop novel infrastructure to do so. Within a few years, each of the six states developed a set of policies to administer a scientific research grant program. These policies ranged from the creation of peer review mechanisms and ethical oversight committees to the wording of contractual agreements between the state and its grantees. Not surprisingly, given the different approaches through which stem cell policy was enacted and the differing experiences and circumstances of each state, substantial variability exists among the policies adopted by the six states. This research views this concurrent policy development and resultant policy variability as a sort of natural experiment and seeks to understand how this variability influences scientists' behavior. Specifically, this article seeks to exploit variability in states' licensing and revenue sharing policies for intellectual property derived from state-funded stem cell research to add to our understanding of how policy choices and financial incentives influence scientists' entrepreneurial behavior.

This variability has arisen because of the different approaches states took to enacting stem cell programs and convincing their citizens that these programs were good investments. At the same time, however, states were concerned about adopting policies that would discourage scientists from conducting entrepreneurial research or commercializing the results of state-funded research. States balanced these competing interests in different manners (see Table 1). As a result, some states have adopted policies modeled explicitly after federal policy, with limited restrictions on scientists' entrepreneurial choices, while others have policies that explicitly require revenue sharing with the state up to certain limits and, thus, presumably affect scientists' incentives. California has adopted the most nuanced policy, requiring revenue sharing from only the institution's share of revenue, thus, seeking to return revenue to the state without affecting scientists' incentives.

The research described here aims to understand the factors that influence scientists' entrepreneurial activity and explore the extent to which scientists' behavior is affected by state policy choices. The analysis makes use of novel data collected through a survey of stem cell scientists in the United States and relies on comparisons between scientists' self assessments of their entrepreneurial activities associated with their state and federally funded stem cell research. In short, overall entrepreneurial activity was similar for state and federally-funded stem cell scientists. However, scientists with both state and federal stem cell funding had significantly more entrepreneurial activity associated with their federally funded research than their state funded research. State revenue sharing policies are one of several factors that likely contribute to this difference.

| | Revenue Sharing |
|---|---|
| **California** | Non-profit grantees: Grantee organizations share revenues with inventor(s) in accordance with their established policies. Grantee organizations pay 25% of its share after payments to inventors to State.<br><br>For-profit grantees: 25% of net licensing revenue in excess of $500,000. 2% to 5% of revenues for self-commercialized products, capped at 3x CIRM grant amount. Different rules for blockbusters. |
| **Connecticut** | State is entitled to royalties at a minimum rate of 5% from any invention resulting from state-funded stem cell research |
| **Illinois** | No revenue sharing requirements |
| **Maryland** | No revenue sharing requirements |
| **New Jersey** | State shall receive a percentage of income generated from any intellectual property resulting from grant: 1% of net sales (capped at grant amount), 1% of royalties for licensed IP (capped at 10x grant amount) |
| **New York** | No revenue sharing requirements |
| | |
| **NIH** | No revenue sharing requirements |

Table 1 – Summary of State Stem Cell Policies

**Data Collection and Analysis**

**Description of survey**

Data were acquired for this analysis through a survey of stem cell scientists in the United States. This survey was administered in November 2010 to stem cell scientists working at academic and non-profit medical research institutions in the United States using a web-based survey tool. The survey was pre-tested on a group of stem cell scientists at Georgia Tech, and, following revisions, sent to a larger sample of 1,525 stem cell scientists. This list of stem cell scientists was derived primarily from two sources: the member directory of the International Society for Stem Cell Research (ISSCR) and a list of recipients of state stem cell grants, developed as part of a related project (*1*). Scientists working with both adult and embryonic stem cells were included in the sample. Although the ISSCR member directory is

likely representative of the overall population of stem cell scientists, the sample may overrepresent state-funded stem cell scientists to some degree. This choice was deliberate as the analysis described below focuses in part on the role of state funding in this field. Both mailing and email addresses were available for 1,313 stem cell scientists, while only email addresses were available for the remaining 217 scientists. Each potential participant for which a postal mail address was available was sent an introductory letter in late October 2010. Approximately, one week later, each potential participant was contacted by email and invited to complete the survey. Two reminders were sent to potential participants who had not completed the survey at roughly one-week intervals.

We were unable to reach 120 of the original sample due to incorrect contact information, yielding a final sample size of 1,410. A total of 438 respondents started the survey, yielding on overall response rate of approximately 31%. The survey began with an informed consent process and continued with a screening question designed to ensure that all respondents were active stem cell researchers. A total of 23 respondents did not meet this screening criterion and did not complete the remainder of the survey. In addition, a total of 27 respondents started the survey but stopped before completing the initial demographics section and are excluded from the analysis.

This left a total of 388 respondents and their responses form the basis of the analysis reported here. The actual number of responses varied by question, as item non-response was permitted. Sixty-six percent of respondents were principal investigators and 26 percent were either post-doctoral researchers or advanced graduate students. Respondents came from 32 different states and their distribution among these states closely paralleled the distribution of

academic biomedical research in the United States, as measured by the NIH's fiscal year 2009 extramural budget.

The survey protocol was approved by the Georgia Tech Institutional Review Board for Human Subjects Research.

**Results**

Each survey respondent was asked about federal and state support for their current stem cell research (see Table 1). Most respondents had funding from at least one of these two sources. Many scientists had support from either federal or state sources but not both. The finding that many scientists had federal but not state funding is not surprising as many stem cell scientists are located in states without state stem cell programs. The finding that many state stem cell scientists do not have federal stem cell research funding is more surprising, but agrees with recent research suggesting a major impact of state stem cell programs has been drawing new scientists into the field (Karmali et al., 2010).

| | Federal Funding | No Federal Funding | Total |
|---|---|---|---|
| State Funding | 88<br>(24%) | 101<br>(27%) | 189<br>(51%) |
| No State Funding | 125<br>(34%) | 58<br>(16%) | 183<br>(49%) |
| Total | 213<br>(57%) | 159<br>(43%) | 372 |

Table 1 – Scientists' reports of federal and state support for stem cell research

Scientists who indicated that they currently had external support from either a federal funding agency or a state stem cell funding program were asked a series of questions about

their expectations for entrepreneurial activity associated with this ongoing research. Specifically, respondents were asked to indicate on a scale from 1 (very unlikely) to 10 (very likely) how likely it was that this externally funded research would lead to each of the following: new collaborations with industry scientists, publications co-authored with industry scientists, the filing of one or more patent applications, and the creation of a new start-up. Scientists who indicated that they currently had both federal and state support for their stem cell research were asked the questions twice, once for each type of funding.

Scientists' responses to the questions on the likelihood of entrepreneurial behavior are shown in Figure 1. Panel A shows the results for the full set of scientists indicating that they had either federal or state funding supporting their current stem cell research. As this figure illustrates, scientists' assessments of the likelihood of entrepreneurial activity associated with their stem cell research was very similar regardless of the funding source. Although slight differences were observed for some questions, none of these differences were significant.

Panel B focuses on the subset of scientists with both state and federal funding for their stem cell research. The results for these scientists are markedly different. This subset of scientists with funding from both sources reported that entrepreneurial activity was more likely for their federally funded research than it was for their state funded research. This difference was statistically significant ($P < 0.01$) for the questions about industry collaborations, patent applications and start-up firms.

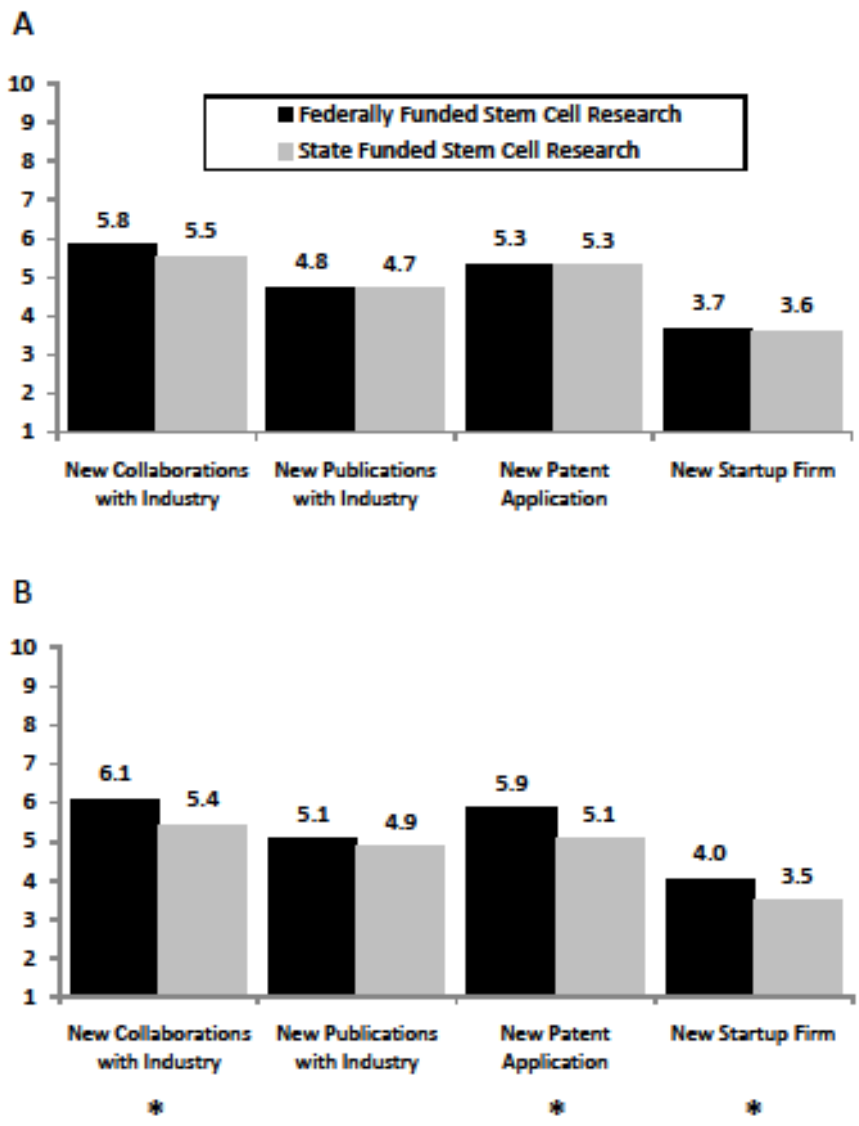


Figure 1 – Likelihood of entrepreneurial activity associated with federal and state funded stem cell research. A. All respondents with either federal or state funding or both. B. Respondents with both federal and state stem cell funding. * indicates that the difference between federal and state funding is statistically significant at the 0.01 level.

Several factors could explain the reported difference in the likelihood of entrepreneurial activity among scientists with both state and federal stem cell funding. One potential explanation is the revenue sharing requirements imposed by several of the state stem cell funding programs. Given the choice, scientists with multiple funding sources might choose to

conduct their most entrepreneurial work with federal funding and rely on state funding for their less entrepreneurial research. To examine this possibility, the survey also asked all scientists who reported receiving funding from a state stem cell funding program if their funding included intellectual property provisions that required sharing of revenue earned from state-funded stem cell research (see Figure 2). Because pre-tested suggested scientists might be uncertain about revenue sharing requirements, when respondents were asked about the existence of revenue sharing requirements, they were given three options: Yes, no and not sure. Scientists who indicated that they did have revenue sharing requirements were asked to describe these requirements briefly in their own words.

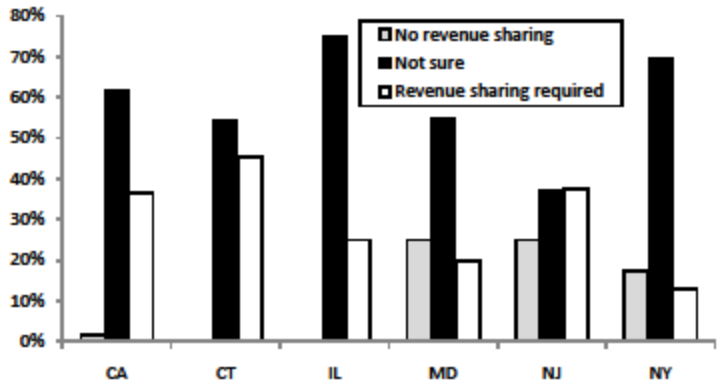


Figure 2 – Scientists' awareness of revenue sharing requirements

These responses reveal uncertainty among state funded stem cell scientists regarding revenue sharing provisions. The "don't know" was the single most common choice selected for five states and tied for the most common response in the other state. Even discounting the "don't know" responses, there was substantial confusion about some state's revenue sharing rules. State-funded stem cell scientists in California and Connecticut who did not choose "don't

know" generally correctly indicated that they were subject to revenue sharing provisions. In contrast, in Maryland and New York roughly the same number of scientists incorrectly indicated that they were subject to revenue sharing provisions as correctly indicated that they were not.

To more fully evaluate the role that these state revenue sharing provisions and scientists' awareness of these provisions plays in scientists' entrepreneurial behavior, regression analysis was utilized. The dependent variable for this analysis was an entrepreneurship index created by summing the four entrepreneurship variables shown in Figure 1 and normalizing the results so that the maximum score (40) equaled 1 and the minimum score (4) equaled 0. The analysis included a range of independent variables, including dummy variables for the respondent's position, and gender, as well as the number of years since the respondent's highest degree was earned. In addition, the analysis included a dummy variable indicating whether or not the respondent used human embryonic stem cells and whether or not they started using stem cells in the last few years. Two independent variables were included to address scientists' previous entrepreneurial activity, specifically whether or not they had filed patent applications either related to stem cells or in other fields in the last three years. In addition two independent variables address scientists' perceptions of the revenue sharing requirements associated with their state stem cell funding.

Results from four ordinary least squares regression models are shown in Table 2. Model 1 and model 2 focus on scientists' entrepreneurial activity associated with federally funded stem cell research while models 3 and 4 show the same analysis focused scientists' entrepreneurial activity associated with state funded stem cell research. Models 1 and 3 exclude the revenue sharing variables, while models 2 and 4 add these variables. Because only

scientists with state funding were asked about revenue sharing requirements, Model 2 includes only scientists with both state and federal funding.

| | (1) | (2) | (3) | (4) |
|---|---|---|---|---|
| DV | Federal Entrepreneurship Index | | State Entrepreneurship Index | |
| Principal Investigator | 0.01 | -0.08 | -0.07 | -0.07 |
| Female | -0.14** | -0.06 | -0.01 | -0.01 |
| Highest Degree since 2000 | 0.06 | 0.06 | -0.01 | -0.002 |
| Highest Degree between 1990 and 1999 | 0.08 | 0.09 | 0.04 | 0.05 |
| Previous Stem Cell Patents | 0.14** | 0.23** | 0.24** | 0.23** |
| Previous Non-Stem Cell Patents | 0.11** | 0.03 | -0.01 | -0.02 |
| New to Stem Cell Research | .03 | 0.07 | 0.04 | 0.04 |
| Uses human embryonic stem cells | .02 | -0.04 | 0.02 | 0.01 |
| State Revenue Sharing | | 0.17* | | 0.08 |
| No State Revenue Sharing | | 0.05 | | 0.04 |
| Constant | 0.32** | 0.35** | 0.35** | 0.33** |
| | | | | |
| N | 160 | 62 | 143 | 143 |
| $R^2$ | 0.23 | 0.41 | 0.19 | 0.20 |

Table 2 – Ordinary lease squares regression analysis of scientists' entrepreneurial activity
** P < 0.01, * P < 0.05

Model 1 shows that only a few of the independent variables are significant predictors of scientists' entrepreneurial activity associated with their federally funded stem cell research. Only previous patent filing is positively associated with the entrepreneurship index, with scientists having filed a stem cell related patent application in the last three years scoring 0.14 higher on the entrepreneurship index and scientists having filed a non-stem cell related patent application in the last three years scoring 0.11 higher on the index. In addition the gender dummy variable was significant. In this model, female respondents scored 0.14 lower on the entrepreneurship index than male respondents. The results are similar when the revenue sharing variables are added in Model 2. As noted previously, the sample size drops

substantially for this analysis as only scientists with both federal and state stem cell funding are included. In this analysis, the gender dummy variable and the variable for previous non-stem-cell related patent applications are no longer significant. Notably, the state revenue sharing variable entered the model significantly. Scientists who indicated that they believed that their state funded stem cell research was subject to revenue sharing requirements scored 0.17 higher on the entrepreneurship index for their federally funded stem cell research. This suggests that the presence of state revenue sharing requirements encourages scientists who have the option to shift their more entrepreneurial research to funding sources with fewer restrictions.

The analysis shown in models 3 and 4 focusing on entrepreneurial activity associated with state funded stem cell research were similar, although fewer variables were significant. In the simple model without the revenue sharing variables, only the dummy variable indicating whether or not the respondent had submitted a stem cell related patent application was significant. Unlike the case of the entrepreneurship index for federally funding research, when the revenue sharing variables were added to this analysis, they were not statistically significant. When model 4 is run limited to scientists with both state and federal stem cell funding, the revenue sharing variables remain insignificant (not shown). This suggests that the presence of state revenue sharing restrictions is causing scientists with both state and federal funding to conduct more entrepreneurial science while not substantially affecting then entrepreneurial nature of their state funded stem cell research.

## Conclusions

The research presented in this article has examined the entrepreneurial activity associated with state and federal funding for stem cell research. In general, scientists with state and federal stem cell funding report similar levels of entrepreneurial activity, such as collaborations with industry and filing of patent applications. Differences in entrepreneurial activity were observed, however, when focusing the analysis on scientists who had both state and federal stem cell funding. These scientists were significantly less likely to engage in entrepreneurial activities with their state funded state cell research than they were with their federally funded stem cell research. Regression analysis illustrated that these scientists' beliefs that their state funded stem cell research was subject to revenue sharing requirements was a significant predictor of their entrepreneurial activity associated with their federally funded research. This suggests that policy choices, such as the implementation of revenue sharing requirements, can have a substantial effect on scientists' entrepreneurial activities.

## References

**Baker, L., and Deal, B. (2004). Economic Impact Analysis: Proposition 71 California Stem Cell Research and Cures Initiative (Analysis Group).**

**Bush, G.W. (2001). Remarks by the President on Stem Cell Research. Public Papers of the Presidents of the United States, 953-956.**

**Karmali, R.N., Jones, N.M., and Levine, A.D. (2010). Tracking and assessing the rise of state-funded stem cell research. Nature Biotechnology *28*, 1246-1248.**

**Knowles, L.P. (2004). A Regulatory Patchwork--Human ES Cell Research Oversight. Nature Biotechnology *22*, 157-163.**

**Seneca, J.J., and Irving, W. (2005). The Economic Benefits of the New Jersey Stem Cell Research Initiative (Rutgers University).**