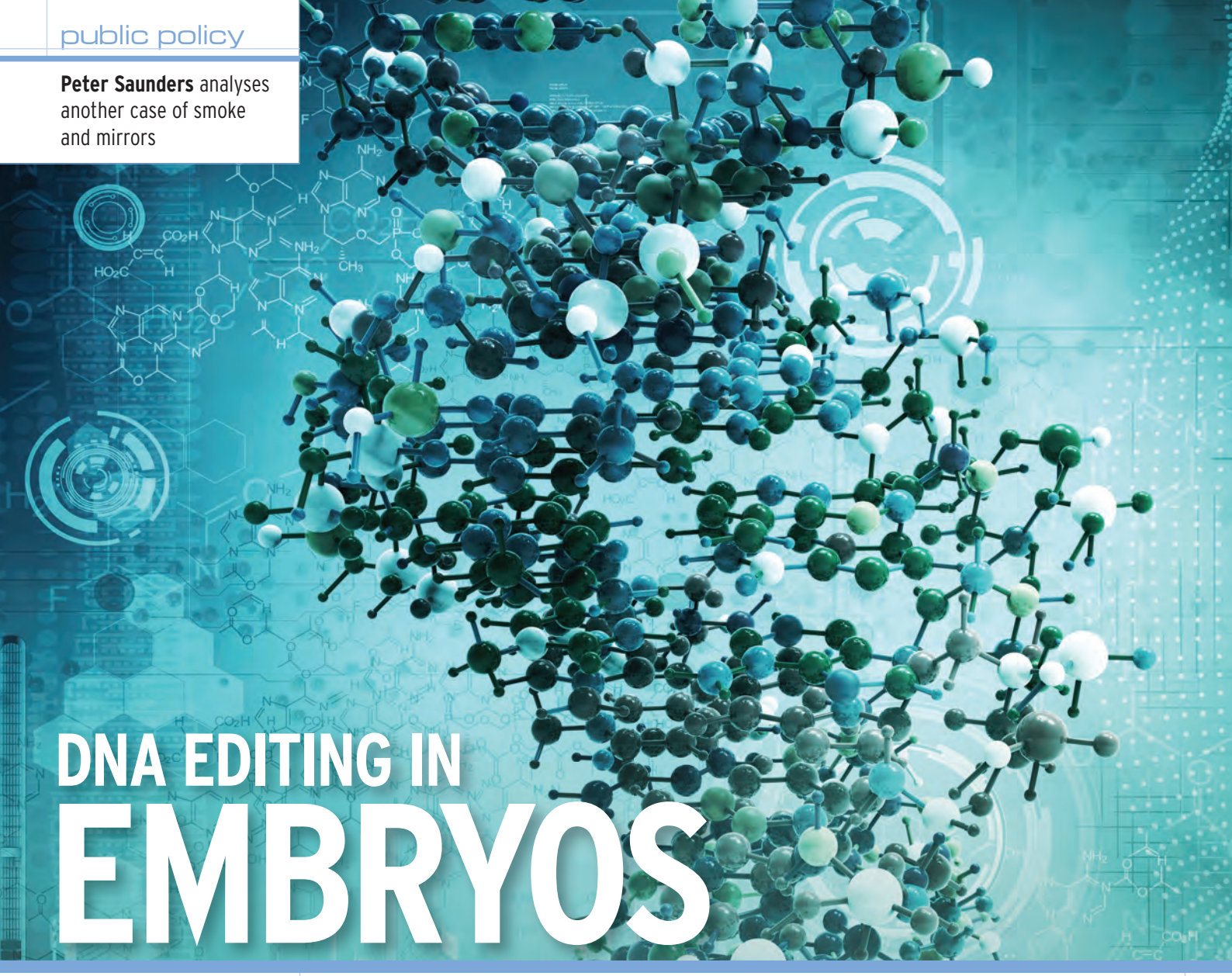
Peter Saunders analyses another case of smoke and mirrors



DNA EDITING IN EMBRYOS

key points

- The UK wants to go it alone with DNA editing in embryos (germline gene editing).
- The process has come in for huge criticism internationally.
- Genetic abnormalities which result in implantation failure (either in IVF or naturally) or miscarriage are chromosomal abnormalities, not abnormalities in single genes.
- We have no way of knowing the consequences of implementation. Here is another example where statutory authorities have failed to stand up to scientists.

Research scientist Dr Kathy Niakan, from the Francis Crick Institute in London, received the go-ahead from the fertility regulator to genetically modify human embryos on 1 February. This is the first time a country has considered the technique in embryos and approved it.[1] She expects to start the new research as early as the first quarter of this year.

Niakan wants to use a new technique called Crispr-Cas9 to 'edit' genes in day-old human embryos left over from IVF in order to discover what role they play in normal embryo development. She plans to start with a gene called Oct4, which is thought to have a critical role in embryo development, and then move onto other genes, but no doubt further requests will follow once the principle has been established.

Controversy

Although gene editing to treat some genetic diseases in *fully developed* human beings appears to have huge early promise (such as in the case of Layla Richards who was saved from terminal leukaemia in London last year[2]), gene editing in embryos (germline gene editing) has come in for huge criticism internationally and has so far only been attempted (unsuccessfully) in China.

The research is highly controversial for several reasons. First, it will result in the destruction of the embryos being studied (each will be destroyed and examined at seven days and Niakan has already used 736 in similar research in the last three years[3]).

Second, it has attracted international criticism, mainly driven by concerns about safety and unforeseen consequences. Any genetic change made in a day-old embryo will be expressed in every cell of the developing human being, including reproductive cells (sperm and egg), and will therefore, if implantation follows, be passed on down the generations.[4]

Third, scientists' claims, propagated by *The Times*[5] and the BBC,[6] that allowing GM embryos would 'give a massive boost to IVF success rates' have little evidence base and appear aimed at seducing regulators into giving a green light for what most countries already ban.

Infertility and miscarriage

Niakan has argued that her research is necessary because 'miscarriages and infertility are extremely common, but they're not very well understood' and that it 'could really lead to improvements in infertility treatment'.[7]

In fact, we already have quite a good understanding of what causes IVF failure and miscarriage and it has very little to do with anything that can fixed by Crispr-Cas9.

The average implantation rate in IVF is about 25%. Inadequate uterine receptivity is responsible for approximately two-thirds of implantation failures, whereas the embryo itself is responsible for only one-third of these failures.

Chromosomal abnormalities, rather than problems with individual genes,[8] are thought to be responsible for most *embryo-related* implantation failure and, amongst these, aneuploidy (an abnormal number of chromosomes) is the most frequent.[9,10] Chromosomal dislocations, deletions and inversions also contribute and all these abnormalities are more common in women of increased reproductive age. Aneuploidy is extremely common. At least 40-50% of blastocysts have aneuploidy,[11,12,13] along with 30% of eggs and 7% of sperm.[14]

Down syndrome is the best known form of aneuploidy and is caused by an additional 21st chromosome (trisomy 21). Edwards' syndrome and Patau's syndrome are caused by trisomy 18 and 13.

Babies with these conditions are often born alive but most other aneuploidies are lethal in utero – causing failed implantation or miscarriages.

The commonest causes of miscarriages are trisomy 16 and 22. In a 2015 study of 832 early miscarriages, 368 (44.23%) were found to be abnormal. 84.24% (310/368) of these were aneuploidies. Trisomy 16 accounted for 121 of these 310 followed by trisomy 22, and X monosomy.[15]

It may be that trisomies of chromosomes other than 13, 18, 16, 21 and 22 (there are 23 chromosomes in each egg and sperm) may also prove lethal before implantation but are less easily detected. This would be a worthwhile area of further research.

The major flaw

The key point here is that the genetic abnormalities which result in implantation failure (either in IVF or naturally) or miscarriage are *chromosomal* abnormalities, not abnormalities in single genes. But only abnormalities in *single genes* can be readily fixed with gene editing of the sort that the Crick Institute is proposing. Gene editing tools like Crispr-Cas9 do not fix chromosomal abnormalities.

This simple fact has not been made clear to the media, to decision makers or the public. In fact researchers like Niakan, who must be aware of it, seem rather to have gone out of their way to fuel the misconception that gene editing will help IVF success rates.

This, it seems to me, is both negligent and disingenuous, as the key factor that is driving the call to approve this controversial new research is the supposed benefit to infertile couples.

British scientists have form in making wild and rash promises about new treatments in order to get approval for controversial research – the hype around animal-human hybrids[16] and three parent embryos (mtDNA) are cases in point.

Few now will remember then Prime Minister Gordon Brown's empty promises in *The Guardian* newspaper on 18 May 2008 of animal-human hybrids ('cybrids') offering 'a profound opportunity to save and transform millions of lives' and his commitment to this research as 'an inherently moral endeavour that can save and improve the lives of thousands and over time millions of people'.[17]

That measure was supported in a heavily whipped vote by the then Labour government as part of the Human Fertilisation and Embryology Bill, now the HFE Act, following a high-profile media campaign by the same science journalists and research scientists. But 'cybrids' are now a farcical footnote in history. They have not worked and investors have voted with their feet.

David King, who runs the watchdog group Human Genetics Watch, remarked at the time, in words that are equally applicable today: 'The decision is very disappointing, but comes as no surprise, since the HFEA can never say no to scientists. These experiments are scientifically useless and morally very problematic. The research lobby has distorted the scientific facts in order to defuse criticism.'[18]

Conclusions

In reality, this project seems to be more about satisfying scientific curiosity about how genes work in the normal development of the human embryo with any therapeutic application a very distant dream.

Gene editing in adults and children has great therapeutic promise for treating and perhaps even preventing some genetic disease. But gene editing of the embryo (germline editing) is extremely controversial and potentially very dangerous. Scientists around the world think that we are mad in Britain to be pursuing it.

At the very least, much more work is needed in animal models before we contemplate using it on human embryos; and in particular we need to establish first in animals whether or not it is likely to have any benefit at all in preventing infertility before we start making rash promises about IVF success rates in humans.

The case for gene editing in embryos needs to be based on real facts and evidence, not false hope, hype and misleading or frankly false claims from research scientists and their irresponsible press office portals (ie the BBC and *Times*).

The HFEA does not have a great track record in carefully scrutinising new scientific developments, and appears to have capitulated too easily in the face of Niakan's specious claims about helping unfertile couples.

There might conceivably one day be a case for germline DNA editing. But this is not it.

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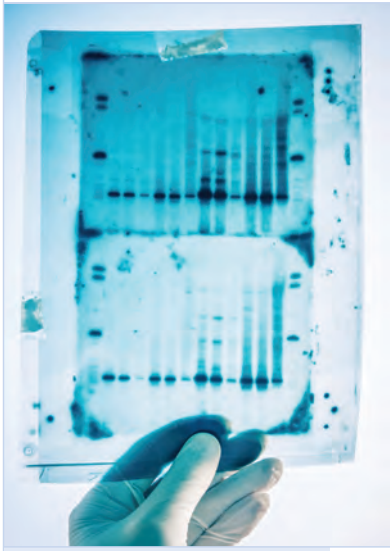

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