Cell Stem Cell
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Identifying Under- and Overperforming Countries in Research Related to Human Embryonic Stem Cells

Aaron D. Levine[1,*]
[1]School of Public Policy, Georgia Institute of Technology, 685 Cherry Street, Atlanta, GA 30332-0345, USA
*Correspondence: aaron.levine@pubpolicy.gatech.edu
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Human embryonic stem cell (hESC) science is governed by a patchwork of policies that vary both between and within countries. To assess how this atypical environment may have influenced this field's development, publication data were analyzed to evaluate the relative performance of countries in the cumulative production of hESC-related research articles versus other areas of biomedical research. Overperforming countries generally offered permissive policy environments for hESC research, while underperforming countries were characterized by protracted policy debates and ongoing uncertainty, regardless of their current policy environment.

The isolation and maintenance of hESCs in their undifferentiated state, first reported in 1998 (Thomson et al., 1998), was an important but preliminary step toward the potential development of novel transplantation therapies and a route toward a greater understanding of human development. Yet because the techniques used to isolate hESCs render early human embryos unviable, this research has generated substantial controversy. Scientists are exploring alternative derivation techniques that may mitigate these ethical concerns (Takahashi et al., 2007), but the development of hESC research has been marked by ethical controversy.

Policymakers in countries around the world have balanced the long-term hope presented by hESC research and the immediate ethical controversy it creates in a variety of ways. The result has been the emergence of a regulatory patchwork (Knowles, 2004) in which policies differ substantially both between and within countries and range from permissive to restrictive (Salter, 2007). Some countries, including the United Kingdom, Singapore, and China, have actively embraced the field, permitting the derivation of new hESC lines both from embryos leftover after fertility treatment and through the use of the somatic cell nuclear transfer (SCNT) under various oversight frameworks. Other nations, such as Canada and Taiwan, have adopted less permissive policies that allow scientists to develop new hESC lines from leftover embryos but not through SCNT. Still others, including Italy and Germany, have taken a more restrictive approach, preventing scientists from deriving new hESC lines entirely and limiting them to work on cell lines derived before a certain date or outside the country. The United States is an unusual case. Federal funds—the funding source for 63% of academic research and development in the country (see National Science Board, 2008)—can only be used for studies on a small number of hESC lines derived before August 9, 2001 (see comments from G.W. Bush). Scientists not using federal funding, in contrast, face no national restrictions. These scientists must comply with relevant state laws, some of which support and some of which restrict hESC research, and overcome logistical hurdles associated with ensuring that no federal money goes toward unapproved research (see report from K. Kaplan and E. Cline).

As the United States illustrates, hESC policies operate on a variety of levels. National policies are prevalent, but state- or province-level rules also matter, as do international policies, such as those promulgated by the United Nations or European Union (EU). Policy can address a variety of activities related to hESC science, including specific research practices, research funding, and oversight mechanisms as well as intellectual property or other issues related to the commercialization of hESC science. The analysis reported here focuses on hESC policy directed toward the derivation of new hESC lines, as many countries have policies distinguishing among various sources of embryos (see http://www.hinxtongroup.org/ for a current listing of country policies), but should be interpreted in light of the full range of possible hESC policies (Salter, 2007).

Given the public interest and political salience of this field, it is not surprising that interest in the impact of this atypical policy environment has also increased. Two initial reports focused on the United States. By comparing data sets of hESC-related publications with relevant controls, these analyses both concluded that the United States was lagging in the production of hESC-related research publications (Levine, 2005; Owen-Smith and McCormick, 2006). More recently, two additional reports have examined the development of hESC science through the lens of research publications in the field (Guhr et al., 2006; Winston, 2007). These reports yield general insight into the development of hESC research, by identifying countries actively producing hESC articles, but do not compare this performance with other fields and cannot attribute it to the policy environment in any systematic manner.

Although the hESC research policy environment has received considerable attention, policy is one of many factors that can influence research output. Some of these factors operate at the level of the individual scientist. These include scientists' personal preferences toward specific fields, research questions or methodologies, their career ambitions (Garner, 1979), and their networks of colleagues and collaborators (Blumenthal et al., 1996). Other factors influence the research enterprise more broadly. These include the differences in the set of institutions involved in the oversight and production of new knowledge (Nelson, 1993), priorities of specific funding agencies (Braun, 1998), historic and projected economic growth, public views toward scientific inquiry (Gaskell et al., 2005), linkages between academic and industry science (Gulbrandsen and Smeby, 2005), and the systems created to evaluate and reward scientists (Geuna and Martin, 2003).

	Country Share			Absolute Difference		Relative Difference	
	hESC	RNAi	Control	hESC	RNAi	hESC	RNAi
United Kingdom	11%	7.1%	5.9%	5.3%	1.2%	1.9	1.2
Israel	5.4%	0.7%	0.8%	4.6%	-0.2%	6.5	0.8
China	5.0%	4.6%	1.9%	3.2%	2.7%	2.7	2.4
Singapore	2.9%	0.4%	0.3%	2.6%	0.0%	8.8	1.1
Australia	3.0%	1.2%	1.3%	1.6%	-0.1%	2.2	0.9
South Korea	3.0%	1.8%	1.9%	1.1%	-0.1%	1.6	1.0
Sweden	2.1%	1.4%	1.5%	0.6%	-0.1%	1.4	0.9
Netherlands	1.2%	2.2%	1.3%	-0.1%	0.9%	0.9	1.7
Germany	5.7%	6.7%	6.0%	-0.3%	0.7%	0.9	1.1
Spain	1.2%	1.1%	1.6%	-0.4%	-0.4%	0.7	0.7
Italy	1.4%	1.1%	2.3%	-0.9%	-1.2%	0.6	0.5
Canada	2.7%	3.7%	3.4%	-0.7%	0.3%	0.8	1.1
Switzerland	0.3%	1.7%	1.5%	-1.2%	0.3%	0.2	1.2
France	2.9%	3.3%	5.1%	-2.2%	-1.8%	0.6	0.6
Japan	10%	9.7%	13%	-3.0%	-3.3%	0.8	0.7
United States	36%	47%	46%	-10%	1.0%	0.8	1.0
Other	6.1%	6.2%	6.1%	0.0%	0.1%	1.0	1.0

Figure 1. Over- and Underperforming Countries in hESC-Related Research

The cumulative share of publications through 2006 citing the initial hESC paper, the initial RNAi paper, and the average cumulative share of articles citing each of the 50 randomly selected control articles are shown for each of 16 countries. Absolute and relative differences between a country's share of publications related to either hESCs or RNAi and the control set are shown. Shaded cells indicate that the absolute difference is significant at the $p < 0.005$ level, using two-sided t tests. All countries that produced at least 1% of publications in one of the three sets are shown, and countries are sorted by their absolute performance in hESC-related research. n = 1,112 (hESC set), 1,951 (RNAi set), and 19,096 (control set).

Here the focus is on comparing the publication output of individual countries in research related to hESCs with their output related to another emerging, but less contentious, field and in biomedical research more broadly. This analysis has two goals. First, it aims to identify which nations are overperforming and which are underperforming in hESC science. Second, it seeks to increase our understanding of the role played by the policy environment and other hESC-specific factors in the international development of this field.

Multiple considerations led this analysis to focus on the impact of country-specific factors. First, despite the increasingly global nature of science, approximately 80% of science and engineering articles published across all fields in 2005 were produced by scientists in a single country (see National Science Board, 2008). Second, even when collaborative research is conducted or transnational research policies are enacted, national laws play an important role. This prominence of national policies is visible, for instance, in recent EU discussions over hESC research, in which divergent preferences at the country level have hindered the creation of coherent EU-wide funding policies.

As peer-reviewed research articles are a major output of basic biomedical research, this analysis relies on publication data to address these questions. Specifically, three sets of research articles were developed and compared. The first set contains all research articles citing the initial hESC paper (Thomson et al., 1998). Many of the articles in this set represent follow-on research using hESCs. Others represent research in a range of related fields, and a few represent reviews or commentaries that slipped through the screening process. For this reason, this analysis focuses on "hESC-related" research rather than hESC research exclusively. The second set contains all research articles citing the initial RNA interference (RNAi) paper (Fire et al., 1998). RNAi is another important, but much less contentious, biomedical research tool. Like hESCs, RNAi has both immediate applications as a research tool and potential clinical applications. The third set is designed to represent biomedical research more generally. It was constructed through a two-step process. Initially, 50 molecular biology and genetics articles from 1998 were randomly selected from the top 1% of most-cited articles in this field. Some of these articles defined new subfields or reported new research tools, similar to the initial hESC or RNAi articles. Others reported important advances in more established subfields. All generated substantial follow-up research. All research articles citing each of these 50 articles were retrieved. Each article in these three sets was then assigned to a single country on the basis of the corresponding author. Compared to previous analyses (Levine, 2005; Owen-Smith and McCormick, 2006), the larger data set used in this study permits an assessment of individual country performance in hESC-related research. Additionally, the time-matched nature of the three sets (all source articles were published in 1998) reduces concerns about the ongoing globalization of biomedicine—notably the well-documented decline in the total share of research produced by U.S. scientists (National Science Board, 2006)—influencing the results. (More methodological details and a list of the 50 papers that formed the basis of the control set are included in the Supplemental Data available online.)

To assess research output at the country level, Figure 1 shows the cumulative share of research publications between 1998 and 2006 in the three sets for 16 countries—all countries that made up at least 1% of one of the three sets. To identify significant over- and underperformers, each country's cumulative share of hESC-related research and RNAi-related research was compared with its average cumulative share of research in the control set using two-sided t tests. Because the use of share data introduced an additional constraint—the requirement that the cumulative share for all countries sum to 100%—a conservative significance threshold of $p < 0.005$ was used. Absolute differences meeting this threshold are shaded in Figure 1. Nine countries show statistically significant differences for hESC-related research, compared with four countries for RNAi-related research.

Notably, the top four overperforming countries in hESC-related research all have long had public policies that support this field, by permitting the derivation of new hESC lines from embryos leftover after fertility treatment and through SCNT. These countries have also complemented their policies with government support for research in this field (Normile and Mann, 2005; Vogel, 2002; see also reports from W. Arnold and T. Webb). The fifth country, Australia, adopted a policy permitting scientists to derive new hESC lines from embryos created but no longer needed for fertility treatment in 2002. This policy explicitly banned SCNT. Following an extensive independent review, a revised

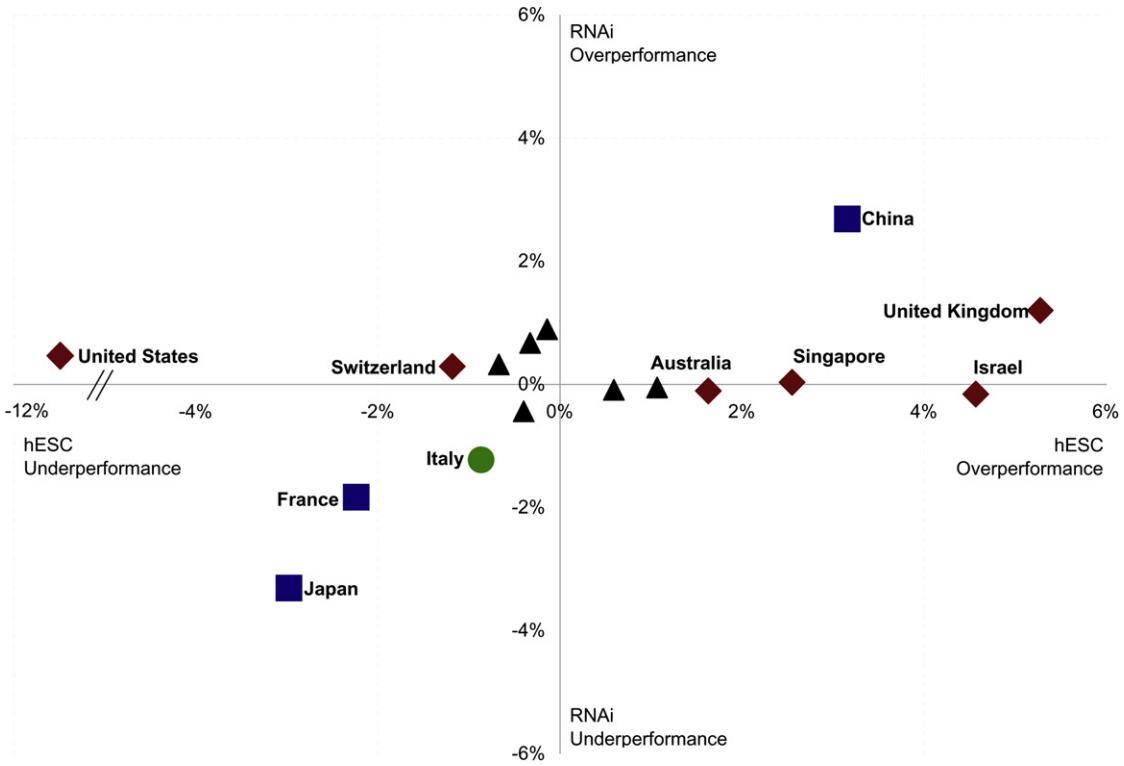

Figure 2. Country Performance in hESC- and RNAi-Related Research

Absolute over-/underperformance compared to the control set is shown for hESC-related research on the x axis and RNAi-related research on the y axis. Blue squares indicate countries with significant differences for both hESC- and RNAi-related research, red diamonds indicate countries with significant differences for only hESC research, and green circles indicate countries with significant differences for only RNAi-related research. Black triangles indicate countries from Figure 1 that did not have significant differences for either technology.

policy permitting scientists to use SCNT with human eggs under a detailed oversight system was adopted in December 2006 (Sinclair and Schofield, 2007).

The relationship between underperformance and the policy environment is less clear, although the countries underperforming in hESC-related research generally lack either permissive policies, complementary government support, or both. The United States, though still the largest single producer of hESC-related research publications, is the largest underperformer by the metric used here. Scientists in the United States produced 36% of hESC-related research compared with 47% of RNAi-related research and 46% of research in the control set. This significant underperformance suggests that federal funding restrictions may have influenced the amount of hESC research conducted by U.S. scientists, despite the presumably positive impact of the emergence of state support for this field. Because privately funded research is not restricted in the United States, these results may also reflect a shift of U.S. hESC research into the private sector, where scientists have less incentive to publish. This group of underperformers also contains Japan, where controversy over hESC research policies and bureaucratic hurdles to acceptable projects have reportedly hindered research (see N. Nakatsuji) and France, where hESC research was initially blocked by a 1994 law that has subsequently been slightly, but only temporarily, relaxed (see report by S. Webb and T. Pain). Several of these underperforming countries have policies today that permit the derivation of new hESC lines from leftover embryos, and Japan has announced plans to permit SCNT. However, in each of these countries, the policy debate has been protracted, forcing hESC scientists to navigate an uncertain policy environment.

Examination of Figure 1 suggests that countries' shares of research related to hESCs differ more from the control set than do their shares of research related to RNAi. Chi-square tests of homogeneity, comparing the raw count of articles by country in the hESC- and RNAi-related sets with the average count of articles by country from the control set, confirmed this observation. Specifically, these tests rejected the null hypothesis that the underlying country distributions of hESC-related research and research in the control set were the same (ChiStat = 66, df = 16, $p = 5.2\ e^{-8}$) but failed to reject the parallel null hypothesis for the comparison between RNAi-related research and the control set (ChiStat = 18, df = 16, NS).

Although Figure 1 highlights over- and underperforming countries in hESC-related research, it is not necessarily the case that these data reflect field-specific considerations. They may instead reflect more systematic influences on the scientific enterprise. To distinguish the influence of hESC-specific factors from more systematic considerations, Figure 2 combines country-level performance for both hESC- and RNAi-related research. When performance for both hESC- and RNAi-related research varies in tandem, it

suggests that systematic considerations play an important role. In contrast, countries that show variation in performance for one field, but not the other, likely reflect field-specific considerations.

Research performance in three countries—China, Japan, and France—appears to reflect systematic characteristics influencing the development of new biomedical technologies. China is the only country to significantly overperform in both fields. This likely reflects China's rapid economic growth and increasing investment in science and technology (for a review and details on the oversight of hESC research in China, see Salter et al., 2006). Japan and France, in contrast, underperform in both fields. Although bureaucracy and field-specific policies may be hindering hESC-related research in these countries, this systematic underperformance suggests that other factors, such as organizational structures for public science that are less conducive to exploring emerging technologies (Clark, 1995; Whitley, 2003), may also be important.

Six countries show significant differences in their performance in hESC-related research but do not show similar differences for RNAi-related research. Policies specific to hESC research or other field-specific factors may explain this observed underperformance in the United States and Switzerland and overperformance in the United Kingdom, Israel, Singapore, and Australia. The scale of overperformance is particularly notable in Singapore and Israel, where focused hESC research efforts appear to have paid dividends. In relative terms, Israel's share of hESC-related research is 6.5 times larger that its share of the control set, while Singapore's share of hESC-related research is 8.8 times larger that its share of the control set.

By systematically comparing country performance in hESC-related research with performance in another emerging, but less contentious, field and biomedical research more broadly, this analysis offers new insight into the international development of hESC science. Six countries showed significant performance differences that were specific to this field. Overperforming countries typically had long-standing supportive policies, while underperforming countries have adopted a range of policies but typically offer research environments characterized by protracted policy debates and uncertainty. These results suggest that policy, broadly defined, has played and will likely continue to play an important role in shaping the international development of hESC science.

SUPPLEMENTAL DATA

Supplemental Data include supplemental text, Supplemental References, and two tables and can be found with this article online at http://www.cellstemcell.com/cgi/content/full/2/6/521/DC1/.

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