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

Gesine Paul and Patrik Brundin
Section for Neuronal Survival
Department of Physiological Sciences
Wallenberg Neuroscience Center
Lund University
Lund, Sweden
**tel: +46 46 22 20 524*
fax: +46 46 22 20 531

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.

  PII: S1359-6446(02)02106-7

Genes are still incompletely understood and arbitrarily defined [10]. Genes as linear sequences of nucleotides could prove to be too simple a formula, especially for defining Intellectual Property. Interestingly, clashes between patent holders could be the cause of a revival of the scientific pursuit for the abstract rules defining the general properties of the gene in the post-genomic era [e.g. 2,13,14].

References

1 Williamson, A.R. (2001) Gene patents: are they socially acceptable monopolies, essential for drug discovery? *Drug Discov. Today* 6, 1092–1093
2 Klar, A.J. (1998) Propagating epigenetic states through meiosis: where Mendel's gene is more than a DNA moiety. *Trends Genet.* 14, 299–301
3 Novick, A. and Weiner, M. (1957) Enzyme induction as an all-or-none phenomenon. *Proc. Natl. Acad. Sci. U. S. A.* 43, 553–566
4 Williamson, A.R. (2001) Gene patents: socially acceptable monopolies or an unnecessary hindrance to research? *Trends Genet.* 17, 670–673
5 Denamur, E. *et al.* (2000) Evolutionary implications of the frequent horizontal transfer of mismatch repair genes. *Cell* 103, 711–721
6 Keeling, P.J. and Palmer, J.D. (2001) Lateral transfer at the gene and subgenic levels in the evolution of eukaryotic enolase. *Proc. Natl. Acad. Sci. U. S. A.* 98, 10745–10750
7 Davis, J.D. *et al.* (2001) Evolution of an autotransporter: domain shuffling and lateral transfer from pathogenic *Haemophilus* to *Neisseria*. *J. Bacteriol.* 183, 4626–4635
8 Lavorgna, G. *et al.* (2001) Were protein internal repeats formed by 'bricolage'? *Trends Genet.* 17, 120–123
9 Jablonka, E. and Lamb, M. (1995) *Epigenetic inheritance and evolution, the Lamarckian dimension*. Oxford University Press
10 Heinemann, J.A. and Roughan, P.D. (2000) New hypotheses on the material nature of horizontally transferred genes. *Ann. New York Acad. Sci.* 906, 169–186
11 Weld, R. and Heinemann, J.A. (2001) Horizontal transfer of proteins between species: part of the big picture of just a genetic vignette? In *Horizontal Gene Transfer,* (2nd edn), (Kado, C. I. and Syvanen, M., eds), pp. 51–62, Academic Press
12 Lewontin, R.C. (2000) *The triple helix: gene, organism and environment.* Harvard University Press
13 Petronis, A. (2001) Human morbid genetics revisited: relevance of epigenetics. *Trends Genet.* 17, 142–146
14 Jones, P.A. and Laird, P.W. (1999) Cancer epigenetics comes of age. *Nat. Genet.* 21, 163–167

Jack A. Heinemann
Department of Plant and Microbial Sciences
University of Canterbury
Christchurch,
New Zealand
e-mail: j.heinemann@pams.canterbury.ac.nz
and Norwegian Institute of Gene Ecology
Tromsø
Norway

Decision-analytic approach: crucial to drug development

In a recent article in *Drug Discovery Today* [1], Poland and Wada describe how pharmacoeconomic modelling can be used to guide drug development decisions. Pharmacoeconomics has become an important tool in guiding strategic pricing considerations and reimbursement planning [2]. However, as the authors show, pharmacoeconomic modelling can also be used to synthesize uncertainties and values to aid in the decision-making process during drug development. The authors decided to use the net present value approach to summarize benefits and costs. This is similar to the investment appraisal approach to clinical trial design suggested by Backhouse [3]. From the perspective of a pharmaceutical company, designing a clinical trial involves a series of investment appraisal decisions. Therefore, applying decision-analytic techniques to clinical trial design allows the explicit analysis of the assumptions and decisions to be made during the drug development process.

The case study by Poland and Wada is of particular interest because Highly Active Antiretroviral Therapy (HAART) has been shown to save costs to society in developed countries with a low unemployment rate, such as Switzerland [4,5]. This is because the human capital approach for estimating productivity costs is then typically used in a cost-effectiveness analysis from the societal perspective. From the healthcare perspective, HAART has been shown to be cost-effective [4,5]. However, from the perspective of the pharmaceutical company, a cost-benefit analysis is required to assess whether the financial revenues outweigh the costs associated with the development of a new compound. The net present value approach does just that. The cost of discovering and developing a new drug has been estimated to exceed US$300 million (1995 US$) [3]. Given the high development costs, it is crucial to make decisions that maximize expected gains from a pharmaceutical company's perspective. A rigorous decision-analytic approach can help in achieving this goal.

Pedram Sendi
University of Basel
Basel
Switzerland

References

1 Poland, B. and Wada, R. (2001) Combining drug-disease and economic modelling to inform drug development decisions. *Drug Discov. Today* 6, 1165–1170
2 DiMasi, J.A. *et al.* (2001) Emerging role of pharmacoeconomics in the research and development decision-making process. *Pharmaceconomics* 19, 753–766
3 Backhouse, M.E. (1998) An investment appraisal approach to clinical trial design. *Health Econ.* 7, 605–619
4 Sendi, P.P. *et al.* (1999) Cost effectiveness of highly active antiretroviral therapy in HIV-infected patients. Swiss HIV Cohort Study. *AIDS* 13, 1115–1122
5 Sendi, P. *et al.* (2001) Highly Active Antiretroviral Therapy: Pharmacoeconomic issues in the management of HIV infection. *Pharmacoeconomics* 19, 709–713

1359-6446/02/$ – see front matter PII: S1359-6446(02)02128-6