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Genetic modification of food animals

Alison Louise Van Eenennaam

Animal breeders have used a variety of methods in selective breeding programs to genetically improve food animal species. Recently this has included the use of both genetic engineering and genome editing, particularly for targeting improvement in traits for which there is no within-species or within-breed genetic variation. Both intraspecies and interspecies allele substitutions and gene knock-ins have been accomplished with genome editing tools, targeting a number of important traits. The regulatory status of such animals is unclear as the definition of a regulated article is not consistent among different regulatory agencies and organizations. In the absence of a harmonized global regulatory approach to the genetic improvement of animals, it will be difficult for breeders to effectively achieve sustainable breeding objectives.

Address
Department of Animal Science, University of California, One Shields Avenue, Davis, CA 95616, USA

Corresponding author: Van Eenennaam, Alison Louise (alvaneenennaam@ucdavis.edu)

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Introduction

Animal breeders have been directing livestock evolution since animals were first domesticated. Initially, the tools available to breeders were simply observations on what was perceived to be the desired appearance and the selective mating of chosen parents. One only needs to look at the differences between a Chihuahua and a Great Dane, relative to their wild ancestor the wolf, to appreciate that conventional selection is a powerful force for genetic change. Over time, the tools and methods used to make genetic improvement have advanced, and this has accelerated the rate of genetic change. Subjective observations were replaced by objective measurements, and sophisticated statistical methods were implemented to isolate heritable genetic effects from environmental influences [1]. The rate of genetic improvement was further accelerated by combining genetic selection methods with advanced reproductive technologies (ART) such as artificial insemination (AI) and embryo transfer (ET).

The impact of selective breeding programs on the footprint of agriculture and food production is difficult to overstate. It has been estimated that historic genetic improvement in selected traits (e.g. milk/meat output, growth efficiency) has resulted in a 1% per year reduction in greenhouse gas (GHG) emissions per unit food produced (e.g., a tonne of beef/sheep meat) [2]. Capper *et al.* [3] compared the environmental footprint of US dairy production between 1944 and 2007 and reported that although the carbon footprint per individual cow had increased over time, the carbon footprint per unit of milk was 63% lower in 2007 than it was in 1944. Perhaps this point is best illustrated by calculating that, *sans* genetic improvement, we would need in excess of 30 million dairy cows in the United States to produce the amount of milk that 9 million cows were able to produce in 2014. Genetic improvement is undoubtedly one of the most powerful drivers of agricultural sustainability.

Given this history and the fact that conventional, or 'artificial', selection is largely uncontroversial, it might be expected that innovations in breeding methods would be mostly undisputed as self-evident approaches to help meet the projected increase in global animal protein demand. However, this is clearly not the case given the decades-old global debate [4] over the use of one particular breeding method, genetic engineering. Plants and animals that are destined for food and which have been genetically modified using this particular breeding method, although interestingly not those modified for medical purposes using exactly the same techniques, generate absolute moral opposition [5] and have been at the epicenter of a controversial and rancorous scientific debate. This review will discuss recent developments in the use of modern biotechnologies in food animal breeding programs.

Genetic engineering

One definition of genetic engineering (GE) is a process in which recombinant DNA (rDNA) technology is used to introduce desirable traits into an organism. The real power of this technology is in enabling breeders to access genetic variation that is not otherwise normally present in the target species, especially for traits such as disease resistance. Genetically engineered animals were first produced in the late 1970s, and the first GE livestock were produced in 1985 [6]. Thirty years later, GE animals have been produced by researchers globally in many different food animal species and for a variety of target

Table 1

Examples of genetically engineered (GE) food animals that have been produced for agricultural applications

Species	Transgene	Origin	Trait/Goal
Cattle	Lysozyme, Lactoferrin	Human	Milk composition; animal health; mastitis resistance
	Prion Protein (PrP) shRNA	Knockout	Animal health
	α-Casein, κ-Casein	Bovine	Milk composition
	Omega-3 (Fat-1)	Nematode	Milk composition
	β-Casein miRNA	Cattle	Milk composition
	Lysostaphin	Bacterial	Mastitis resistance
	SP110	Murine	Bovine Tuberculosis resistance
	Myostatin shRNA	Knockout	Increased muscle yield
Chicken	alv6 envelope glycoprotein	Viral	Disease resistance
	short hairpin RNA	Viral	Disease resistance
	LacZ	Bacterial	Animal Health
Carp	Growth Hormone	Piscine	Growth rate
	Lactorferrin	Human	Disease resistance
Catfish	Cercopin B	Insect	Disease resistance
Goat	Lysozyme	Human-Bovine	Animal Health
	Stearoyl-CoA desaturase	Rat-Bovine	Mastitis resistance
	Lactoferrin	Human	Prophylactic treatment
	Human beta-defensin 3	Human	Milk composition
	Myostatin shRNA	Knockout	Increased muscle yield
	Prion Protein (PrP) shRNA	Knockout	Animal health
Pig	Phytase	*E. coli*-Mouse	Feed uptake; decreased phosphorus in manure
	Growth hormone, growth hormone releasing factor, insulin-like growth factor-1	Human-Porcine	Growth rate
	cSKI	Chicken	Muscle development
	Lysozyme	Human	Piglet survival
	Unsat. fat. acid (FAD2)	Spinach	Meat composition
	Omega-3 (Fat-1)	Nematode	Meat composition
	α-Lactalbumin	Bovine	Piglet survival
	Mx, Iga, mouse monoclonal antibody (mAb)	Murine	Disease Influenza resistance
Salmon	Growth hormone	Piscine	Growth rate
	Lysozyme	Piscine	Animal health
	wflAFP-6	Piscine	Cold tolerance
Sheep	Growth hormone, growth hormone releasing factor	Ovine	Growth rate
	IGF-1, wool intermediate filament keratin, CsK	Ovine, Bacterial	Wool growth
	Visna resistance	Viral	Disease resistance
	Omega-3 (Fat-1)	Nematode	Meat composition
	Prion Protein (PrP)	Knockout	Animal health
	Mouse monoclonal antibody	Murine	Disease Influenza resistance
Trout	Follistatin	Piscine	Muscle development

Adapted from Lievens *et al.* [7] and Laible *et al.* [8].

traits (Table 1), although to date none have successfully moved all the way from the laboratory to retail food outlets.

Unsurprisingly, many of the applications in Table 1 align with common animal breeding objectives targeted by conventional breeding programs. To date, the inefficiencies of producing GE animals using random integration following microinjection of an rDNA construct or viral transformation methods, along with the uncertainties and expense of the regulatory process, have impeded the commercialization of GE animals for food purposes [9]. Some GE food animals have been approved for biomedical pharmaceutical production including goats producing ATryn® (human antithrombin-III), rabbits producing Ruconest™ (Rhucin® outside the EU), and chickens producing Kanuma™ (sebelipase alfa). There have also been some trials using GE insects for pest control applications. Only a single GE animal, the fast-growing AquAdvantage Atlantic salmon, has been approved for food purposes. The founder of this GE fish line was generated in 1989 [10], and the product underwent a lengthy and unpredictable regulatory evaluation [11]. Although it was approved in December 2015 by the United States Food and Drug Administration (FDA), its future is still uncertain. Commercial sale of the fish for food is currently blocked by a pending federal bill introduced to the United States House of Representatives on March 4, 2016 requiring mandatory labeling of the product and an additional review of 'the study of genetically modified salmon's impact on wild salmon stocks carried out by the FDA' by an independent scientific organization.

Genome editing methods

Genome or gene editing refers to the use of site-directed nucleases (SDN) to precisely introduce a double stranded