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Funding embryonic stem-cell research: will commerce counteract collaboration?

US legislation currently restricts access of embryonic stem-cell research to federal funding. However, we think that it is important that stem-cell research is not funded by private sources alone. The biotechnology industry and the general public are optimistic and hope that clinical applications of stem-cell research will develop soon. However, there is the obvious danger that the high hopes associated with stem-cell research will lead to patience running out long before the basic science is in place and responsible clinical trials can be started.

Embryonic stem cells (ES cells) are totipotent cells that have the ability to proliferate *in vitro* and to self-renew and, upon differentiation, they can develop into virtually any type of tissue [1]. ES cells have, therefore, been proposed as a potential source of donor tissue for transplantation therapies for a wide range of diseases, including diabetes, heart failure and disorders of the nervous system (in particular, brain and spinal injuries, multiple sclerosis, and Parkinson's and Alzheimer's diseases).

Although human ES cells have a great therapeutic potential, they are also considered a difficult ethical issue. A great deal of attention has recently been directed towards ES cells, partly as a result of the decision on public funding in the USA. Much of the research on ES cells is currently performed in the commercial sector. Therefore, many lines of ES cells are not available for the use of, or proper scrutiny by, the scientific community. Consequently, adequate public funding is now required for non-commercial research groups, so they can follow and contribute to the rapid developments taking place in ES cell research. However, on 9 August 2001, US President Bush finally announced his long awaited decision. He declared that public funding of human ES cell research is acceptable under the guidelines of the National Institutes of Health, but only if it meets certain criteria. For example, such research is eligible for funding if the ES cells are derived from an embryo created for reproductive purposes before 9 pm on 9 August 2001. Informed consent must have been obtained for the donation of the embryo and the donation must be devoid of financial inducements. Research involving the creation of new ES cell lines is not permitted for public funding. The anticipation of the announcement by President Bush caused the stock price of some stem-cell companies to rise by ~30% during the days preceding the announcement.

Academic institutions, which depend almost solely on public funding, can now take part in human ES cell research in the USA, but only if existing cell lines are used. However, research on human ES cells can still be performed by privately funded researchers (including biotech companies), who do not need to follow the new US regulations. Therefore, the regulations leave ES cell research largely in the hands of private commercial enterprises, which are not bound by federal rules. It is estimated that there are 64 human ES cell lines worldwide, of which 49 currently are characterized (http://escr.nih.gov/). The vast majority of known ES cell lines in the USA are derived by privately funded researchers. They will be available to publicly funded researchers now, but sometimes at a price. Wisconsin Alumni Research Foundation (Madison, WI, USA) is offering cells from their ES cell line for US$5000. Meanwhile, BresaGen (Athens, GA, USA), owner of four human ES cell lines, will give their cell lines to researchers without charge, but only if they have the right to negotiate intellectual property rights.

Apart from the questions of commercial rights, there are major scientific issues at stake. Most of the reported 64 human ES cell lines are not fully characterized (e.g. sufficient number of passages *in vitro*, resistance to cryopreservation, marker expression and karyotype analysis, immunophenotyping). Research on mouse ES cells suggests that ES cell lines eventually 'expire', because mutations accumulate. Therefore, President Bush's decision could present US researchers with a difficult challenge: to prove the potential of stem-cell therapies before the currently available cell lines have accumulated mutations that render them useless for clinical application. In conclusion, the new US regulations could bring commercially driven research even more to the forefront of stem-cell research. It will certainly restrict the number of scientists in this promising field of research and,

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unfortunately, much of the data generated will not be available immediately for scrutiny by traditional peer-review mechanisms. For example, one company that has generated pluripotent cells from bovine skin will not present the work in detail until it has secured a patent, a process that could take up to a year.

Thus, a pitfall with stem-cell research, partly generated by the new US regulations, is that it could be completely dominated by commercial interests. We think the societal interest should always be at the forefront and that public insight has to be prominent in an area of science that raises so many ethical concerns, and so much hope.

Reference

1 Odorico, J.S. *et al.* (2001) Multilineage differentiation from human embryonic stem cell lines. *Stem Cells* 19, 193–204

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Gene patents: are they socially acceptable monopolies, essential for drug discovery? – Reply ▲

Initial letter: Williamson, A.R. (2001) *Drug Discovery Today* 6, 1092–1093

Reply from Jack Heinemann

Are DNA sequences too simple as intellectual property?

Are the criteria for patenting genes [1] too broad, thus capturing too much property for too little novelty? The assumptions behind the criteria are that:

- genes are fully describable as DNA compositions;
- the DNA is always causally linked to particular activities; and
- the connection between DNA and phenotype or activity is created by obvious and invariant processes, for example, the central dogma reactions (transcription to translation).

Patents could be undermined whenever a particulate gene is inappropriately given agency as the defining cause of a particulate, irreducible activity. Genes are still significant mysteries, despite how well some have been characterized, and their relationship to phenotype remains a primary challenge for geneticists to describe. Our working definition of the gene is a scientific heuristic, not designed to be a legal definition. To call all genes DNA (i.e. nucleic acid compositions) substitutes an example for an abstract rule, one that is already proving to be too simple even to describe relatively straightforward traits [e.g. 2,3] and one that ignores important developments in epigenetics and bioinformatics.

In many ways, DNA contributes to our definition of ourselves and other living things; in the same way, the engine of a car is important for making a car what it is and does. However, to ascribe a value to DNA compositions because they were found in the context of DNA in an organism is the same, in my opinion, as ascribing a value to screws because they were discovered in the context of an engine. The DNA does not necessarily describe the defining essence of 'any potential use, even ones not disclosed and unknown to the patentee' [4] captured by the patent.

Genes are frequently mosaic structures. Subunits of genes reappear in many DNA compositions [e.g. 5–7], therefore, genes – and even proteins – can be linear arrays of recombinant domains that meld into a particular nucleotide composition [8]. Obviously, it would be overly inclusive to patent the composition 'G', but a US patent could conceivably allow a composition that relates to a phenotype or biochemical activity – as it is or within a larger expression unit – to claim all proteins with similar short sequences like, for example, an ATPase domain. By contrast, to recognize genes as actual, or potential, whole expression units could be overly restrictive because modifications of the composition that do not perturb a subgenic activity could undermine the patent.

Epigenes introduce even more uncertainty into assigning the causation – of an activity or phenotype – to a discrete nucleotide composition. Epigenes include molecules other than DNA that are capable of propagating heritable information [9,10]. Thus, what makes DNA special among polymers is also a property of the molecular epigene [11]. Nucleotide compositions do not capture the defining essence of epigenes. To ignore epigenes could again provide a patent holder with undue rights over material discovered by others or could undermine the exclusivity of the patent.

The uses of a DNA composition can be associated with an unknown number of components in an interactive network of components generated from within the organism, and encountered from outside, without the DNA composition being the defining component of the gene [12]. In maize, for example, the same nucleotide composition can map to four different phenotypes, pairs of which are mutually exclusive and all are strictly inheritable [10]. If the commercial property were the methylation pattern on a DNA composition, and methylation radiates out from two different nucleotide sequences at different times but causes methylation of both DNA sequences each time, who owns that property of the DNA sequence and when? Patents granted on DNA compositions might be challenged based on an uncertainty in where the 'uses' of one patent holder's matter ends and another's begins.

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