



Invited review: Breeding and ethical perspectives on genetically modified and genome edited cattle

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ABSTRACT

The hot topic of genetic modification and genome editing is sometimes presented as a rapid solution to various problems in the field of animal breeding and genetics. These technologies hold potential for future use in agriculture but we need to be aware of difficulties in large-scale application and integration in breeding schemes. In this review, we discuss applications of both classical genetic modifications (GM) using vectors and genome editing in dairy cattle breeding. We use an interdisciplinary approach considering both ethical and animal breeding perspectives. Decisions on how to make use of these techniques need to be made based not only on what is possible, but on what is reasonable to do. Principles of animal integrity, naturalness, risk perception, and animal welfare issues are examples of ethically relevant factors to consider. These factors also influence public perception and decisions about regulations by authorities. We need to acknowledge that we lack complete understanding of the genetic background of complex traits. It may be difficult, therefore, to predict the full effect of certain modifications in large-scale breeding programs. We present 2 potential applications: genome editing to dispense with dehorning, and insertion of human genes in bovine genomes to improve udder health as an example of classical GM. Both of these cases could be seen as beneficial for animal welfare but they differ in other aspects. In the former case, a genetic variant already present within the species is introduced, whereas in the latter case, transgenic animals are generated—this difference may influence how society regards the applications. We underline that the use of GM, as well as genome editing, of farm animals such as cattle is not independent of the context, and should be considered as part of an entire process, including, for example, the assisted reproduction technology that needs to be used. We propose that

breeding organizations and breeding companies should take an active role in ethical discussions about the use of these techniques and thereby signal to society that these questions are being responsibly addressed.

Key words: genome editing, genetic modification, cattle, ethics, breeding program

INTRODUCTION

The European Food Safety Authority (EFSA) defines genetic modification (GM) as follows: “Genetic modification of an animal involves altering its genetic material by adding, changing or removing certain DNA sequences in a way that does not occur naturally. It aims to modify specific characteristics of an animal or introduce a new trait, such as disease resistance or enhanced growth” (EFSA, 2017). The generation of transgenic animals implies insertion of DNA sequences from another organism using genetic engineering. It opens up possibilities to introduce traits from other species into farm animals, which could not be done through traditional breeding. For a genetic modification to be inherited, it must be present in the gametes and integrated into a chromosome. In the case of genome editing, no foreign DNA is incorporated in the genome, and there is no consensus on whether genome edited organisms should be referred to as GM (Cotter et al., 2015; Bruce, 2016b; Nuffield Council on Bioethics, 2016). Similar genetic changes may or may not occur naturally in the same species or breed. The classification may be important in the process of obtaining legal approval for applications. For the discussion in this review, however, the preconditions and effects of the genetic changes are more important than the classification of the techniques.

A rapidly increasing number of publications suggest agricultural applications of GM or genome editing of livestock. Modification or editing of animal genomes raises several ethical questions, and societal acceptance of GM animals has been shown to be influenced by both the species modified and whether the animals are to be used for production of food or pharmaceuticals (Frewer

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et al., 2013a,b). Citizen concerns reflect the complex ethical and safety considerations that need to be made by authorities before GM animals and products can be released on the market. Commercialization of GM animal products is a complex matter. The first GM animal for human consumption, the AquaAdvantage salmon (AquaBounty Technologies, Maynard, MA), was only recently approved (FDA, 2015), more than a decade after the first attempts of approval. This salmon is produced using classical GM, and there is currently no comparable case of an animal product for human consumption from genome edited animals. Besides the species involved and the perceived importance of the product, the type of technology used and the absence or presence of alternative ways to reach the goal can influence ethical and practical considerations. Farm animal genomes can now be modified without leaving traces of the technology used and with increasing precision and efficiency (Laible et al., 2015), and these are relevant aspects. Even if technical and legal obstacles are settled, ethical issues and practical breeding questions regarding introduction and multiplication of modified or edited genetic variants in the populations will remain. In this process, possible ethical concerns need to be considered. There are probably lessons to be learned from societal reactions to previous attempts to introduce GM in livestock. To prepare for possible reactions to genome editing, early ethical discussions within the scientific and animal breeding community could be valuable.

Most articles about GM farm animals deal with biotechnical developments, but there is increased interest in societal and ethical aspects, too, requiring multidisciplinary approaches (Frewer et al., 2013a). Nevertheless, there is a lack of scientific papers combining deep discussions between animal breeders and ethicists in the author team, which is why we chose an interdisciplinary approach in this review. Most researchers in animal breeding and genetics (including the 3 geneticist authors), appreciate development of methods and techniques that increase efficiency in breeding. We also tend to take already routinely applied inventions for granted and instead direct our focus, and possibly ethical concerns, toward inventions still in the pipeline. For a researcher in ethics (such as the last author), this may seem incomplete. With this article, we want to discuss potential applications of GM and genome editing of cattle for food production considering both the breeding program and its ethical aspects. By choosing this focus, we do not consider all potential ethical concerns on keeping, breeding, and utilizing animals for the benefit of humans. Also, genetic change of livestock through conventional selective breeding and associated assisted reproduction techniques, are artificial and raise

ethical questions. In this review, however, we focus on some of the ethically relevant aspects of methods directly linked to the use of GM and genome editing.

We start with a short background on the use of GM and genome editing in livestock, and on assisted reproduction techniques (**ART**) that enable such genetic changes, followed by possible consequences of applications in breeding schemes. Each part is followed by an ethical reflection. In later sections, we focus on 2 cases: (1) genome editing to eliminate dehorning, and (2) insertion of human genes into bovine genomes to improve udder health. These cases are compared in a general discussion focusing on ethical parameters selected from the sections above, followed by some conclusions.

GENETICALLY MODIFIED AND GENOME EDITED CATTLE

Several recent review articles have been published about genetic modifications of animals generated by different methods in various species, including cattle. Genetic modifications of cattle have often targeted the udder, aiming for improved udder health or milk quality aspects. Lievens et al. (2015) classified GM animals of 15 species as either food-producing livestock, medical bioreactors, or companion animals. Five out of 6 studies of GM cattle in their review dealt with cattle as livestock, in which improved animal health or milk composition were the goals; only 1 study focused on cattle as bioreactors.

Laible et al. (2015) presented an overview of different methods used on farm animal species: genetic changes of cattle applicable in agriculture have been generated using both genome editing and classical GM techniques such as microinjection, and random or targeted cell-mediated techniques. The development of these methods applicable in cattle for different purposes was further described by Wang (2015). In a recent overview, Tan et al. (2016) presented the background to genome editing in livestock and discussed future applications and challenges for the techniques. Although technical details and comprehensive overviews of GM and genome edited farm animals can be found in other publications, we will discuss here a few specific cases from an interdisciplinary breeding and ethics perspective.

Reproduction Techniques—A Precondition

The advancements in controlled genetic modifications of farm animals would not have been possible without the development and refinement of ART, including in vitro fertilization, in vitro cultivation of embryos, and cloning techniques. The use of somatic cell nuclear transfer (**SCNT**) or embryo microinjections, together

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