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Icelandic genetics

To the editor:

A recent commentary on the health sector database in Iceland described some of the sovereignty and business aspects of this issue (*Nature Biotechnology* **17**, 407, 1999). During the past few weeks there have been significant developments that may effectively prevent the construction and operation of the database that deCODE Genetics has championed.

First, Mannvernd[1], an association for ethics in science and medicine, has filed a complaint to the EFTA Surveillance Authority, challenging the new law based on its infringement of monopoly agreements that Iceland is party to. Based on the European Economic Area Accord, it seems unlikely that the Icelandic government can award a single company an exclusive license to construct and run a health sector database.

Second, the World Medical Association Council, after hearing presentations from the Icelandic government and the Iceland Medical Association (IMA), voted to support the opposition of the IMA to the database[2]. The IMA objects to the database law on the following grounds: (1) invasion of privacy; (2) breach of patient/physician trust; (3) lack of independent review mechanisms; (4) abuse of patient consent; (5) disregarding of established scientific standards; (6) use of medical records as a commodity; and (7) creation of a centralized database of an entire population.

Consequently, a significant number of Icelandic physicians will not be sending their patients' data to the database unless a patient requests it in writing. Therefore, as a practical matter, the controversial database may never be constructed.

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1. http://www.mannvernd.is/english/index.html
2. Duncan, N. World Medical Association opposes Icelandic gene database. *Br. Med. J.* **318**, 1096 (1999).

Are sequences of plasmid DNA used in gene therapy erroneous?

To the editor:

Plasmid DNA offers an attractive way to deliver therapeutic genes for gene therapy[1] and genetic immunization[2]. Nucleotide sequences of plasmids are usually considered as composed of only four bases. However, because of its bacterial origin, plasmid DNA contains the two modified bases 6-methyladenine and 5-methylcytosine.

These methylated bases are the consequence of the existence of bacterial DNA modification systems. Dam and Dcm DNA methylases are two of these DNA methyltranferases[3]. They are found in almost all of the laboratory strains of *E. coli* and they respectively methylate the adenine residues of all the GATC sequences and the internal cytosine in all of the CC(A/T)GG motifs. Thus, although four bases are used to synthesize DNA, the nucleotide sequence of any plasmid DNA is in fact composed of six bases as a consequence of this epigenetic phenomenon. The omission of these modifications in the reported sequences of plasmid DNA is probably related to the fact that they do not affect the message of the genetic code. However, consequences of the changes introduced by bacterial methylation is far beyond a simple problem of chemical formula.

Methylation of GATC sequences in plasmid DNA has for instance been reported to introduce artificial hormone responsive elements in plasmid DNA[4] and to destabilize the double helix[5]. On the other hand, spontaneous base substitution hotspots are known to occur at 5-methylcytosine in *E. coli* and are associated with a CCAGG□ CTAGG change[6]. The presence of such foreseeable nonsense or missense mutations in the coding sequence of even a very small percentage of injected plasmids could have a dramatic effect if they give a dominant gain of aberrant function to the corresponding immunogenic or therapeutic protein. In addition, the fact that difference in the CpG dinucleotide methylation status between eucaryotic and procaryotic DNA is involved in immunostimulatory reactions when plasmid DNA is injected in mammals[7] raises the intriguing possibility that methylated GATC and CC(A/T)GG sequences may also trigger some yet uncharacterized biological reactions in a dose dependant manner.

Thus, because switching plasmid DNA from a tool for molecular biologists to a drug for human therapy requires exact information of the the chemical formula of injected DNA and because omission of the methylated status of nucleotides induces loss of chemical, biophysical, biochemical and potentially biological and legal information, we suggest that all methylated mucleotides are systematically mentioned in any plasmid DNA relevant to human therapy.

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1. Aihara, H. & Miyazaki, J. *Nat. Biotechnol.* **16**, 867–870 (1998).
2. Brower, V. *Nat. Biotechnol.* **16**, 1304–1305 (1998).
3. Palmer, B.R. & Marinus, M.G. *Gene* **143**, 1–12 (1994).
4. Truss, M. et al. *Nucl. Acid. Res.* **20**, 1483–1486 (1992).
5. Barras, F. & Marinus, M.G. *Trends Genet.* **5**, 139–143 (1989).
6. Coulondre, C. et al. *Nature* **274**, 775–780 (1978).
7. Krieg, A.M. et al. *Trend Microbiol.* **6**, 23–27.

GM crops in Europe

To the editor:

Your April editorial, "Genetically modified muddle" (*Nature Biotechnology* **17**, 311, 1999) left out of account one important factor in assessing the European consumers' attitude to genetically modified (GM) crops and food.

This factor is the concentration of GM technology and economic power in the hands of a handful of very large international bioagricultural companies as a consequence of recent acquisitions and consolidations. Certainly they are highly regulated, but their long-term decisions are made, as they must be, with the interests of their shareholders particularly in mind, and, because they are so few, they have the potential to drive the technology and its applications in their own interests rather than the interests of consumers or producers.

This concentration of power and lack of obvious consumer benefits is very different to that in the medical arena. Admittedly biopharmaceutical companies are also very large, but even the largest have market shares of only 5–10%, and their potential for driving technology and products in directions that consumers may not want is therefore less. And also, of course, the potential medical benefits of genetic engineering are enormous and clear to everyone.

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Erratum

In the May correspondence section, a typographical error was made in Dr. Stuart Kauffman's letter regarding patent amplification. The opening line should read "As the co-inventor of the Kauffman/Ballivet patent…" and not "As the inventor of the Kaufmann/Ballivet patent…"