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### Citation for published version:

Fahrenkrug, SC, Blake, A, Carlson, DF, Doran, T, Van Eenennaam, A, Faber, D, Galli, C, Gao, Q, Hackett, PB, Li, N, Maga, EA, Muir, WM, Murray, JD, Shi, D, Stotish, R, Sullivan, E, Taylor, JF, Walton, M, Wheeler, M, Whitelaw, B & Glenn, BP 2010, 'Precision genetics for complex objectives in animal agriculture', Journal of Animal Science, vol. 88, no. 7, pp. 2530-2539. <https://doi.org/10.2527/jas.2010-2847>

### Digital Object Identifier (DOI):

[10.2527/jas.2010-2847](https://doi.org/10.2527/jas.2010-2847)

### Link:

[Link to publication record in Edinburgh Research Explorer](#)

### Document Version:

Publisher's PDF, also known as Version of record

### Published In:

Journal of Animal Science

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# JOURNAL OF ANIMAL SCIENCE

*The Premier Journal and Leading Source of New Knowledge and Perspective in Animal Science*

## **Precision genetics for complex objectives in animal agriculture**

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*J ANIM SCI* 2010, 88:2530-2539.

doi: 10.2527/jas.2010-2847 originally published online March 12, 2010

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.journalofanimalscience.org/content/88/7/2530>



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# Precision genetics for complex objectives in animal agriculture

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**ABSTRACT:** Indirect modification of animal genomes by interspecific hybridization, cross-breeding, and selection has produced an enormous spectrum of phenotypic diversity over more than 10,000 yr of animal domestication. Using these established technologies, the farming community has successfully increased the yield and efficiency of production in most agricultural species while utilizing land resources that are often unsuitable for other agricultural purposes. Moving forward, animal

well-being and agricultural sustainability are moral and economic priorities of consumers and producers alike. Therefore, these considerations will be included in any strategy designed to meet the challenges produced by global climate change and an expanding world population. Improvements in the efficiency and precision of genetic technologies will enable a timely response to meet the multifaceted food requirements of a rapidly increasing world population.

**Key words:** cross-breeding, genetic engineering, genetic technology, hybridization, phenotypic diversity, selection

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J. Anim. Sci. 2010. 88:2530–2539  
doi:10.2527/jas.2010-2847

## INTRODUCTION

Agricultural science has been enormously successful in providing an inexpensive supply of high-quality and safe foods to developed and developing nations. These advancements have largely come from the implementation of technologies that focus on efficient production and distribution systems as well as selective breeding and genetic improvement of cultured plants and ani-

mals. Although population growth in developed nations has reached a plateau, no slowdown is predicted in the developing world until about 2050, when the population of the world is expected to reach 9 billion (United Nations, 2008). To meet the global food demand will require nearly double the current agricultural output, and 70% of that increased output must come from existing or new technologies (United Nations, 2002).

The global demand for animal products is also substantially growing, driven by a combination of population growth, urbanization, and rising incomes. However, at present, nearly 1 billion people are malnourished (United Nations, 2008). Animal products contain

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Received January 21, 2010.  
Accepted February 26, 2010.

concentrated sources of protein, which have AA compositions that complement those of cereal and other vegetable proteins, and contribute calcium, iron, zinc, and several B group vitamins. In developing countries where diets are based on cereals or bulky root crops, eggs, meat, and milk are critical for supplying energy in the form of fats. In addition, animal-derived foods contain compounds that actively promote long-term health, including bioactive compounds such as taurine, L-carnitine, creatine, and endogenous antioxidants such as carosine and anserine (Chan and Decker, 1994; Williams, 2007). Furthermore, those foods are a rich source of CLA, forms of which have anti-cancer properties (Kelley et al., 2007), reduce the risk of cardiovascular disease (Tricon et al., 2004), and help fight inflammation (Zulet et al., 2005).

## A MANDATE FOR ANIMAL SCIENTISTS

Animal production will play a pivotal role in meeting the growing need for high-quality protein that will advance human health. Our technological prowess will be put to the test as we respond to a changing world and increasingly diverse stakeholders. Intensifying food production likely will be confounded by declining feedstock yields due to global climate change, natural resource depletion, and an increasing demand for limited water and land resources (Foley et al., 2005). Additionally, whereas the moral imperative to feed the malnourished people of the world is unequivocal, a well-fed, well-educated, and vocal citizenry in developed nations places a much greater emphasis on the environmental sustainability of production, the safety of food products, and animal welfare, often without regard for impact on the cost of the food. These diverse priorities will place important constraints on animal agriculture in the coming decades. Despite these daunting challenges, the sheer magnitude of potential human suffering calls on us to assume the reins from our recently lost colleague, Norman Borlaug, to harness technological innovation within our disciplines to keep world poverty, hunger, and malnutrition at bay. As was the case during the Green Revolution, advancements in genetics and breeding will provide a wellspring for a needed revolution in animal agriculture. Indeed, we have entered the era of the genome for most agricultural animal species. Genetic blueprints position us to refine our grasp of the relationships between genotype and phenotype and to understand the function of genes and their networks in regulating animal physiology. The tools are in hand for accelerating the improvement of agricultural animals to meet the demands of sustainability, increased productivity, and enhancement of animal welfare (Green et al., 2007).

## A FUTURE WITH GENETIC SELECTION

The goals of animal genetic improvement are firmly grounded in the paradigm of animal production, which

naturally refers to concepts of efficiency, productivity, and quality. Sustainability and animal welfare are central considerations in this paradigm; an inescapable principle is that the maximization of productivity cannot be accomplished without minimizing the levels of animal stress. Furthermore, the definition of efficiency (product per unit input) requires sustainability. Unnecessary compromises to animal well-being or sustainability are morally reprehensible and economically detrimental to consumers and producers alike.

The vast majority of outcomes from genetic selection have been beneficial for animal well-being. Geneticists try to balance the enrichment of desirable alleles with the need to maintain diversity (Lacy, 1997; Notter, 1999) because they are keenly aware of the vulnerability of monoculture to disease. Genetic improvement programs must always conserve genetic diversity for future challenges, both as archived germplasm and as live animals (Blackburn, 2004). However, unanticipated phenotypes occasionally arise from genetic selection for 2 reasons. First, every individual carries deleterious alleles that are masked in the heterozygous state but can be uncovered by selective breeding. Second, the linear organization of chromosomes leads to certain genes being closely linked to each other on the DNA molecules that are transmitted between generations. Thus, blind selection for an allele that is beneficial to 1 trait also enriches for all alleles that are closely linked to it and either through pleiotropy (genes influencing more than 1 trait) or linkage disequilibrium, undesirable correlated responses in other traits may occur. Geneticists are aware of this and closely monitor the health and well-being of populations that are under selection (e.g., Eitan and Soller, 2004) to ensure that any decrease in fitness is detected and that ameliorative actions are taken to correct problems either by the elimination of carriers from production populations, altering the selection objective to facilitate improvement in the affected fitness traits, or by introducing beneficial alleles by crossbreeding. Increasingly precise molecular tools now allow the rapid identification of genetic variants that cause single-gene defects and facilitate the development of DNA diagnostics to serve in genetic management plans that advance the production of healthy animals. Whole-genome genotyping with high-density, SNP assays will enable the rapid determination of the overall utility of parental lines in a manner that is easily incorporated into traditional quantitative genetic improvement programs (Meuwissen et al., 2001). The approach is known as genomic selection (**GS**) and essentially allows an estimation of the genetic merit of an individual by adding together the positive or negative contributions of alleles across the genome that are responsible for the genetic influence on the trait(s) of interest. Under GS, genetic improvement can be accelerated by reducing the need for performance testing and by permitting an estimation of the genetic merit of animals outside currently used pedigrees. Genomic selection also provides for development of genetic di-

agnostics using experimental populations, which may then be translated to commercial populations, allowing, for the first time, the opportunity to select for traits such as disease resistance and feed efficiency in extensively managed species such as cattle. The presence of genotype  $\times$  environment interactions will also require the development of experimental populations replicated across differing environmental conditions to enable global translation of GS.

The speed with which the performance of animals can be improved by GS is determined by generation interval, litter, or family size, the frequency of desirable alleles in a population (rare variants are likely to be missed in the development of genetic prediction models), and the proximity (and phase relationship) on chromosomes of good and bad alleles. Although predicting genetic merit using DNA diagnostics may be less precise than directly testing the performance of every animal or their offspring, the reduction in generation interval by far offsets this. For example, in dairy populations, the rate of genetic improvement is expected to double with the application of GS (Hayes et al., 2009). Preliminary results from the poultry industry suggest that GS focused on leg health in broilers and livability in layers can rapidly and effectively improve animal welfare (Cheng et al., 2010). Although price constraints currently limit the widespread adoption of high-density SNP genotyping assays ( $\geq 50,000$  SNP) in livestock species, low-cost, reduced-subset assays containing the most predictive 384 to 3,000 SNP are under development in sheep, beef, and dairy cattle. These low-cost assays are expected to be rapidly adopted and will be expanded in content as the price of genotyping declines. Animal selection based on GS is also expected to reduce the loss of genetic diversity that occurs in traditional pedigree-based breeding because the ability to obtain estimates of genetic merit directly from genotypes avoids the restriction of selection to the currently used parental lineages. Also, despite the increase in the rate of genetic improvement, selection for complex traits involving hundreds or thousands of genes will not result in the rapid fixation of desirable alleles at all of the underlying loci.

### A FUTURE WITH GENETIC ENGINEERING

Whereas GS will accelerate animal improvement in the postgenomic era, parallel and overlapping efforts in animal improvement based on genome-informed genetic engineering (GE) must ensue to ensure that productivity increases at pace with the expanding world populations. The tools of functional genomics and the availability of genome sequences provide detailed information that can be used to engineer precise changes in traits, as well as monitor any adverse effects of such changes on the animal (Miller et al., 2006; Doyon et al., 2008; Geurts et al., 2009). These tools are also enabling a deeper understanding of gene function and the integration of gene networks into our understanding animal

physiology (Schadt, 2009). This understanding has begun to identify major effect genes and critical nodes in genetic networks as potential targets for GE.

### TECHNOLOGICAL REVOLUTION IN GENETIC ENGINEERING

The genomics revolution has been accompanied by a renaissance in GE technologies. Novel genes can be introduced into a genome (Clark et al., 2007), and existing genes can either be inactivated or their expression tuned to desirable levels using recently developed RNA interference (Fire et al., 1998; NPG, 2005). The specificity and efficiency of these approaches is expected to continue to improve. The technical advancements in GE are so significant that Greger (2009) advocated that scrutiny of the procedures for generating transgenic farm animals is undeserved and that discussion should focus on the welfare implications of the desired outcome instead of unintended consequences of GE. This position is also reflected by the rigorous regulatory mechanism established by the FDA for premarket approval of GE animals (FDA, 2009), which considers the risks of a given product to the environment and the potential impact on the well-being of animals and consumers. Indeed, this review mechanism was recently adopted as an international guideline by Codex Alimentarius (2008), which has already found GE to be a safe and reliable approach to the genetic improvement of food animals (US Code of Federal Regulations, 2009). In addition, guidelines that promote good animal welfare, enhance credibility, and comply with current regulatory requirements, for the development and use of GE animals have been developed as a stewardship guidance (Biotechnology Industry Organization, 2009). The stewardship guidance assists the industry and academia in developing and adopting stewardship principles for conducting research and developing and commercializing safe and efficacious agricultural and biomedical products from GE animals for societal benefit.

### SELECTION AND ENGINEERING ARE COMPLEMENTARY

Both GS and GE are viable, long-term approaches to genetic improvement, but when should one approach be employed over the other? Genes are not all equal in their effects upon changes in phenotype. The products encoded by some genes have major effects on biochemical pathways that define important characteristics or reactions in an organism. Other genes have lesser, but sometimes still important, effects. In general, genetic modification by GE is used to add major-effect genes, whereas genetic selection is applied to all genes, including the far larger number of lesser-effect genes that appear to be responsible for about 70% of the genetic variation within a given trait (Cole et al., 2009). One of the most significant advantages of GE is the abil-

ity to introduce new alleles that do not currently exist within a population, in particular, where the allele substitution effect would be very large. This approach can include gene supplementation and genome editing, the latter enabling the precise transfer of an alternative allele without any other changes to the genome of an animal (i.e., without selection markers, or even the genome-wide changes caused by crossbreeding). In this case, molecular methods can be used to supplement or replace a target allele present in one population with a preferred allele present in another.

The key issue is, of course, the identification of the genes and alleles that should be targeted for GE in livestock species. Likely, many genes for which naturally occurring variation creates subtle phenotypic effects exist, whereas GE of these genes with novel alleles might provide profound improvements in animal health and performance. Undoubtedly, the discovery of these genes will come from research with model organisms where the effects of the allelic forms on fitness can be extensively studied, emphasizing the importance of support for basic agricultural research.

### ENHANCED PRODUCTIVITY AND SUSTAINABILITY

Early research efforts in livestock GE were focused on increasing the efficiency and yield of production for a diversity of species. The use of more productive GE animals [i.e., animals that produce more units of output (e.g., gallons of milk, pounds of meat) with the same or less inputs] should be given due consideration in the context of sustainability. Making a conscious choice to use less productive animals necessitates the use of more land per unit of product or the use of more animals to produce a constant amount of animal product or both. This choice could cause conflict when open land is scarce, or other uses (e.g., habitat conservation) compete with the use of land for agriculture. The use of the best available technologies and inputs (best genotypes and best ecological management) to produce greater output per unit of input offers overt sustainability advantages (Pretty, 2008). Rapid growth and increased production result in a reduced number of animals being required for a fixed amount of output. Additionally, the environmental footprint per unit of animal product is reduced for more productive animals, regardless of the agricultural production system used. Bradford (1999) estimated that a small incremental increase of 2% per year in average milk production per cow globally, with no change in cow numbers, would result in a 60% increase in the global milk supply by the year 2020.

The observation by Palmiter et al. (1982) that supplementing the mouse genome with an extra GH gene increased muscle growth greatly stimulated research into this approach for enhancing the productivity of meat animals. However, early transgenic animal GH supplementation experiments (in the late 1980s) achieved mixed results. Whereas growth enhancement

was observed in experiments with both fish and mammals (Nottle et al., 1999; Zbikowska, 2003), in some experiments increased GH concentrations compromised the health of animals (Hammer et al., 1985; Pursel et al., 1989; Nancarrow et al., 1991; Dunham, 2009). From this research, much was learned about the GH axis, methods for transgenesis, the need for controlled gene expression, and best practices for transgenic animal stewardship. One successful outcome of this early work was a transgenic salmon whose genome contains an extra copy of the salmon GH gene (Table 1).

After nearly 15 years of research and development, the GH-transgenic salmon are now in an advanced stage of regulatory review by the FDA and could constitute the first transgenic animal product approved for human consumption in the United States. These fish produce the same amount and kind of circulating GH as wild-type salmon, but they produce it throughout the entire year. This modification has resulted in fish that reach market weight faster and consume less food per kilogram of product than wild-type salmon because they process their food 10 to 30% more efficiently. The more efficient utilization of protein in the diet of an animal leads to a reduction in the excretion of nitrogenous waste (Coffey, 1996; Silence, 1996). Concerns over the potential environmental impact of feral transgenic fish have been studied extensively (Devlin et al., 2004, 2009; Sundstrom et al., 2007) and practically addressed by eliminating the possibility of gene flow from transgenic to wild salmon by implementing a redundant biological and physical containment production system, which exclusively utilizes sterile female fish. These fish are reared in land-based facilities with multiple redundant physical containment features. Because of the controlled production environment, the fish are neither exposed to disease challenges nor are they reservoirs for disease transmission as they might be in conventional salmon net pen aquaculture. The ability to grow these salmon in land-based facilities closer to population (consumption) centers dramatically reduces transportation costs compared with conventional salmon aquaculture, affecting the economics and environmental footprint of salmon production. Finally, because these fish can be raised in inland fisheries, they represent a unique food security opportunity, potentially rejuvenating a nearly extinct US Atlantic salmon industry.

To address the sustainability of pork production, a line of GE pigs was developed with the ability to digest and metabolize natural P in their feed, which non-GE pigs cannot accomplish. These pigs referred to as Enviropigs, have a genome supplemented with a gene from *Escherichia coli* that produces phytase exclusively in their salivary glands (Golovan et al., 2001). This genetic modification reduces the excretion of undigested P in pig feces by 30 to 60%, which will ameliorate surface water eutrophication from swine production, as well as eliminate the environmental footprint of phytase production as a feed supplement (Forsberg et al., 2003). Clinical analysis of the health of Enviropigs using hematology,

**Table 1.** Current and envisioned genetically engineered (GE) livestock applications for agriculture<sup>1</sup>

| Current GE application                      | Species         | Gene   | Approach                        | Reference   |
|---|-----------------|--|---------------------------------|---|
| <b>Productivity</b>                         |                 |  |                                 |   |
| Enhanced growth rate                        | Various         | GH   | Transgene                       | Hammer et al., 1985; Vize et al., 1988; Pursel et al., 1989; Nancarrow et al., 1991; Pursel et al., 1997; Rahman et al., 1998; Cook et al., 2000; Martinez et al., 2000; Nam et al., 2001; Aerni, 2004; Bessey et al., 2004 |
| Enhanced milk production                    | Swine           | $\alpha$ -Lactalbumin  | Transgene                       | Wheeler et al., 2001; Marshall et al., 2006   |
| Enhanced growth rate                        | Swine           | <i>IGF1</i>  | Transgene                       | Pursel et al., 2004   |
| <b>Disease resistance</b>                   |                 |  |                                 |   |
| Bovine spongiform encephalopathy resistance | Cattle          | Prion protein PrP  | Knockout                        | Richt et al., 2007a,b   |
| Mastitis resistance                         | Cattle          | Lysostaphin  | Transgene                       | Wall et al., 2005   |
| Mastitis resistance                         | Cattle          | Lactoferrin  | Transgene                       | van Berkel et al., 2002   |
| Mastitis resistance                         | Goats           | Lysozyme   | Transgene                       | Maga et al., 2006a,c  |
| Visna virus resistance                      | Sheep           | Visna virus envelope gene                                    | Transgene                       | Clements et al., 1994   |
| GCH virus resistance                        | Grass carp      | Lactoferrin  | Transgene                       | Zhong et al., 2002  |
| Bacterial resistance                        | Channel catfish | Cecropin B gene  | Transgene                       | Dunham et al., 2002   |
| <b>Environmental</b>                        |                 |  |                                 |   |
| Decreased P in manure                       | Swine           | Phytase  | Transgene                       | Golovan et al., 2001  |
| Nutritional value                           |                 |  |                                 |   |
| Humanization                                | Cattle          | Human $\alpha$ -lactalbumin                                  | Transgene                       | Wang et al., 2008   |
| Humanization                                | Cattle          | Human lactoferrin  | Transgene                       | Yang et al., 2008   |
| Fat content                                 | Swine           | Spinach $\Delta^{12}$ fatty acid desaturase                  | Transgene                       | Saeki et al., 2004  |
| Fat content                                 | Swine           | n-3 fatty acid desaturase                                    | Transgene                       | Lai et al., 2006  |
| Fat content                                 | Goats           | Stearoyl-CoA desaturase                                      | Transgene                       | Reh et al., 2004  |
| Protein content                             | Cattle          | $\beta$ -Casein, $\kappa$ -casein                            | Transgene                       | Brophy et al., 2003   |
| <b>Envisioned GE applications</b>           |                 |  |                                 |   |
| Allele replacement                          | Species         | Gene   | Proposed approach               | Background information  |
| Increased lean-muscle growth                | Various         | Various  | Homologous recombination        | Miller et al., 2006; Geurts et al., 2009  |
| Increased postnatal growth                  | Various         | Myostatin  | Dominant negative/RNAi/knockout | McPherron and Lee, 1997   |
| Enhanced mammary gland development          | Various         | <i>Socs2</i>   | RNAi/knockout                   | Horvat and Medrano, 2001  |
| Sex selection                               | Various         | <i>Socs1</i>   | RNAi/knockout                   | Lindeman et al., 2001   |
|   | Various         | <i>DMRT1</i> , sex-specific gamete enrichment                | Dominant negative/RNAi          | Herrmann et al., 1999; Smith et al., 2009   |
| <b>Suppressing infectious pathogens</b>     |                 |  |                                 |   |
| Coronavirus resistance                      | Various         | RNA viruses (e.g., foot and mouth, fowl plague, swine fever) | RNAi                            | Clark and Whitelaw, 2003; Whitelaw and Sang, 2005   |
| Avian flu resistance                        | Swine           | Aminopeptidase N   | RNAi/knockout                   | Schwegmann-Wessels et al., 2002   |
| Low lactose milk                            | Poultry         | Avian influenza  | RNAi                            | Sang, 1994; Tompkins et al., 2004   |
| Low lactose milk                            | Cattle          | Lactase  | Transgene                       | Stacey et al., 1995   |
| Humanization                                | Cattle          | $\alpha$ -Lactalbumin  | RNAi/knockout                   | Jost et al., 1999   |
| Increased ovulation rate                    | Cattle          | $\beta$ -Lactoglobulin                                       | RNAi/knockout                   | Wang et al., 2008   |
| High n-3 fatty acid milk                    | Sheep           | <i>GDF9</i> , <i>BMP15</i> , <i>ALK6/BMPR1B</i>              | RNAi/knockout                   | Melo et al., 2007   |
| Resistance to brucellosis                   | Cattle          | n-3 and n-6 fatty acid desaturase                            | Transgene                       | Morimoto et al., 2005   |
| Nutritional enhancement                     | Cattle          | <i>NRAMP1</i>  | Transgene                       | Barthel et al., 2001  |
|   | Cattle          | Human catalase   | Transgene                       | He et al., 2008   |

<sup>1</sup>GCH = grass carp hemorrhage virus; RNAi = RNA interference.

clinical chemistry, and urology revealed no substantive difference between these GE and non-GE pigs except for a marked improvement in P retention, an outcome expected to enhance animal health by improving nutrient utilization and bone strength. Proteomic analysis of liver and muscle tissues from Enviropigs demonstrated no significant difference in the proportions of the major proteins as compared with those of age-matched non-GE pigs (Golovan et al., 2008; Hakimov et al., 2009).

## ENHANCING ANIMAL WELFARE

As mentioned, a focus on animal welfare positively influences productivity, and, therefore, indirectly enhances the sustainability of animal production. Numerous targets of GE aim to deliver even more direct, simultaneous improvements in animal welfare and sustainability (Table 1). For example, GE could provide a humane method for sex selection in dairy and egg industries, where cows and hens provide the animal product. The development of male animals could be avoided ab initio and eliminate inefficiencies in animal production and welfare concerns associated with sex selection and castration. Gene supplementation that feminizes male embryos (Smith et al., 2009) or eliminates the production of male sperm in sires (Herrmann et al., 1999) is technically feasible; the latter approach has the desirable outcome that the animals that are produced are not themselves genetically engineered.

Based on the global importance of pork, researchers have developed GE pigs to improve the sustainability of production, enhance animal welfare, and add nutritional value (Table 1). For example, the expression of bovine  $\alpha$ -lactalbumin and IGF in the mammary gland of lactating sows results in increased milk production, which directly enhances animal welfare as demonstrated by improved growth, intestinal development, and overall survival of piglets at weaning (Wheeler et al., 2001). In a striking example of the value of GE in enhancing animal welfare, Wall et al. (2005) at the USDA-ARS engineered Jersey cattle to express the antibacterial protein lysostaphin in their milk, an accomplishment that dramatically enhanced the resistance of these cows to infection by *Staphylococcus aureus*, the most common and most difficult to treat cause of mastitis. This genetic improvement, could not only improve the well-being of around 2 million dairy cattle per year in the United States alone, but also could decrease the economic costs of mastitis, which are currently estimated to exceed \$2 billion per year in the United States (A. Saeman, National Mastitis Council, Verona, WI, personal communication).

## ENHANCING HUMAN NUTRITION AND HEALTH

One promising aspect of GE is the potential for the development of functional foods that enhance food safe-

ty, human nutrition, and health (Table 1). For example, in China the nutritional value of bovine milk has been improved by GE to express human  $\alpha$ -lactoglobulin and human lactoferrin, proteins normally found in human milk but missing from bovine milk (Wang et al., 2008; Yang et al., 2008). Given the increasing prevalence of obesity and cardiovascular disease in developed nations, changes in product composition in conjunction with improvements in dietary practices could contribute to improvements in consumer health. The amounts and type of fats in animal products are topics of frequent public discourse, and from the perspective of sustainability, improved feed conversion efficiency increases the ratio of lean-to-fat deposition in livestock. Net benefits include reduced production costs, improved product quality, reduced excretion of nitrogenous wastes into the environment, decreased grazing pressure on fragile landscapes, and reduced pressure on world feed supplies (Sillence, 2004). A decrease in the prevalence of deleterious fats and cholesterol and an increase in the prevalence of MUFA and n-3 fatty acids are consistent with dietary recommendations for cardiovascular health and an objective difficult to achieve in the absence of GE. In fact, 3 proof-of-principle studies have been published: 1) GE goats that expressed a rat stearoyl-CoA desaturase in the mammary gland and yielded milk with a reduced saturated fatty acid content and increased content of CLA, a beneficial antioxidant fatty acid (Reh et al., 2004); 2) a GE pig made transgenic for a  $\Delta^{12}$  fatty acid desaturase gene from spinach that produced the PUFA, linoleic acid (18:2n-6) and  $\alpha$ -linolenic acid (18:3n-3), which are essential for human (and pig) nutrition (Saeiki et al., 2004); and 3) a GE pig that was developed to express an n-3 fatty acid desaturase capable of converting n-6 fatty acids to n-3 fatty acids (Lai et al., 2006). Although fish provide an excellent source of dietary n-3 fatty acids, which are important for fertility, cardiovascular health, immune system health, mental health, and cancer prevention (Prather, 2006), worldwide fisheries will be challenged to sufficiently supply n-3 fatty acids to the developing world. As the most widely consumed meat, pork logically should be considered as an alternative source of n-3 fatty acids. Consistent with this strategy, the pigs developed by Lai et al. (2006) produce increased content of n-3 fatty acids from n-6 analogs, and their tissues have a reduced ratio of n-6/n-3 fatty acids. Such animals may be useful as models for human health and for providing a dietary source that could enhance the health of consumers in developed and developing countries.

The first FDA approval of a GE animal product, the anticoagulant ATryn (recombinant human antithrombin), firmly established the importance and safety of engineered mammary gland-based protein expression systems. Additional GE projects in cattle and goats have targeted the mammary gland for the expression of proteins to enhance the welfare of animals, and the safety and stability of milk products (Table 1). Bacte-

rial diarrhea, which is responsible for more than 2 million infant deaths per year in developing countries, results from campylobacter, salmonellae, shigellae, and some strains of *E. coli* infections. Transgenic goats that express the human lysozyme protein, a natural antimicrobial protein in breast milk, were developed to produce milk with an enhanced shelf life that would improve the gastrointestinal health of goat kids and children (Maga et al., 2006a,c; Brundige et al., 2008). Experiments in vitro and in vivo have established that milk from these goats has antimicrobial properties, whether pasteurized or not, and that this milk inhibits the enteric bacteria *E. coli* when fed to piglets (a nonruminant model for children; Maga et al., 2006b). Approval of this product could make a significant contribution to the alleviation of hunger and disease (Brundige et al., 2009).

## FOOD AND HEALTH SECURITY

Transgenic technologies can also provide an effective means for enhancing animal health. Because hosts and pathogens have coevolved, long-term selection may not be the most effective approach for the enhancement of disease resistance. Although GS has provided enhanced disease resistance to some organisms (e.g., parasites; Stear et al., 2007), it is unlikely to generate specific resistance to microorganisms (bacteria and viruses) because they evolve more rapidly than do their hosts. Precise and efficient GE tools instead provide a route to make significant, sudden improvements in general and pathogen-specific innate and humoral immunity (Table 1). The improvement of disease prevention in livestock will increase the quality of life of production animals, contribute to the needed acceleration of food production, and serve to enhance food security worldwide. Developing animals resistant to viral pandemics (Reed et al., 2009) is in the best interest of all constituencies as a means to improve animal welfare and to enhance food and human health security.

## CONCLUSIONS

The dietary needs of the world in the very near future cannot be met without the immediate and ongoing utilization of GS and GE. Obfuscation by opponents of animal genetics, and more generally by opponents of animal agriculture, will stall the delivery of solutions in the face of mounting risks (Murray and Maga, 2010). Humane applications of GS for sustainable animal production, in conjunction with genetic improvement by GE, are key technologies that will be vital for meeting the future food needs of the world. Although animal genetics alone will not solve the future food problems of the world, to fail to apply the best available technologies to the solution of contemporary and future food shortages would be morally reprehensible.

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