An international gap in human ES cell research

To the editor:

Controversy surrounds basic and translational research involving human embryonic stem (hES) cells. In the United States, federal debates about funding for research involving new hES cell lines have been delayed another year[1]. Legal challenges to the largest state-initiated hES cell funding program are proceeding slowly through the courts[2]. While policy makers struggle to define a stable, politically and scientifically tenable approach to supporting basic hES cell research, a high-profile case of fraud has led to the retraction of two of the field's breakthrough papers[3]. Today's combination of scientific and political turmoil further exacerbates worries about the legitimacy, potential and future of hES cell research.

Public, political and scientific controversy about the state of this emerging field raises the stakes for US policy-makers' decisions about whether and how to support basic hES cell research. Concerns regarding the ability of the United States to keep pace in this volatile arena have been heightened by foreign research successes and international efforts to develop large-scale research infrastructures (for example, the UK Stem Cell Bank (http://www.ukstemcellbank.org.uk/), the Stem Cell Network in Canada (http://www.stemcellnetwork.ca/index_en.php) and the Australian Stem Cell Centre (http://www.nscc.edu.au/ascc_home.html). In the absence of expanded federal policies to support hES cell research, fragmented state, not-for-profit and commercial funding arrangements may prove insufficient, shifting the center of gravity in this important field away from the United States. Such a change could take with it scientists[4] as well as future therapeutic and commercial opportunities. At this juncture, we feel it is important to systematically examine the state of published hES cell research in order to empirically ground debates about federal policies, funding models, and their alternatives and impacts.

We identified hES cell research articles published between November 1998 and December 31, 2004 using the ISI Science Citation Index (Philadelphia, PA) database (see **Supplementary Methods** online). Our searches yielded 1,392 unique citations. Less than 9.5% (132) of those articles used or derived hES cell materials in the course of original research. We coded the text of those articles to determine where hES cell research is being conducted and which cell lines are being used.

Between November 1998 and December 2004, 132 articles published in 55 scientific journals have relied on hES cells. Authors are affiliated with 97 organizations spread around the globe. Forty-five (46.4%) of those institutions are located in the United States. The remainder are spread across 17 different nations with important concentrations in Israel, the United Kingdom and South Korea. Fifty percent (66) of these articles involved the use of multiple cell lines.

These publications used or reported the derivation of 70 different hES cell lines. The vast majority, 82% (18), of the US National Institutes of Health's (NIH; Bethesda, MD) approved and available lines are represented (http://stemcells.nih.gov/research/registry). Eight lines that the NIH lists as approved but "not yet available for shipping" were also used. Federally approved hES cell lines are used extensively in research. Nevertheless, 44 newly derived hES cell lines that are not approved for US federal funding were used in recent research.

Human embryonic stem cell research overwhelmingly relies on materials derived at the University of Wisconsin. Eighty-nine publications (67.4%) used at least one of Madison, Wisconsin–based WiCell Research Institute's (WiCell) H-series of hES cell lines and 69 publications (52.3%) relied exclusively on H lines and their variants. Easy access to the hES lines has been essential to the field's development, but concentration may presage difficulties if limited genetic variation hinders scientific progress. Only 14.4% (19) of publications described the use or derivation of lines not approved by the NIH. Much of that research was conducted outside the United States or in an international collaboration. Slightly over 87% (115) of publications were published after US policies stabilized (2002–2004). Human embryonic stem cell research is still in its infancy, but the last three years have witnessed remarkable growth, with publication rates nearly tripling in 2003 and 2004.

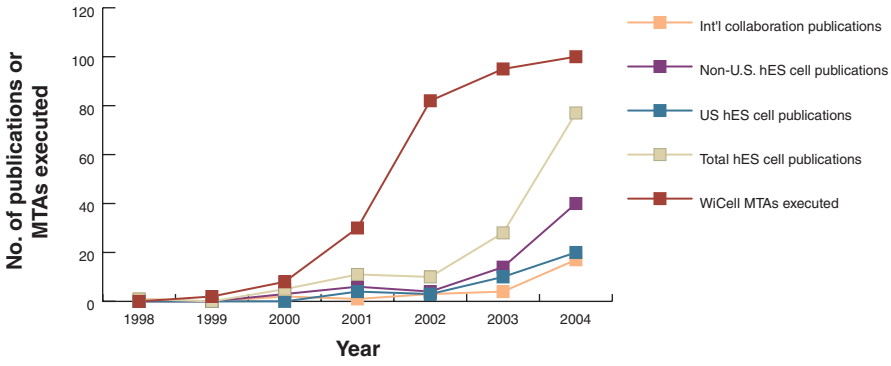

Figure 1 The number of publications using or deriving hES cells increases over time in each category and MTAs executed for access to the WiCell-owned H-lines led that trend. Recent years show a distinct gap between US and non-US rates. If these trends continue unchecked, the gap is likely to grow and research by international collaborations may surpass research conducted inside the United States.

Figure 1 highlights a significant gulf between US and non-US publication rates. The apparent difference after 2002 is significant ($\chi^2(2) = 8.293$, $P < 0.05$, $N = 115$; **Supplementary Results** online). The United States is falling behind in the international race to make fundamental discoveries in hES cell–related fields. If such discoveries can be translated into therapeutic and commercial opportunities, publication disparities may place US corporations and, more importantly, patients at a disadvantage.

US researchers may face greater difficulties than international scientists to the extent that federal restrictions limit the isolation and use of new cell lines. Data on material transfer agreements (MTAs) executed through 2004 for access to the WiCell owned H-lines indicate that more research groups, representing regions across the world, bought cell lines than had yet published research using them (**Fig. 1**). But might public controversy, uncertain federal funding and challenges associated with developing alternative means of support lead US scientists to shy away from hES cell research? Publication data suggest otherwise (**Supplementary Results**)

In 2003, researchers affiliated with 24 institutions published their first hES cell articles. Eleven of those institutions are located in the United States, 13 in other nations. Similarly, 2004 saw 50 new organizations enter the hES cell research game. Of those, 21 are in the United States, 29 outside. New research teams across the globe are publishing hES cell–related research and there seems to be no difference in rates of entry.

Do divergent publication rates also mask differences in the impact of scientific research in hES cell–related fields? US researchers may be publishing fewer but higher-quality articles that appear in higher-profile venues. Alternatively, non-US and internationally collaborative papers that may more easily draw on new or multiple cell lines could produce more influential discoveries. The individual publications examined here are too young to allow citation analysis. Thus, we turned to a blunter measure of publication impact based on the ISI citation impact factor for journals where hES cell publications appear. We weighted the number of 2002–2004 publications in each category by the impact factor of the journals in which they appeared (**Supplementary Results**)

On average, post 2002 US articles appeared in journals with an impact factor of 15.772 (s.d. = 14.237, $N = 32$). Non-US publications had an average impact factor of 8.743 (s.d. = 10.038, $N = 53$), whereas international collaborations weighed in at 12.495 (s.d. = 13.184, $N = 23$) (**Supplementary Results**). US publications appeared in highly influential journals. Nevertheless, it is commonplace for non-US scientists to publish in the most influential venues and highly unlikely that established scientists in the West will publish in lower-profile journals, such as the *Chinese Medical Journal* or the *Korean Journal of Genetics*, that appear in our sample. Recent concerns about the validity of research conducted by Hwang and colleagues[5,6] aside, if US federal policies lead the current publication gap to be matched by gulfs of training and differential access to new materials, we suspect that the relative influence of US stem cell science will decline.

Although our data imply that this productivity gap is surmountable, US congressional delays and the Bush administration's resistance to an expansion of federal funding suggest a real danger for US biomedicine.

Although our data imply that this productivity gap is surmountable, US congressional delays and the Bush administration's resistance to an expansion of federal funding suggest a real danger for US biomedicine and an opportunity for publicly funded research programs in other nations. Although the sky is not falling over the United States, a storm is brewing for its stem cell science; the force and effects of the storm will be exacerbated by conflicts over federal policies and fragmented efforts to develop alternatives.

As more states follow California's lead, future US hES cell research is likely to be conducted under a patchwork of restrictive federal policies and more permissive private, commercial and state-level funding arrangements. In addition to the difficulties and costs such a collage of policies will impose on researchers, alternative infrastructures have yet to be completely established and may never be as extensive, consistent or legitimate as the federally administered programs that have traditionally supported the scientific pre-eminence of the United States.

Expanding the purview of federal hES cell funding can still prevent the United States from slipping off the leading edge of developments in this vital field. More aggressive policies may help avoid growing pains and hold-ups as state and private funding initiatives develop workable infrastructures to evaluate and support cutting edge research without duplicating efforts, hindering collaborations, sparking interstate rivalries, sacrificing broad access to findings and materials in return for commercial support, or intensifying pressures for quick clinical breakthroughs at the expense of fundamental understanding. If public controversy and political priorities must necessitate a new federalism in science policy, US policymakers would be wise to at least allow for a smooth transition, for time to develop a scientific base and for systematic research to analyze the effects of new policy arrangements.

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

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