

# The long and winding road

German scientists must persevere in the stem-cell debate, despite the occasional setback.

The German media last week trumpeted the claim that a patient in Dusseldorf with terminal heart failure has been successfully treated with adult stem cells from his own bone marrow. Although clinical researchers know that little can be learnt from a single case study, the result has already been unreasonably exploited by opponents of human embryonic stem-cell research.

The finding was published in the September issue of a German-language medical journal (M. Brehm and B. E. Strauer *Deut. Med. Wochenschr.* **132**, 1944–1948; 2007). Opponents of human embryonic stem-cell research, such as Julia Klöckner, a Christian Democrat who chairs a stem-cell committee in the German parliament, leapt on the result, claiming that the clinical success of using adult stem cells renders research on embryonic stem cells less necessary than before. They make this point just as the parliament prepares to consider whether it should modify the country's strict stem-cell laws.

The majority of scientists agree that work on both adult and embryonic sources of stem cells should run in parallel until much more is understood about their biology. But Germany is out of step with most European countries in permitting research only on human embryonic stem-cell lines that were created before January 2002, when regulations were first laid down. This situation has caused ambiguity in collaborative European Union (EU) research programmes: some partners can use new lines, but German participants could be put in jail if they did so themselves.

The past year has seen a significant shift in attitudes, however. Last November, Germany's main research-funding agency, the DFG, set the ball rolling, saying it believed that it was now time to eliminate the cut-off date. Respecting the moral dimension to which Germans are particularly sensitive, it did not suggest that German scientists should be allowed to derive their own embryonic stem-cell lines, as this involves destroying human embryos.

Response to the DFG's report has been broadly positive. A few months ago a majority in the National Ethics Council, which advises

chancellor Angela Merkel on bioethics, supported bringing the cut-off date forward to 2007. This would allow Germans to use all the cell lines involved in current EU projects. A parliamentary hearing in May also indicated that politicians of various hues would support such a relaxation in the rules. There is even wider support for any breach of the regulations to be regarded as a civil, rather than a criminal, matter.

Scientists helped to prepare the ground for this shift in opinion by patiently and thoroughly discussing with politicians and others the complex scientific issues involved. But opponents of human embryonic stem-cell research have also stepped up their campaigns. They see the recent success with adult cells as a vindication. Yet on the basis of one patient's history, it isn't even known if the recovery can be attributed to stem-cell therapy. Political leaders should be wary of taking such results at face value — especially when the stakes for human health are so high.

The reception afforded the Dusseldorf patient has disillusioned some German scientists, who feel that their painstaking efforts to get their case across have been undermined and devalued. But they should continue to promote their position whenever they can — and should adapt their strategy to match the situation in which they find themselves.

Public opinion is a fickle thing. It will not always be easy for the ad hoc group of biologists who have been working on the stem-cell issue in Germany to react to fast-moving events and make their voices clearly heard. There is no established national scientific academy in Germany to take the lead on the issue and the societies representing biologists have not quite been able to find their voice. Despite all this, researchers should persevere in their efforts to participate in — and, indeed, to lead — the stem-cell debate at every level. Eventually, their arguments will prevail. ■

**"It will not always be easy for the biologists working on the stem-cell issue in Germany to make their voices clearly heard."**

## Genome abuse

Citizens are right to resist government pressure to expand population DNA databases.

Terrorism, crime and illegal immigration are fuelling state surveillance, and are being used to justify it to the public, who too often seem asleep to the risks of abuse. This is particularly true of national DNA databases, where in several countries there is an insidious creep to log not only serious offenders but also other classes of the population, such as immigrants and minor offenders.

So it was refreshing to see resistance articulated this month in France and the United Kingdom. Prominent French scientists led

public protests against a government bill to use DNA tests on immigrants to see whether they are related to family members already resident in the country. Such protests might seem an overreaction. Many countries already practise DNA testing of immigrants, with varying rules for use. In 1985, the first use of DNA fingerprinting for legal purposes led to a Ghanaian boy being allowed to join his family in the United Kingdom after he proved kinship (A. J. Jeffreys *et al.* *Nature* **317**, 818–819; 1985).

But the objectors are correct to argue that the French proposal, far from promoting greater fairness, is aimed at erecting another obstacle to immigration. The scientific opposition is also linked to a strong bioethical and legal tradition in France of the concept of the family as a social unit, not reduced to mere biological ties, reflecting the reality that (as in all countries) many children are not the biological offspring of

their legal father. Given this culture, there is no reason why only immigrants with a biological link should qualify for integration with their families in France. Furthermore, DNA testing of immigrants elsewhere has destroyed families by uncovering true biological relationships.

The scientists' case has enjoyed public and political support, and has embarrassed the government, which sought to defuse the controversy last week by postponing a final decision to 2009. The outcry has also thrown an overdue spotlight on issues surrounding such population databases — issues being tackled in Britain, which has the world's largest DNA fingerprint database. The National DNA Database contains samples of 4 million people or 6% of the population, and one in ten males. The Nuffield Council on Bioethics, in a landmark report this month, does a service by drawing attention to the dangers of proposals to expand the database (see <http://tinyurl.com/2upt8x>).

There is a widespread misperception, encouraged by governments and media success stories, that DNA evidence is infallible in clinching convictions or acquittals. The technology is sound, but errors or deliberate falsifications in sample taking and handling are not uncommon, and a match with a sample at the scene of a crime may amount to proof only that the person was present at some point.

Since 2003, DNA samples and fingerprints have been compulsorily taken from Britons arrested for criminal offences. But the government now proposes extending the database to include fingerprints

and DNA from anyone arrested, even for minor offences such as dropping litter. And voices within the UK government and the judiciary have suggested that the entire population should be sampled. The US government, meanwhile, is proposing to extend its database to include DNA from anyone arrested by federal agents.

The Nuffield report is right to denounce the infringements on liberty and privacy represented by such extensions as being disproportionate to any possible benefits. Suspicion of involvement in a minor offence cannot justify taking a biological sample without consent. In the United States, the largest group likely to be affected is illegal immigrants — and there is no reason to suspect this group of being more likely to engage in serious crime.

DNA fingerprints themselves contain relatively little personal information, but the biological samples are open to misuse. Although supposedly limited to direct matching of individuals for crime cases, DNA data are already used for the much less scientifically robust practices of searching for family relatives of a crime's perpetrator, and to try to reduce possible suspects to ethnic groups.

History teaches us that it is a fallacy that only those without a clear conscience need fear a knock on the door at midnight. Governments' enthusiasm for DNA databases needs to be matched by commensurate statutory protection, transparency and oversight — and vigilance by citizens. ■

## Toxic alert

A method of knocking out genes in mice needs more discrimination than many have recognized.

One of the most common ways to investigate the role of a gene in human physiology is to delete its equivalent from a mouse genome and to observe the effect. The use of one enzyme in particular, the recombinase 'Cre', has revolutionized the study of gene function in mice. The technique allows researchers to introduce mutations and gene deletions in a tissue or cell type at any stage.

Hundreds of studies using this technology have been published since it was introduced more than ten years ago, shedding light on areas such as important developmental processes and the role of numerous genes in, for example, the immune or nervous systems, or in various diseases.

Briefly, it works by introducing the target DNA sequence used by the Cre enzyme, known as a *loxP* site, to either end of the gene sequence in question. By subsequently introducing the Cre enzyme, the sequence is excised. Gene targeting can be regulated by controlling where Cre is expressed or activated.

But the technology is not without its pitfalls. A number of issues have been described in a recent overview (M. Schmidt-Supprian and K. Rajewsky *Nature Immunol.* **8**, 665–668; 2007). Readers, authors and editors alike need to be alert to one particular problem: the potential toxicity of Cre expression to cells.

The induction of cell death as a consequence of Cre activity, unrelated to the targeting of any specific gene, is thought to occur when

Cre targets sites similar to *loxP* that are present in genomic DNA, thereby inducing mis-recombination and DNA damage. Most mice strains in which Cre is expressed seem to develop normally and do not show any overt signs of Cre toxicity, and it is somewhat unclear exactly under what conditions it arises. It has been suggested to result from long-term expression of high levels of the enzyme.

Regardless of the exact mechanism and circumstances, Cre toxicity is clearly a potential problem, yet in the view of some researchers it has been neglected or played down in the community. In fact, one study has systematically analysed studies using a particular Cre mouse strain and found that in more than half of the cases the appropriate control for potential Cre toxicity — the use of the same mice without the *loxP*-flanked target gene — was not included (J.-Y. Lee *et al. J. Biol. Chem.* **281**, 2649–2653; 2006). *Nature* is aware that it has in the past published papers in which such controls were lacking, although many will no doubt have been independently validated with other techniques at the time or subsequently.

It can be argued that potential toxicity due to Cre expression becomes pertinent only when the observed phenotype resulting from gene targeting involves cell death, but the complexity of biological processes probably warrants attention to the issue in all experiments. Researchers planning experiments should take into account the need for additional mice as controls. Editors at *Nature* will consider the issue and the appropriate controls with referees during the assessment of submitted papers.

No technology is without caveats, and — as the *Nature Immunology* article concludes — there will always be a degree of uncertainty with which researchers have to live. But in the interest of best scientific practice, everyone involved would be wise not to neglect the dangers and subtleties at play even in routine experiments. ■