Every Silver Lining has a Cloud: The Scientific and Animal Welfare Issues Surrounding a New Approach to the Production of Transgenic Animals

Robert D. Combes\(^1\) and Michael Balls\(^2\)

\(^1\)Independent Consultant, Norwich, UK; \(^2\)c/o FRAME, Russell and Burch House, Nottingham, UK

Summary — The scientific basis and advantages of using recently developed CRISPR/Cas-9 technology for transgenesis have been assessed with respect to other production methods, laboratory animal welfare, and the scientific relevance of transgenic models of human diseases in general. As the new technology is straightforward, causes targeted DNA double strand breaks and can result in homozygous changes in a single step, it is more accurate and more efficient than other production methods and speeds up transgenesis. CRISPR/Cas-9 also obviates the use of embryonic stem cells, and is being used to generate transgenic non-human primates (NHPs). While the use of this method reduces the level of animal wastage resulting from the production of each new strain, any long-term contribution to reduction will be offset by the overall increase in the numbers of transgenic animals likely to result from its widespread usage. Likewise, the contribution to refinement of using a more-precise technique, thereby minimising the occurrence of unwanted genetic effects, will be countered by a probable substantial increase in the production of transgenic strains of increasingly sentient species. For ethical and welfare reasons, we believe that the generation of transgenic NHPs should be allowed only in extremely exceptional circumstances. In addition, we present information, which, on both welfare and scientific grounds, leads us to question the current policy of generating ever-more new transgenic models in light of the general failure of many of them, after over two decades of ubiquitous use, to result in significant advances in the understanding and treatment of many key human diseases. Because this unsatisfactory situation is likely to be due to inherent, as well as possibly avoidable, limitations in the transgenic approach to studying disease, which are briefly reviewed, it is concluded that a thorough reappraisal of the rationale for using genetically-altered animals in fundamental research and by the pharmaceutical industry, and for its support by funding bodies, should be undertaken. In the meantime, the use of CRISPR/Cas-9 to generate new transgenic cells in culture is to be guardedly encouraged.

Key words: animal wastage, CRISPR/Cas-9, non-coding regions, non-human primates, non-predictive disease models, reduction, targeted effects, transgenesis.

E-mail address for correspondence: robert_combes3@yahoo.co.uk

Introduction

The new approach referred to in the title is called CRISPR/Cas-9, and was originally developed in 2012 (1, 2). The silver lining is the fact that it optimises, simplifies, and shortens the time taken for producing new transgenic animal strains. But the cloud, for those concerned about animal welfare at least, is the fact that its application will not only increase the range and diversity of transgenic rodent strains, but will greatly expedite transgenesis in other species, including non-human primates (NHPs; 3).

Since 1974, when the first genetically-modified mouse was created, there have been many attempts to improve the efficiency and speed of transgenesis (4). To achieve stable integration and expression of the transgene in host DNA, the majority of transgenic mice are produced by the microinjection of a DNA fragment equivalent to several kilobases into the pronuclei of fertilised eggs. The transgene is constructed by using recombinant DNA technology, during which it is inserted into a vector (DNA fragment), and then amplified to yield high copy numbers. The vector is engineered to carry an appropriate promoter, to permit