MRC Harwell

The Mary Lyon Centre
An International Centre For Mouse Genetics
Advancing medicine and knowledge through the discovery and investigation of mouse models of human disease

Nuffield Council on Bioethics
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Genome Editing Call for Evidence

Dear Andy,

The Mary Lyon Centre is a large-scale mouse genetics infrastructure at MRC Harwell, near Oxford. Our activities are focused on applying mouse genetics, mutagenesis and phenotypic screening to investigate mammalian gene function at a systems level. This work is also aimed at discovering new animal models which may shed light into aspects of human disease. We are a partner of the International Mouse Phenotyping Consortium (IMPC) and therefore part of a global effort to annotate the function of the entire mouse genome.

Genome editing is affording us the opportunity to investigate the function of mouse genes in a number of ways that would technically/financially be problematic otherwise. Gene targeting strategies in the mouse are well developed and very successful, however do have some limitations. These include loci that are refractory to routine approaches, limitations on the genetic background available in embryonic stem cells, timelines which often preclude PhD or 3-year post-doctoral projects and the high associated expense and risk.

Genome editing promises to deliver genetically altered (GA) mouse strains quicker, more efficiently, without introducing other, potentially compromising genetic elements (such as selection cassettes required for targeting) and most importantly, in a rapid timeframe likely to be less than 6 months for most loci. However, in terms of animal care and governance of animal facilities there are a number of issues which need to be explored and managed:

- Care of genetically altered lines: The rapid and potentially prolific generation of many different lines of genetically altered animals will signal a change in the type of animal care required from some facilities. Larger colonies of established, well characterized lines will be replaced by many different smaller colonies of mice with unknown welfare needs.

- Genetic quality control: In the animal holding rooms it will become essential to have systems in place which can manage and ensure no cross-contamination between different GA lines potentially carrying multiple alterations of the same gene. This will require some animal care and scientific staff to increase their knowledge of genetics.

- Complexity of potential genetic make-up: Employing current CRISPR/Cas9 methodologies for creating new mutations results in initial animals that are mosaic and are likely to transmit unexpected new alleles, as well as those for which they have been genotyped. CRISPR/Cas9 technologies also make multiple edits of the genome within the same founder individual possible. This is a level of genetic complexity that is unprecedented when compared to any standard method for genome engineering. This will raise additional challenges in terms of training of both scientific and animal care staff in the context of an otherwise seemingly simple and accessible technique.

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- Line integrity: As GA mouse lines will be easier and cheaper to produce, there will be a temptation to remake strains at individual establishments rather than import from central repositories. This runs the risk of genetic drift of background strains and laboratories within the same field working on non-standardised models.

- Moving laboratory animal science closer to clinical practice: For many years the direct connections between laboratory animal work and the patient groups has been somewhat limited. The identification of a specific mutation carried by a family involved in a genomic program opens up the prospect of 'personalised' transgenic animals more than ever before, a closer link between the animal research and the individual patients and the prospect that not everyone will support a model being generated of 'their own' mutation.

Without a doubt, genome editing is a tremendous opportunity for genetic science. It will make accessible parts of the genome we have failed or would never have attempted to access before. However, like every other technological leap forwards, it needs to be accompanied by relevant training, quality control and discussion on its implications to the groups which are most likely to benefit.

Yours sincerely,

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