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Humans 2.0

Of the germline engineering approaches, mitochondrial replacement, rather than gene editing, is poised to have the greatest impact on our lives.

The genetically modified walk among us. Hundreds of cancer survivors walk around with engineered chimeric antigen receptor immune cells in their veins. A few visually impaired patients see with eyes that contain the gene encoding all-*trans* retinyl ester isomerase delivered by an adeno-associated virus (AAV). Some children born with severe combined immune deficiency now harbor engineered cells expressing adenosine deaminase in their bones. And the ranks of the genetically modified will be further swelled by the 2016 decision in the United Kingdom to legalize mitochondrial replacement therapy (MRT).

As the articles in this issue clearly illustrate, genetic technologies are poised to have an increasing influence on our lives. In terms of germline engineering technology, both embryo gene editing and MRT are currently being explored as interventions to prevent genetic diseases lacking cures.

To date, just three studies have reported the use of CRISPR–Cas9 in diploid human embryos. In March, Jianqiao Liu's laboratory in China showed it was feasible to correct via homology-directed repair (HDR) mutations associated with diabetes mellitus and beta thalassemia (*Mol. Genet. Genomics* **292**, 525–533, 2017). In August, a US group led by Shoukrat Mitalipov reported (*Nature* **548**, 413–419, 2017) correction of a heterozygous *MYBPC3* mutation associated with cardiomyopathy—the HDR-mediated mechanism of which remains controversial (*bioRxiv* https://dx.doi.org/10.1101/181255). And in September, Kathy Niakan's UK team described the knockout of *OCT4* (*POU5F1*) via non-homologous end joining (NHEJ), detailing its deleterious effects on the embryo development and gene expression (*Nature* **550**, 67–73, 2017).

These early studies show the potential of germline editing in advancing our knowledge of the early stages of human embryo development. They may also help to unravel some disorders of early development and causes of infertility—research goals that this journal supports.

MRT, on the other hand has a much longer history of technology development (see p. 1059), both in the context of mitochondrial disease and fertility (although the latter is controversial). Eight years ago, the Mitalipov laboratory showed that meiotic spindle transfer MRT is safe and effective in non-human primates, prompting four independent scientific reviews by the UK Human Fertilisation and Embryology Authority (HFEA) and ultimately leading to the approval of MRT last year. Even so, the procedure is not without concerns: in some cases, mitochondrial reversion is seen, where healthy donor mtDNA is successively outcompeted by small starting proportions of carryover carrier mtDNA during cell division (*Nature* **540**, 270–275, 2016).

For both germline editing and MRT, national authorities have emphasized the need for caution in terms of IVF clinical applications. Last February, the US National Academies released a report entitled "Human Genome Editing: Science, Ethics, and Governance," concluding that "clinical trials using heritable germline genome editing should be permitted" only in "serious conditions" where the target loci have been convincingly demonstrated to predispose an individual to or cause disease, where the corrected genes are known to be associated with ordinary health in the population, and where no "reasonable alternatives" exist. Similarly, the HFEA has recommended application of MRT only in situations "where inheritance of the disease is likely to cause death or serious disease and where there are no acceptable alternatives."

In this respect, MRT and germline editing look like very different propositions. For women who carry high levels of abnormal mtDNA in their oocytes, embryo selection approaches, such as preimplantation genetic diagnosis (PGD), are not suitable. Thus, MRT offers a lifeline for the ~150 births per year in the United Kingdom affected by mitochondrial disease.

In contrast, the only cases where germline editing may be preferable to PGD is when all embryos carry a harmful mutation (e.g., one parent is homozygous for the dominant mutation, as in Huntington's, or both parents are homozygous for a recessive mutation as in some forms of deafness). In all other cases, it is difficult to imagine why an IVF clinic would go to all the trouble of engineering an embryo—with all the attendant risks of off-target effects and genetic mosaicism—when in most cases PGD alone could be used to simply select a healthy embryo.

In the coming months, we will see the initiation of the first clinical trials of MRT at the Newcastle Fertility at Life center in the United Kingdom. To ensure rapid progress with these germline engineering procedures, it is critical that clinical studies remain under stringent oversight and that there is close follow-up of offspring over time. History has shown us that private IVF clinics rarely do follow-up studies. In the 2000s, for instance, at least 30 children were born using a primitive form of MRT before the US Food and Drug Administration shut down the operation; little if any kind of health tracking of the modified children was ever carried out. Similarly, just last year, an application of MRT in a Leigh syndrome patient was carried out in a Mexican IVF clinic (*Reprod. Biol. Online* **33**, 529–533, 2016). Again, there has been little attempt to put in place a procedure for detailed follow-up on the child.

In the United States, there are no MRT trials. This is because a moratorium on any kind of germline engineering was passed by the US Congress earlier this year (Public Law No 115-31 §736, 2017). The US funding ban applies to all clinical research on human embryos and captures both MRT and heritable gene editing.

US lawmakers argue that the ethical and societal concerns of germline engineering justify their ban. But if the UK trials of MRT prove successful, pressure will grow for them to reconsider their decision. MRT could save as many as 1,000 American children from mitochondrial disease every year. Unlike heritable gene editing, this type of germline engineering is ready to make a difference in many human lives.