'The next two years might see a turning point for hESC researchers in the USA'

editorial

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Science aside: the trajectory of embryonic stem cell research in the USA

Embryonic stem cells (ESCs) are derived from pre-implantation embryos in a process that compromises the survival of the embryo. ESCs are extraordinary cells in many ways: they are immortal, relatively easy to expand and manipulate in a culture dish and, most importantly, have the potential to differentiate into any cell and tissue type. Consequently, patients are expected to benefit enormously from human ESC (hESC) research, both directly, through the development of hESC-based cellular therapies, and indirectly, through the use of hESCs in drug screening, biomarker discovery, disease modeling and basic research. The potential of hESCs might even be key to solving the Herculean tasks faced by Western countries that are being challenged by the combined effects of increasing life expectancies and an aging 'Baby Boomer' generation affected by degenerative diseases.

Although the development of breakthrough therapeutic applications of hESCs is likely to take many years, the field is currently faced with legal, ethical and political issues. Here, we analyze, from the perspective of hESC researchers in the USA, the most pressing issues of research funding, the detrimental effects of inadequate federal oversight and guidance, the ambiguities relating to intellectual property, and what can be expected to happen during the next two years leading up to the Presidential election at the end of 2008.

Federal policies on embryo research

Federally funded research involving human embryos within the USA was banned in 1980 [1], perhaps as a negative reaction to the first successful demonstration of human *in vitro* fertilization (IVF) in the UK in 1978. Despite great scientific and medical interest in topics such as IVF, contraception and early human development, a lack of federal funding support through the National Institutes of Health (NIH) left the field open, by and large, to privatized research alone. To some degree, the restrictive federal policies are reflections of the strong political influence of conservative religious doctrine, foremost the feeling that a fertilized egg in a petri dish is morally equivalent to a human. However, the restrictions in the USA are largely confined to federal funding limitations, in contrast

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to some conservative European nations that have chosen to limit or even ban certain procedures.

During the first week of his new administration in 1993, President Clinton removed the ban on embryo research. The White House then asked newly appointed NIH Director Harold Varmus to craft guidelines permitting federal funding for studies involving human embryos. These efforts were countered by Congress in 1996 in the form of the Dickey-Wicker amendment, which prohibited government funding for research 'in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than allowed for research on fetuses *in utero*' [1]. This amendment has been interpreted by the current administration to prevent funding of hESC research, even research on stem cells themselves, save for limited federal funding permitted under President Bush's declaration of August 9, 2001, which allows grants using hESCs derived as at the time of his speech (http://www.whitehouse.gov/news/releases/2001/08/20010809-2.html).

Since 2001, the scientific community and patient advocacy groups have rallied support for a more generous policy that would permit federal research support for more stem cell lines. The most successful of these bills was HR 810 in the 2005/2006 legislative year of the 109th Congress. Co-authored by two Congresspersons, Republican Michael Castle and Democrat Diana DeGette, this measure called for all hESC lines derived from 'left-over' embryos created for IVF treatments to be NIH eligible (http://thomas.loc.gov/cgi-bin/bdquery/z?d109:HR00810). The measure was passed by both the House and the Senate, only to be subjected to the first veto of President Bush's career in the White House (http://www.whitehouse.gov/news/releases/2006/07/20060719-5.html).

The same bill was recently resubmitted as HR 3 in the 110th Congress and, although it passed the House and its outlook in the Senate is promising, the President has already promised to veto it again (see: http://www.washingtonpost.com/wp-dyn/content/article/2007/01/11/AR2007011101285.html). Therefore, although support for hESC research continues to grow both among the general public (http://www.civilsocietyinstitute.org/010407%20CSI%20stem%20cell%20survey%20report%20FINAL.pdf) and in Congress, the future of such bills during President Bush's tenure is bleak.

However, states such as California, Connecticut, New Jersey, Massachusetts and Missouri have responded by supporting hESC work through legislation and funding initiatives. Among these, the enactment of the 'Missouri Stem Cell Research and Cures Initiative' in November 2006 was of particularly important. This ballot measure succeeded in a state seen by many as a 'bellwether' for conservative values, making stem cell research an object of constitutional protection within its borders (http://www.missouricures.com/documents/Initiative.pdf). However, other states have passed laws that are more restrictive than the current federal policy, one example being the criminalization of human somatic cell nuclear transfer in Michigan.

The pro-hESC research state initiatives are beneficial in that they provide conducive legal frameworks and critically needed research funds, yet the patchwork of independent, often incongruent, and seldom coordinated state initiatives is ill suited to comprehensive national scientific development. For example, it raises questions about the legality of the same scientific work in different states, which is a particular obstacle to interstate collaborations. It also produces artificial geographic incentives and shifts of research capital based more on politics than on the availability of biomedical resources and scientists. Furthermore, many states within the USA do not have the financial resources to establish their own hESC research grant initiatives. As a result, increased federal funding is important to create a greater degree of financial leveling for this research nationwide.

Challenges to current research

There is wide consensus that the few NIH registry hESC lines are insufficient for disease modeling and the development of therapies. To support research on non-NIH registry lines, scientists need to procure non-federal funds, such as those provided by the various state initiatives. To give up entirely on federal support is, however, unrealistic for most academic scientists, as the NIH is the largest sponsor of biomedical research in the world. This leads them into the perilous state of using both federal and non-federal funds. The NIH provides only minimal guidance on how researchers should separate federal funding of eligible research from alternatively funded ineligible research, through a short list of examples and FAQs (http://stemcells.nih.gov/info/faqs.asp#funding), information that is at best ambiguous and at worst garbled [2].

The basic rule for the required separation of funding is deceptively simple: standard accounting and cost principles are to be followed, which is essentially the same principles that also apply to other activities that are ineligible for federal funding, such as research sponsored by industrial partners or foreign governments. However, those rules create staggering administrative obstacles when applied to research on hESCs, and the lack of clear, comprehensive hESC research-specific guidance leaves many of even the simplest questions unanswered, as highlighted by a recent workshop of the Association of American Medical Colleges (https://services.aamc.org/Publications/index.cfm?fuseaction=Product.displayForm&prd_id=169&prv_id=200; see also [2]).

Left to guess how to interpret what little information is provided, individual institutions and scientists spend considerable time and effort on the development of institutional guidelines, and err on the side of caution, given the significant consequences for scientists and institutions if they guess wrong (e.g. grant recoupment, penalties, criminal prosecution and, potentially, barring the researcher or institution from receiving other federal funds). Additionally, the individual interpretations by institutes will cause regulatory idiosyncrasies that will complicate collaborative research efforts.

Patents

In many countries, hESCs are not patentable. In the USA, hESCs, and the Thomson method of deriving them, are patented. In fact, extremely broad, composition of matter-type patents were, some say somewhat accidentally [3], awarded by the US Patent and Trademark Office (USPTO) to James Thomson and the Wisconsin Alumni Research Foundation (WARF). Historically, WiCell, a Wisconsin-based company acting on behalf of WARF, has burdened even academic licensees with significant restrictions, prohibiting commercial sponsorship of research that involves any sort of benefit or right, including intellectual property, for the sponsor, unless that sponsor has a license from WiCell. Collaborations between academic scientists and innovative biotech companies

often are crucial to the advancement of a new research field, yet many small companies cannot afford a commercial hESC license [4]. Only recently has WiCell announced policy changes that lift restrictions on commercial sponsorship of academic research and the sharing of hESC research materials (http://www.wicell.org), although they do not apply to research conducted in commercial settings.

By contrast, Geron, the sponsor of the first derivation of hESC by Thomson, holds a license from WARF that grants it exclusive rights to the development of stem cell-derived products in key therapeutic areas, including diabetes, Parkinson's and heart disease. Taken together, the current situation is such that federal hESC research dollars are being spent for basic research that effectively enables Geron to develop commercial therapeutic or diagnostic products [5] while leaving little hope for commercial spin-offs from academia in those areas without Geron acquiescence. Because federal funding for stem cell research is limited, restricting commercial research in this way seriously limits research funding, commercial research collaborations [6] and biomedical progress.

The USPTO has agreed to re-evaluate the WiCell patents at the request of the Foundation for Taxpayer and Consumer Rights, which argued that the Thomson methods were not novel enough to justify the patents, and that the financial terms demanded by WiCell create an 'unjustified restraint' on scientific research (Request for *Ex Parte* Reexamination, Attachment to PTO-1465, re. Patent Nos. 5,843,780 [7], 7,029,913 [8] and 6,200,806 [9]; http://www.pubpat.org/warfstemcell.htm).

Looking ahead

The intellectual property obstacles to research progress might ease over the next two years. First, it is unlikely that the WiCell patents will necessarily limit other methods of deriving hESCs. In particular, the Thomson patents presently only cover 'embryonic' (blastocyst-derived) hESCs. Indeed, a host of alternative methods of deriving hESC-like cells has recently been developed that do not involve the use of normal human blastocyst-stage embryos and, therefore, should not infringe on the WiCell patents. Second, although two years might be a short time for the USPTO to act on the current re-evaluation, the scientific and advocate criticism of the patents is unanimous. With mounting pressure to address stem cell research effectively, there might be channels by which the need for rapid resolution can be legitimately and effectively communicated. Indeed, tangible results of the criticism of WiCell's licensing policy have already been seen, as evidenced by WiCell's recent policy change announcement. Third, thanks to efforts by the International Society for Stem Cell Research to promulgate consensus guidelines ([10]; http://www.isscr.org/guidelines/index.htm), international collaborations will be facilitated. If effective, mutually satisfactory collaboration agreements can evolve, it should be possible for scientists to allocate their own roles in their research collaborations in a manner that enables portions of the work to continue in places, including parts of Europe, where patents pose no obstacles. Developing such international collaborations should be a key agenda item for the next two years.

Additionally, the momentum generated by the initiatives of individual States to not only protect but, in some cases, to fund research will continue to bring scientific advances and, with them, a collateral interest from within the private sector to build upon these findings and commercialize them whenever possible. This will be added to any breakthroughs made with the limited federal funding currently available. Combined with ever increasing public endorsement, bipartisan support within Congress, and the potential for a more salubrious ability to protect intellectual property over the next few years, we feel that the next two years might well see a turning point for hESC researchers in the USA.

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