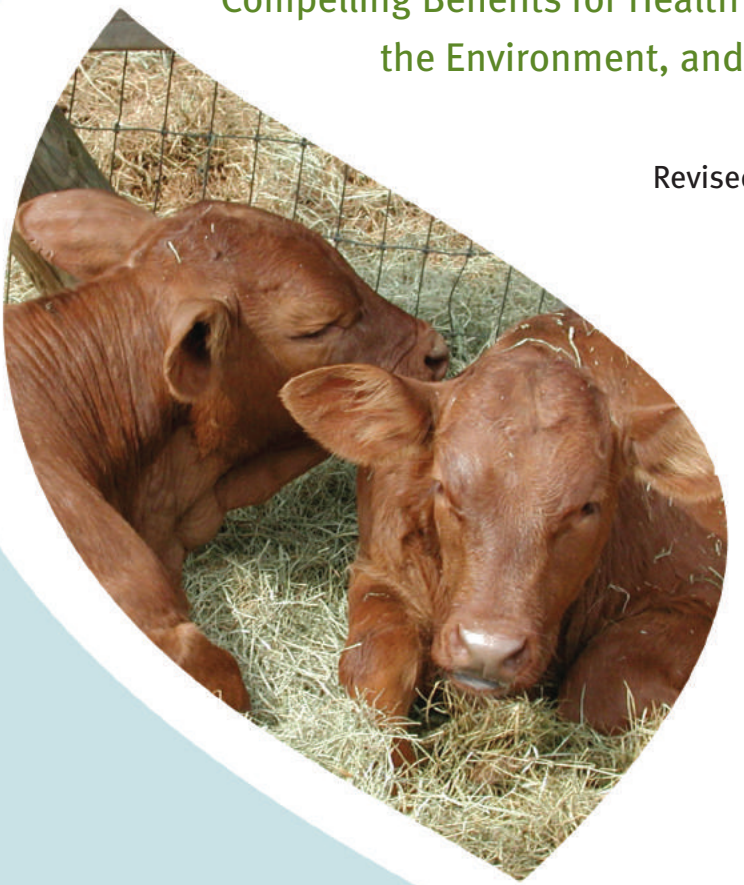
GENETICALLY ENGINEERED ANIMALS AND PUBLIC HEALTH

Compelling Benefits for Health Care, Nutrition, the Environment, and Animal Welfare



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GENETICALLY ENGINEERED ANIMALS AND PUBLIC HEALTH:
Compelling Benefits for Health Care, Nutrition, the Environment, and Animal Welfare

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Abstract

Genetically engineered animals embody an innovative technology that is transforming public health through biomedical, environmental and food applications. They are integral to the development of new diagnostic techniques and drugs for human disease while delivering clinical and economic benefits that cannot be achieved with any other approach. They promise significant benefits in human health and food security by enabling dietary improvements through more nutritious and healthy meat and milk. Genetically engineered animals also offer significant human health and environmental benefits with livestock more efficient at converting feed to animal protein and reducing waste production. Finally, genetic engineering will improve the welfare of the animal by imparting resistance to disease and enhancing overall health and well being. These numerous benefits will be realized as these products become commercially available. The first product from a genetically engineered animal was approved by the United States government in 2009. Provided that the United States' science-based regulatory process results in additional approvals of genetically engineered animals, products will be commercialized. In addition, proactive stewardship guidance has been developed by industry to address questions about the regulatory process by the public and developers. These accomplishments will enhance investment in research and advance innovation toward product development.

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Executive Summary

Animal biotechnology, executed judiciously, will provide compelling and practical benefits to mankind, as we have seen from other fundamental advances in life science. Genetic engineering is the deliberate modification of the animal's genome using techniques of modern biotechnology. Genetically engineered agricultural animals are being developed to transform and improve public health. These public health benefits can be grouped into five broad areas of scientific development.

1. Genetically engineered animals will improve human health through production of novel replacement proteins, drugs, vaccines, research models and tissues for the treatment and prevention of human disease.

2. Genetically engineered animals will contribute to improving the environment and human health with the consumption of fewer resources and the production of less waste.

3. Animals that are genetically engineered will have improved food production traits enabling them to help meet the global demand for more efficient, higher quality and lower-cost sources of food.

4. Genetic engineering offers tremendous benefit to the animal by enhancing health, well-being and animal welfare.

5. Finally, genetically engineered animals have produced high-value industrial products such as spider silk used for medical and defense purposes.

Today, there are more than two dozen drugs in development derived through genetic engineering of farm animals, and numerous agricultural animal applications with beneficial environmental and husbandry attributes suitable for commercialization. The practical benefits of this technology have not yet reached American patients and consumers, however continued successful application of the new United States (U. S.) federal government regulatory process should be aggressive, enabling scientific innovation. The public health benefits can only be realized when we apply the regulatory framework, thus enabling these animals to provide human health, environmental and food and agricultural benefits. The predictable, rigorous, science-based U. S. regulatory pathway is essential and will allow this technology to deliver practical benefits through the science of genetic engineering of agricultural animals.

Introduction

The objective of this paper is to evaluate the benefits of development-stage technologies that are based on genetic engineering, review the policy and regulatory challenges and provide a recommendation that will result in benefits realized in products for consumers.

There are precedents for understanding how a new area of beneficial science can create uncertainty and fear, and how these initial concerns can be resolved through science. In the early 1970s, unease spread through the media about a new scientific technique called recombinant deoxyribonucleic acid (DNA). The concept was easy to understand: you take a gene out of one living thing and put it in another. When scientists proposed to insert human genes into bacteria, where they could be more easily manipulated, opponents worried about unforeseen social and scientific implications. They called for legal moratoria or stringent regulation that promised to thwart any reasonable development efforts. Many envisioned evil applications—deadlier strains of old viruses or designer babies. The technology, they argued, was dangerous.

Genetic engineering is the deliberate modification of the animal's genome using techniques of modern biotechnology.

But the benefits were compelling. Before this technology came along, fundamental advances on cellular disease didn't seem possible. Recombinant DNA changed all that, and in a short time, gave rise to new medicines and insights into many common diseases. Yet in the 1970s, some polls suggested many Americans were against the research, captive to concerns about its perceived risks, and willing to forgo obvious public health opportunities. Prominent critics of the technology were convinced that "recombinant" bacteria were unsafe and capable of infecting people. When they proposed a moratorium on further research, some British researchers mixed the recombinant bacteria into their milk and drank it with no ill effects. The point was made. The moratoria never passed. And medical practice has been transformed as a result. [1]

Animal biotechnology also was hampered by government restrictions on scientific research, championed by a small number who worry about the implications of such advances. The technology encompasses everything from the genetic modification of animals in order to improve their ability to produce food to animals that acquire the capacity to produce drugs or other natural proteins in their milk. This is a science broadly referred to as genetic engineering. Genetic engineering is the deliberate modification of the animal's genome using techniques of modern biotechnology.

The science of animal biotechnology is posed to provide the compelling benefits based on recent successes on policy and regulatory guidance, provided both internationally and domestically. Research and development in the two primary applications of this science—food production and drug development—are inextricably linked. Consequences of the regulatory success have been broadly felt across the science. The policies apply to genetically engineered animals intended for the food supply and for improved and lower-cost human drug development.

[1] Gottlieb, S. Consequences of the Biotechnology Revolution, New York Sun, A11, May 1, 2002.

How the Science Enables Solutions

Science has given history its forward direction. There is good reason to believe that animal biotechnology will enable the kind of practical benefits we have seen from other fundamental advances in life science. While there have always been those in society who resist scientific change, the attacks against genetically engineered animals—enhanced for improved production of food, novel human drugs and for environmental protection among other purposes - have been intense and sustained.

Genetically engineered animals—which often incorporate genes from other organisms in a process called transgenesis—are being developed to transform and improve public health. The broad possibilities encompass the treatment of human disease, the production of safer or more effective human proteins, new drugs and vaccines, the easing of shortages of human tissue and organs available for transplant patients through new avenues of supply, the enhancement of the environment and sustaining food security and quality through the improved efficiency of food production and production of more nutritious foods. [2,3,4,5,6]

Genetically engineered animals are being developed to transform and improve public health.

The creation of the first genetically engineered farm animals was documented in 1985 and the capability for biopharmaceutical production by these animals was demonstrated shortly thereafter. Today, there are more than two dozen drugs in development derived through transgenic methods, and numerous agricultural animal applications with beneficial environmental and husbandry attributes suitable for commercialization.

While there are fundamental misunderstandings about the potential risks from this new technology, there are also ample gaps in peoples' knowledge of its potential benefits. These public health benefits can be grouped efficiently into the following five broad areas of scientific development:

- Novel and more efficient production of replacement proteins, drugs, vaccines, research models and tissues for the treatment and prevention of human disease;
- Production of animals with improved food production traits enabling them to become more efficient, higher quality and lower-cost sources of food;
- Engineering of "environmental friendly" animals capable of meeting human needs more efficiently, with the consumption of fewer resources and the production of less waste, allowing direct positive impacts on human health;
- Enhanced animal welfare and health through genetic engineering to increase resistance to disease, minimizing the need for animal care interventions; and
- Production of high-value industrial products such as spider silk used for medical and defense purposes.

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[2] Fulton, S. (2000) Roundup on bioprocess validation issues: transgenic animal production of biopharmaceuticals. Genetic Engineering News 20:36.

[3] Echelard, Y. (1996) Recombinant protein production in transgenic animals. Current Opinion in Biotechnology 7: 536-540.

[4] Young, M.W., H. Meade, J. Curling, C. Ziomek, and M. Harvey. (1998) Production of recombinant antibodies in the milk of transgenic animals. Res Immunol. 149(6):609-610.

[5] Reggio, B.C., H.L. Green, M. Sansinena, L.H. Chen, E. Behboodi, R.S. Denniston, Y. Echelard and R.A. Godke. (2002) Production of cloned transgenic goats as a potential source for human pharmaceuticals. Theriogenology 57:445.

[6] Hammer, R.E., V.G. Pursel, C.E. Rexroad, R.J. Wall, D.J. Bolt, K.M. Ebert, R.D. Palmiter, and R.L. Brinster. (1985) Production of Transgenic Rabbits, Sheep, and Pigs by Microinjection. Nature 315:680-683.

Few efforts to date have attempted to catalogue the near—and medium—term health benefits from transgenic technology, especially when it comes to the medical applications. This paper will attempt to fill that void, by evaluating the genetic engineering technologies (Tables 1–5), and providing some qualitative and quantitative measures of their potential public health impact.

The greatest success to realizing these opportunities has recently been realized with new policy and regulatory guidance in the U. S. and abroad. Furthermore, the U. S. government approved the first product from a genetically engineered animal in early 2009. While regulatory pathways for developing drug products based on genetically engineered animal methods had been generally developed,[7 8 9 10 11] similar regulatory pathways remained ambiguous when it came to genetically engineered animals intended for human consumption, despite the absence of any data or experience to justify such confusion. In part, that was a result of less familiarity among policymakers and consumer groups when it comes to using genetically engineered animals to produce food or industrial proteins, versus using animals as sources for drug production.

The greatest success to realizing these opportunities has recently been realized with new policy and regulatory guidance in the U. S. and abroad.

In the final analysis, those seeking to promote the development of genetically engineered animals because of their demonstrated ability to deliver safer, more novel, and lower cost protein drugs (or those who, at worst, took an ambivalent view of genetic engineering when it is applied to these medical purposes) could not endorse the technology in this one context without simultaneously allowing a regulatory pathway to develop genetically engineered animals for other agricultural purposes. Yet this contradiction existed for a period of about a decade when it came to both the perception by some, and the regulation of genetically engineered animals. Breaching this intellectual partition, and establishing a rigorous, science-based regulatory pathway, was essential if this technology was to be allowed to deliver practical benefits in the areas science is now enabling.

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[7] A two-day multidisciplinary conference sponsored by the Pew Initiative on Food and Biotechnology provided an in-depth exploration of the potential benefits and risks of genetically engineered animals and a review of the current laws and regulatory policies that apply. Biotech in the Barnyard brought together representatives of industry, academia, consumer groups, animal welfare groups and government agencies to share information and exchange views.

[8] Guidelines on the Use of Transgenic Animals in the Manufacture of Biological Medicinal Products for Human Use, Committee for Proprietary Medicinal Products (CPMP), (1995).

[9] Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived from Transgenic Animals, FDA Center for Biologics Evaluation and Research (CBER), (1995).

[10] Notes for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Medicinal Products, Committee for Proprietary Medicinal Products (CPMP), (1999); CPMP/BWP/1230/98.

[11] Gavin, W.G. (2001) The Future of Transgenics. Regulatory Affairs Focus 6:13-19.

Genetically Engineered Animals and the Improved Production of Existing Human Proteins, Drugs, Vaccines, and Tissues

For years, genetically engineered animals, particularly mice, have been used to help scientists understand how genes work and interact with one another. More recently, researchers have introduced genes coding for the production of specific protein sequences into other species in order to manufacture large quantities of those proteins for medical purposes.

In biology, genetic sequences provide the instruction set or "code" for the manufacture of specific proteins, which comprise everything from enzymes to hormones, and are themselves the vehicles for carrying out the body's many functions. Transgenic animals are so named because they contain a "transgene" from another individual or organism that codes for the production of a particular protein that scientists are interested in expressing.

There are now dozens of products derived from genetically engineered animals under development that hold promise of benefit to human health.

While there are a number of different techniques for developing genetically engineered animals, the critical requirement is stable integration of the desired genetic sequence into the host animal's DNA, while minimizing other potentially detrimental alterations. Once this requirement is demonstrated and traditional out-breeding has begun, the next step is raw product recovery of the protein that is being developed, typically during the animal's lactation. The subsequent steps, the process for adapting and breeding these genetically engineered animals, is well understood and has been standardized across various commercial and research enterprises. Scientists continue to refine these standard approaches, drawing on developments from molecular genetics and reproductive physiology, and the new techniques offer perhaps even more potential public health opportunities. The aim of developing new approaches is to increase the efficiency of producing and reproducing useful founder animals.[12]

Transgenic animals were initially recognized as a novel platform for the production of recombinant drug products for a number of reasons. First, it was demonstrated that transgenic approaches could reliably and safely express novel proteins due to the unique nature of the mammary gland's capacity for production of complex molecules. Second, genetically engineered animals showed the ability to produce significantly greater amounts of protein with higher expression levels and volume output than the traditional protein culture systems. These culture systems are currently the dominant approach to commercial production of protein medicines across industry. Third, transgenics demonstrated the potential for a significant reduction in the cost per unit protein due to the animal being the true "biorector," requiring less complicated monitoring and industrial hardware than a traditional recombinant cell culture system. Finally, genetically engineered animals held out the possibility of developing safer and more sustainable and flexible manufacturing sources for vital human protein replacements and blood products.

As a result of these public health opportunities, there are now dozens of products derived from genetically engineered animals under development that hold promise of benefit to human health.[13] They range from therapeutic advances, such as animals that produce blood clotting proteins that are potentially safer than current plasma-derived products (being free

[12] Rudolph, N.S. (1999) Biopharmaceutical production in transgenic livestock Tibitech 17:367-374.

[13] Keefer, C.L., J. Pommer and J. M. Robl. (2007) The role of transgenic livestock in the treatment of human disease. Council on Agricultural Science and Technology Issue Paper 35: 1-11.

from risk of infection or contamination) to gains in efficiency and access, for example from animals capable of producing lower cost pharmaceuticals, tissue components and vaccines in their milk.

The most immediate medical applications of transgenics involve efforts to produce novel recombinant biological drug and blood components. Right now there are several methods traditionally used for industrial production of these proteins. For example, bacterial systems such as Escherichia coli are commonly used and are very efficient. These systems generally offer a low-cost route of production. But these approaches are limited to the production of simple or "non-glycosylated" proteins (meaning that the protein itself is not significantly modified by the addition of sugar subgroups, a level of complexity that usually makes proteins harder to copy or manufacture). Indeed, the active forms of many important human therapeutic proteins are glycosylated in a mammalian-specific manner. Bacterial systems are also usually reserved for the production of proteins that do not require a sophisticated folding process to reach their active state.

A second approach—the production of protein drugs in fungal systems—enables efficient production of some secreted proteins. But glycosylation in these systems adds a number of unwanted subgroups which strongly affect the functional properties of the protein. Still a third approach, baculovirus systems, exploits the hugely productive capacities of certain insect viruses to produce a wide range of proteins, but these have yet to be scaled-up to industrial levels.

The prevalent method today for producing glycosylated proteins is mammalian cell culture. This approach is commonly used in the production of monoclonal antibody drugs such as the breast cancer drug, Herceptin®, or the lymphoma drug, Rituxan®. This approach enables manufacturers to produce properly shaped and active proteins, but it suffers from high costs and low yields, raising the price of the finished drugs. Manufacturing costs can account for up to a third of the cost of some complex protein drugs. Finally, genetically engineered plant systems are useful for large scale production. However, similar to the fungus-based production methods, glycosylation in plants can add a number of plant-specific sugars to which some human patients have adverse reactions.

By comparison to all these techniques, manufacturing approaches based on genetically engineered animals appear to be a desirable alternative for producing complex glycosylated proteins. These combine both the expression levels available with bacterial systems and the ability for "post-translational modifications" or, in other words, the fine tailoring that can be achieved with tissue culture. Compared to cellular expression, protein production through transgenics also enables lower product costs. Milk, egg white, blood and silk worm cocoon from genetically engineered animals are all potential sources for recombinant proteins produced at an industrial scale. [14]

Owing to these advantages, there are as many as two-dozen different human and animal drugs developed through transgenics that are in the early and mid stages of development with active Investigational New Drug Applications (INDs) or Investigational New Animal

[14] Rudolph, N.S. (1999) Biopharmaceutical production in transgenic livestock, Tibitech 17:367-374.

Drug Applications (INADs) on file with the U.S. Food and Drug Administration (FDA). In addition to these advanced programs, there are literally hundreds of transgenic medical protein products that are in pre-clinical development. These drugs and biologics being created by genetically engineered animals can be roughly divided into four broad categories, each of which will be reviewed in greater detail in the sections that follow. These include: 1) blood products, 2) other protein-based drugs, 3) vaccine components and 4) replacement tissue products. Within each of these four categories, some examples of the protein-based medical products that are in development follow.

Blood Products

In February, 2009, the first protein drug from a genetically engineered animal was approved for medical use in the United States. In addition, a number of different proteins derived from the blood of transgenic animals are in various stages of development. In some cases, the uses of genetically engineered animals for bio-manufacturing enables scientists to develop proteins with unique attributes that might offer commercial or therapeutic advantages over compounds made through traditional production sources.

The list of products under development is broad. It includes widely used and vital blood products such as clotting factors, antithrombin,[15][16][17][18] and human albumin.[19][20] The first product approved in the U. S. from a genetically engineered animal is ATryn®, which had been granted orphan drug status by the FDA for the treatment of hereditary antithrombin deficiency, or HD, to prevent excessive bleeding in patients undergoing high-risk surgical procedures or childbirth.[21] ATryn® was approved by the FDA in February 2009 through both a Biologics License Application and a New Animal Drug Application to be marketed in the United States. ATryn® was previously approved in the European Union for the treatment of HD patients undergoing surgical procedures. Rhucin®, a recombinant human C1 esterase inhibitor produced in the milk of transgenic rabbits is also in clinical trials in Europe. Rhucin® treats acute attacks of hereditary angioedema (HAE), a rare disease characterized by painful swelling of soft tissue.[22]

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[15] Lu, W., T.G.K. Mant, J.H. Levy and J.M. Bailey. (2000) Pharmacokinetics of recombinant transgenic antithrombin in volunteers. Anesthesia and Analgesia 90:531-534.

[16] Zhou, Q., J. Kyazike, Y. Echelard, H.M. Meade, E. Higgins, E.S. Cole and T. Edmunds (2005). Effect of genetic background on glycosylation heterogeneity in human antithrombin produced in the mammary gland of transgenic goats. J. Biotechnology 117:57-72.

[17] Dickneite, G. (2008) A comparison of the pharmacokinetics of antithrombin derived from human plasma and from transgenic goats and the prevention of sepsis in an animal model. Biopharm Drug Dispos 29: 356-365.

[18] Morrow, T. (2009) Transgenic goats are key to antithrombin production. Manag Care 18: 46-47.

[19] Echelard, Y., M.M. Destrempes, J.A. Koster, C. Blackwell, W. Groen, D. Pollock, J.L. Williams, E. Behboodi, J. Pommer and H.M. Meade. (2002). Production of recombinant human serum albumin in the milk of transgenic cows. Theriogenology 57:779.

[20] Echelard, Y., J.L. Williams, M.M. Destrempes, J.A. Koster, S.A. Overton, D.P. Pollock, K.T. Rapiejko, E. Behboodi, N.C. Masiello, W.G. Gavin, J. Pommer, S.M. Van Patten, D.C. Faber, J.B. Cibelli, H.M. Meade. (2009) Production of recombinant albumin by a herd of cloned transgenic cattle. Transgenic Res 18: 361-376.

[21] Information on the clinical trial can be found at: http://clinicaltrials.gov/ct2/show/NCT00110513?cond=%22Antithrombin+III+Deficiency%22&rank=1

[22] Van Doorn, M. B., J. Burggraaf, T. van Dam, A. Eerenberg, M. Levi, C. E. Hack, R. C. Schoemaker, A. F. Cohen and J. Nuijens. (2005) A phase I study of recombinant human C1 inhibitor in asymptomatic patients with hereditary angioedema. J. Allergy Clin. Immunol. 116:876-883.

While HD is a rather rare disease in its frequency among the population, afflicted patients must receive treatment if they are to have any hope of a normal life. Low levels or inactive forms of the protein antithrombin cause the disease. As a consequence, some patients develop blood clots in their large veins, a medical condition referred to as venous thromboembolism. These blood clots can cause organ damage or even death. Sometimes the clots can form spontaneously, putting an individual at sudden and unexpected risk. Other research suggests that HD can contribute to the loss of a fetus during pregnancy. HD patients are perhaps at greatest risk during events that are independently associated with a probability of thrombosis, such as surgery and delivery. [23]

Genetically engineered animals are also being used for the development of safer and less expensive blood clotting factors for the treatment of hemophilia, with a number of these products also in advanced stages of development. Hemophilia is caused by genetic conditions in which the patients' failure to express enough coagulation factors may lead to excessive bleeding. Type A hemophilia is due to the lack of factor VIII. Type B hemophilia is due to the lack of factor IX. It is largely inherited. People with the disease are missing some or all of a vital protein needed to form blood clots. In about 30 percent of cases, there is no family history of the disorder and the condition results from a spontaneous gene mutation. Hemophilia B is far less common than Hemophilia A, occurring in about one in 25,000 male births. It affects about 3,300 individuals in the United States. All races and economic groups are affected equally.

Genetically engineered animals are being used for the development of safer and less expensive blood clotting factors for the treatment of hemophilia.

A person with hemophilia, when injured, does not bleed harder or faster than a person without hemophilia, one bleeds longer because the blood is slower to clot. Small cuts or surface bruises are usually not a problem, but more traumatic injuries may result in serious problems and potential disability, or even death. People with severe hemophilia, about 60 percent of patients, have bleeding following an injury and may have frequent spontaneous bleeding episodes, often into the joints and muscles.

The preferred treatment is to provide supplemental coagulation factors prophylactically to prevent episodes of excessive bleeding. But the price and availability of recombinant coagulation factors often allows for use in only limited circumstances. When patients are unable to get access to sufficient replacements of these proteins, uncontrolled internal bleeding can cause pain, swelling, and permanent damage to joints and muscles.

While the missing blood-clotting protein can be produced in mechanical bioreactors, the cost of this standard treatment runs up to $200,000 per year, per patient. Right now, the only sources of replacement factor IX are the plasma of blood donors (which raises certain safety concerns, including the potential for transmission of disease) and recombinant factor IX produced in Chinese hamster ovary cells (which is expensive and of limited supply). The limited supply and high cost of both the plasma derived and recombinant factor make prophylactic treatment prohibitively expensive. [24]

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[23] Filip, D.J., J.D. Eckstein, J.J. Veltkamp. (2006) Hereditary antithrombin iii deficiency and thromboembolic disease, American Journal of Hematology 1(3):343-349.

[24] Kashyap, R., VP Choudhry. (2001) Indian Journal of Pediatrics 68:151.

This is another area where genetically engineered animals offer some significant public health opportunities. Scientists have developed genetically engineered animals, including sheep and pigs, able to produce Factor IX, a structurally complex blood clotting protein. [25] [26] [27] The pigs, which are perhaps closest to commercialization, produce the factor in their mammary glands at a productivity level 250-1,000 fold higher than mechanical reactors. The protein can then be extracted from their milk. The high concentration makes the protein easy and inexpensive to purify. Researchers are also using genetically engineered animals in the experimental production of factor VIII, for the treatment of Hemophilia A. [28] Using genetically engineered animals to produce these and other blood factors offers a myriad of potential medical opportunities, not only the prospect of a safer and more renewable source of clotting factors, but also the potential for a lower cost product available for more routine use, perhaps improving the standard of care.

Protein-Based Drugs

Researchers have also developed a number of genetically engineered animals capable of producing complex protein-based drugs, often at a lower cost and through perhaps more reliable and safer production means than traditional manufacturing processes. [29] Protein-based drugs differ from protein products synthesized in the blood in that they are produced in vivo by other organs. This technology is even being applied to the development of complex proteins such as monoclonal antibodies [30] as well as many other important human replacement proteins and protein drugs such as polyclonal antibodies, [31] [32] plasminogen activator, [33] [34] [35] [36]

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[25] Choo, K.H., K. Raphael, W. McAdam and M.G. Peterson. (1987) Expression of active human blood clotting factor IX in transgenic mice: use of a cDNA with complete mRNA sequence. Nucleic Acids Research 15(3):871-884.

[26] Schnieke, A.E., A.J. Kind, W.A. Ritchie, K. Mycock, A.R. Scott, M. Ritchie, I. Wilmut, A. Colman, K.H.S. Campbell. (1997)Human Factor IX Transgenic Sheep Produced by Transfer of Nuclei from Transfected Fetal Fibroblasts. Science 278(5346):2130-2133.

[27] Lindsay, M., G.-C. Gila, A. Cadizb, W.H. Velandera, C. Zhangc, K.E. Van Cott. (2004) Purification of recombinant DNA-derived factor IX produced in transgenic pig milk and fractionation of active and inactive subpopulations. Journal of Chromatography 1026:149-157.

[28] Paleyanda, R.K., W.H. Velander, T.K. Lee, D.H. Seandella, F.C. Gwazdauskas, J.W. Knight, L.W. Hoyer, W.N. Drohan, H. Lubon. (1997) Transgenic pigs produce functional human factor VIII in milk. Nature Biotechnology 15:971-975.

[29] Higgins, E., J. Pollock, P. DiTullio, H. Meade. (1996). Characterization of the glycosylation on a monoclonal-antibody produced in the milk of a transgenic goat. Glycobiology 6: 1211.

[30] Pollock, D.P, J.P. Kutzko, E. Birk-Wilson, J.L. Williams, Y. Echelard, H.M. Meade. (1999) Transgenic Milk as a Method for the Production of Recombinant Antibodies. Journal of Immunological Methods 231:147-157.

[31] Sullivan, E.J., J. Pommer, J.M. Robl. (2008) Commercialising genetically engineered animal biomedical products. Reprod Fertil Dev. 20(1):61-6.

[32] Kuroiwa, Y., P. Kasinathan, Y. Choi, R. Naeem, K. Tomizuka, E.J. Sullivan, J.G. Knott, A. Duteau, R.A. Goldsby, B.A. Osborne, I. Ishida, J.M. Robl. (2002) Cloned transchromosomic calves producing human immunoglobin. Nat. Biotech. 20:889-894 .

[33] Denman, J., M. Hayes, C. O'Day, T. Edmunds, C. Bartlett, S. Hirani, K.M. Ebert, K. Gordon, J.M. McPherson. (1991). Transgenic expression of a variant of human tissue-type plasminogen activator in goat milk: purification and characterization of the recombinant enzyme. Bio/Technology 9: 839-843.

[34] Ebert, K., P. DiTullio, C. Berry, J. Schindler, S. Ayers, T. Smith, L. Pellerin, H. Meade, J. Denman, B. Roberts. (1994). Induction of human tissue plasminogen activator in the mammary gland of transgenic goats. Biotechnology 12(7): 699-702

[35] Ebert, K.M., J. Selgrath, P. DiTullio, J. Denman, T.E. Smith, M.A. Memon, J.E. Schindler, G.M. Monastersky, J.A. Vitale, K. Gordon. (1991). Transgenic production of a variant of human tissue-type plasminogen activator in goat milk: Generation of transgenic goats and analysis of expression. Bio/Technology 9: 835-838

[36] Pittius, C.W., L. Hennighausen, E. Lee, H. Westphal, E. Nicols, J. Vitale, K. Gordon. (1988). A milk protein gene promoter directs the expression of human tissue plasminogen activator cDNA to the mammary gland in transgenic mice. Proc. Natl. Acad. Sci. 85: 5874-5878.

human alpha-fetoprotein,[37] alpha-1-proteinase inhibitor, alpha glucosidase and others.[38 39 40 41 42] Advanced scientific techniques have been developed to help ensure the purity and safety of these proteins to levels of confidence that in many cases match or exceed traditional production techniques.[43 44]

To take just one example, researchers recently created a line of transgenic swine that produce recombinant human erythropoietin or "epo," a naturally occurring human hormone that boosts the body's production of red blood cells. The transgenic swine produced the hormone in their milk through a potentially more efficient and lower cost process than traditional methods employed by the drug's two main manufacturers. Epo is used commercially in patients with diseased kidneys no longer able to produce the protein, as well as cancer patients being treated with chemotherapy who develop anemia as a consequence of bone marrow depletion from their cancer drug regimens. Erythropoetin-based drugs are some of the most widely used protein-based drugs, and are expensive to manufacture. In advanced preclinical experiments, the amino acid sequence of the swine-produced form of the protein matched that of commercial Epo produced from cultured animal cells. The high yields of the swine-derived protein could offer cost-effective alternatives for clinical applications as well as providing other potential clinical advantages.[45] Recently, transgenic goats have been reported that produce human recombinant butyrylcholinesterase in their milk.[46 47 48] The recombinant butyrylcholinesterase is a potential therapeutic agent for delaying the formation of amyloid toxic oligomers in Alzheimer's disease.[49]

The high yields of the swine-derived protein could offer cost-effective alternatives for clinical applications as well as providing other potential clinical advantages.

[37] Parker, M.H., E. Birck-Wilson, G. Allard, N. Masiello, M. Day, K.P. Murphy, V. Paragas, S. Silver, M.D. Moody (2004). Purification and characterization of a recombinant version of human alpha-fetoprotein in the milk of transgenic goats. Protein Expression & Purification. 38: 177-183.

[38] Behboodi, E., L. Chen, M. Destrempes, H.M. Meade, Y. Echelard (2002). Transgenic cloned goats and the production of therapeutic proteins. in Principles of Cloning. Elsevier Science (USA).

[39] Cammuso, C., C. Porter, S. Nims, D. Gaucher, D. Melican, S. Bombard, N. Hawkins, A. O'Coin, C. Ricci, C. Brayman, N. Buzzell, C. Ziomek, W. Gavin. (2000) Hormonal induced lactation in transgenic goats. Animal Biotechnology. 11: 1-17.

[40] Echelard, Y., C.A. Ziomek, H.M. Meade. (2000) Expression of recombinant proteins in the milk of transgenic goats. Proceedings of the 7th International Conference on Goats. 1: 25-29.

[41] Pollock, D.P., J.P. Kutzko, E. Birck-Wilson, J.L. Williams, Y. Echelard, H.M. Meade, 1999. Transgenic milk as a method for the production of recombinant antibodies. Journal of Immunological Methods. 231:147-157

[42] Edmunds, T., S. Van Patten, J. Pollock, E. Hanson, R. Bernasconi, E. Higgins, P. Manavalan, C. Ziomek, H. Meade, J. McPherson, E. Cole. (1998). Transgenically produced human antithrombin: structural and functional comparison to human plasma-derived antithrombin. Blood 91(12):4561-4571.

[43] Ziomek, C. (1999). Validation strategies for biopharmaceuticals: viral risk minimization for transgenic proteins from milk. Genetic Engineering News 15:54.

[44] Ziomek, C.A. (1996). Minimization of viral contamination in human pharmaceuticals produced in the milk of transgenic goats. Dev. Biol. Stand. 88: 265-268.

[45] Parka, J.K., Y.K. Leea, P. Leea, H.J. Chunga, S. Kima, H.G. Leea, M.K. Seoa, J.H. Hana, C.G. Parka, H.T. Kim. (2006) Recombinant human erythropoietin produced in milk of transgenic pigs. Journal of Biotechnology 122(3):362-371.

[46] Baldassarre, H., D.K. Hockley, M. Dore, E. Brochu, B. Hakier, X. Zhao, V. Bordignon. (2008) Lactation performance of transgenic goats expressing recombinant human butyryl-cholinesterase in the milk. Transgenic Res 17:73-84.

[47] Baldassarre, H., D.K. Hockley, B. Olaniyan, E. Brochu, X. Zhao, A. Mustafa, V. Bordignon. (2008) Milk composition studies in transgenic goats expressing recombinant human butyrylcholinesterase in the mammary gland. Transgenic Res 17:863-872.

[48] Baldassarre, H., M. Schirm, J. Deslauriers, C. Turcotte, V. Bordignon. (2009) Protein profile and alpha-lactalbumin concentration in the milk of standard and transgenic goats expressing recombinant human butyrylcholinesterase. Transgenic Res 18:621-632.

[49] Podoly, E., T. Bruck, S. Diamant, N. Melamed-Book, A. Weiss, Y. Huang, O. Livnah, S. Langermann, H. Wilgus, H. Soreg. (2008) Human recombinant butyrylcholinesterase purified from the milk of transgenic goats interacts with beta-amyloid fibrils and suppresses their formation in vitro. Neurodegener Dis 5:232-236.

Vaccine Components

Genetically engineered animals are also being used in the manufacture of novel vaccine components. This offers the opportunity for more rapid manufacture of vaccines, perhaps enabling vaccines to be developed in direct and rapid response to viral outbreaks (for example, responding to a pandemic flu). It also offers the opportunity for vaccines to be produced at a lower cost because of the efficiency and high capacity of the transgenic methods. [50] [51] [52] [53] Each animal is, in effect, a product-specific production plant.

For these reasons, the application of transgenics to vaccine production has not only public health benefits, but also national security implications. Our ability to respond effectively to an emerging viral or bacterial threat or a pandemic could be predicated on our ability to quickly scale up manufacturing of a novel vaccine uniquely tailored to an emerging virus or bacteria. Genetically engineered animals are uniquely suited to providing that capability.

The application of transgenics to vaccine production has not only public health benefits, but also national security implications.

To take just one example of where this technology is being deployed in the production of experimental vaccines, researchers have demonstrated that it may be possible to produce malaria vaccines using genetically engineered animals—at a lower cost than traditional vaccine manufacture methods, and in high volumes. A single goat producing 700 liters/year of milk at the yields researchers obtained experimentally (0.9 g/liter of purified antigen) [54] could supply enough vaccine components called antigens to vaccinate 8.4 million people annually. Thus a herd of three goats could conceivably produce enough antigen to vaccinate 20 million African children per year. Successful development of this potential requires that the antigens produced in the milk of genetically engineered animals retain biological efficacy. For vaccines, as opposed to therapeutic agents, this means that they must retain appropriate immunogenicity. Research has demonstrated that vaccine components produced in genetically engineered animals indeed retain these properties and show evidence of efficacy.

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[50] Stowers, A.W., L.H. Chen, Y.L. Zhang, M.C. Kennedy, L.L. Zou, L. Lambert, T.J. Rice, D.C. Kaslow, A. Saul, C.A. Long, H. Meade, L.H. Miller. (2002). A recombinant vaccine expressed in the milk of transgenic mice protects Aotus monkeys from a lethal challenge with Plasmodium falciparum. Proceedings of the National Academy of Sciences of the United States of America. 99(1):339-344.

[51] Behboodi, E., S.L. Ayres, E. Memili, M. O'Coin, L.H. Chen, H.M. Meade and Y. Echelard. (2004). Health and reproductive profiles of nuclear transfer goats producing the MSP1-42 malaria antigen. Proceedings of the Annual Conference of the International Embryo Transfer Society. 16 (1,2): 29.

[52] Rudolph, N. S. (1999) Biopharmaceutical production in transgenic livestock. Trends Biotechnol. 17:367-374.

[53] Stowers, A.W., L. Chen, Y. Zhang, M.C. Kennedy, L. Zou, L. Lambert, T.J. Rice, D.C. Kaslow, A. Saul, C.A. Long, H. Meade, L.H. Miller. (2002) A recombinant vaccine expressed in the milk of transgenic mice protects Aotus monkeys from a lethal challenge with Plasmodium falciparum. Proc Natl Acad Sciences 99(1):339-344.

[54] Podoly, E., T. Bruck, S. Diamant, N. Melamed-Book, A. Weiss, Y. Huang, O. Livnah, S. Langermann, H. Wilgus, H. Soreg. (2008) Human recombinant butyrylcholinesterase purified from the milk of transgenic goats interacts with beta-amyloid fibrils and suppresses their formation in vitro. Neurodegener Dis 5:232-236.

Replacement Tissues

Finally, when it comes to the direct benefits of genetic engineering to human health through improvements in medical care, another frontier of research involves the use of genetically engineered animals to produce human replacement tissues, cells or organs for human transplant. The science of using animal-derived tissues for human transplantation is referred to as xenotransplantation. Pigs have advantages over other animals as a tissue source in this context, as they are easy to breed, have anatomical and physiological characteristics compatible with humans, and are well studied for several pathogens potentially transmissible to humans. [55] Unlike most non-human primates that are known to carry diseases which are potentially dangerous or even fatal to humans (i.e. HIV and HTLV), caesarean-derived piglets can be maintained free from pathogens that could infect humans, when housed and grown in environmentally controlled facilities with filtered air and water supplies, and by using sterilized plant-based feed which is validated as free from animal proteins. [56]

Xenotransplantation presents the opportunity to change completely the transplantation field by providing a vastly expanded supply of human compatible donor tissues.

Xenotransplantation presents the opportunity to change completely the transplantation field by providing a vastly expanded supply of human compatible donor tissues. This will enable a solution for overcoming the worldwide organ shortage crisis, a new source for replacement tissues including heart valves, skin and orthopedic tissues. While this field took some time to mature (starting in the early 1990's), with the advent of nuclear transfer technology, [57] and the successful production of alpha 1,3 galactosyltransferase knockout (GT-KO) pigs, [58] the critical barrier of organ rejection caused by pre-formed anti-pig (anti-Gal) antibodies was overcome. As a result, in contrast to tissues from normal, unmodified pigs which are rejected in minutes to hours, survival of transgenic GT-KO pig organs, including heart and kidneys, when transplanted into non-transgenic primates, can survive as long as six months. [59 60] Despite these recent advances, transgenic pig tissues are not yet ready for human clinical testing, but research aimed at further genetic modification of the donor animal, and validation of the technology is progressing rapidly.

This approach also holds out promise for more effective treatments for diabetes. Insulin-producing pancreatic islet cells from pigs are showing substantial promise, and are likely to be the first live xenograft tissues tested in human clinical trials. Using protocols similar to those optimized for human islet cell transplantation, pre-clinical studies in monkeys have

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[55] Mohiuddin, M.M. Clinical xenotransplantation of organs: why aren't we there yet? (2007) PLoS Med. 4(3):e75.

[56] Lai, L., R.S. Prather. (2004)Cloning pigs as organ donors for humans. Eng Med Biol Mag.23(2):37-42.

[57] Polejaeva, I.A., S.H. Chen, T.D. Vaught, R.L. Page, J. Mullins, S. Ball, Y. Dai, J. Boone, S. Walker, D.L. Ayares, A. Colman, K.H. Campbell. (2000) Cloned pigs produced by nuclear transfer from adult somatic cells. Nature 407:81-90.

[58] Phelps, C.J., C. Koike, T.D. Vaught, J. Boone, K.D. Wells, S. Chen, S. Ball, S.M. Specht, I.A. Polejaeva, J.A. Monahan, P.M. Jobst, S.B. Sharma, A.E. Lamborn, A.S. Garst, M. Moore, A.J. Demetris, W.A. Rudert, R. Bottino, S. Bertera, M. Trucco, T.E. Starzl, Y. Dai, D.L. Ayares. (2003) Production of ±1,3-galactosyltransferase-deficient pigs. Science 299(5605):411-414..

[59] Tseng, Y.L., K. Kuwaki, F.J. Dor, A. Shimizu, S. Houser, Y. Hisashi, K. Yamada, S.C. Robson, M. Awwad, H.J. Schuurman, D.H. Sachs, D.K. Cooper. (2005) alpha1,3-Galactosyltransferase gene-knockout pig heart transplantation in baboons with survival approaching six months. Transplantation 80(10):1493-1500.

[60] Yamada, K., K. Yazawa, A. Shimizu, T. Iwanaga, Y. Hisashi, M. Nuhn, P. O'Malley, S. Nobori, P.A. Vagefi, C. Patience, J. Fishman, D.K. Cooper, R.J. Hawley, J. Greenstein, H.J. Schuurman, M. Awwad, M. Sykes, D.H. Sachs. (2005) Marked prolongation of porcine renal xenograft survival in baboons through the use of alpha-1,3-galactosyltransferase gene-knockout donors and the cotransplantation of vascularized thymic tissue. Nat. Med. 11:32.

demonstrated three to six months cure of diabetes. [61] [62] Recent studies using islet cells from pigs transgenic for a human CD46 complement inhibitor gene [63] are showing even greater efficacy, and may signal the beginning of human trials for treatment of diabetes soon.

In relation to whole organ xenografts, because the liver does not require a perfect tissue match and it is relatively resistant to antibody-mediated rejection, the liver is the organ for which there is the greatest chance of near-term success. The use of transgenic pig livers on a temporary basis (capable of functioning for as little as two weeks to a month), likely will provide opportunities for patients with acute liver failure, when used as a "bridge" to transplant until a human liver can be obtained. Timelines for human trials with bridging transgenic pig livers are similar to those indicated for pig islet transplants. Heart and kidney xenografts are somewhat further off, as they must survive longer without rejection. Due to physiological incompatibilities, heart and kidney xenografts likely will require further genetic modification of the donor pigs, including the addition of other human genes, such as complement inhibitor genes to mop up anti-non-gal antibody reactions, anti-coagulant genes that inhibit blood clots, or genes that have properties that further suppress or modify the human immune rejection response. [64] [65] [66] [67] [68] [69] [70] [71]

Further applications for xenotransplantation include providing an unlimited source of corneas for patients with corneal blindness. *In vivo* studies in nonhuman primates indicate that even wild-type (unmodified) pig corneas remain functional for several months when treated locally

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[61] Cardona, K., G.S. Korbutt, Z. Milas, J. Lyon, J. Cano, W. Jiang, H. Bello-Laborn, B. Hacquoil, E. Strobert, S. Gangappa, C.J. Weber, T.C. Pearson, R.V. Rajotte, C.P. Larsen. (2006) Long-term survival of neonatal porcine islets in non-human primates by targeting co-stimulation pathways. Nat. Med. 12:304.

[62] Hering, B.J., M. Wijkstrom, M.L. Graham, M. Hårdstedt, T.C. Aasheim, T. Jie, J.D. Ansite, M. Nakano, J. Cheng, W. Li, K. Moran, U. Christians, C. Finnegan, C.D. Mills, D.E. Sutherland, P. Bansal-Pakala, M.P. Murtaugh.;(2006). Prolonged diabetes reversal after intraportal xenotransplantation of wild-type porcine islets in immunosuppressed nonhuman primates. Nat. Med. 12:301.

[63] McKenzie, I.F., Y.Q. Li, P.X. Xing, I. Dinatale, M. Koulmanda, B.E. Loveland, M.S. Sandrin. (2003) CD46 protects pig islets from antibody but not cell-mediated destruction in the mouse. Xenotransplantation 10:615.

[64] Cooper, D.K., A. Dorling, R.N. Pierson 3rd, M. Rees, J. Seebach, M. Yazer, H. Ohdan, M. Awwad, D. Ayares. (2007) ±-1,3-galactosyltransferase gene-knockout pigs for xenotransplantation: Where do we go from here?, Transplantation 84:1-7.

[65] Cooper, D.K., M. Ezzelarab, H. Hara, D. Ayares. (2008) Recent advances in pig-to-human organ and cell transplantation. Expert Opin. Biol. Ther. 8(1):1-4.

[66] Schuurman, H.J., R.N. Pierson 3rd. (2008) Progress towards clinical xenotransplantation. Front Biosci. 3:204-220.

[67] Fung, J., A. Rao, T. Starzl. (1997) Clinical trials and projected future of liver xenotransplantation. World J Surg. 21(9):956-961.

[68] Cooper, D.K. (2003) Clinical xenotransplantation--how close are we? Lancet.362(9383):557-559.

[69] McGregor, C.G., W.R. Davies, K. Oi, S.S. Teotia, J.M. Schirmer, J.M. Risdahl, H.D. Tazelaar, W.K. Kremers, R.C. Walker, G.W. Byrne, J.S. Logan. (2005) Cardiac xenotransplantation: recent preclinical progress with 3-month median survival. J Thorac Cardiovasc Surg.130(3):844-851.

[70] McGregor, C.G., S.S. Teotia, G.W. Byrne, M.G. Michaels, J.M. Risdahl, J.M. Schirmer, H.D. Tazelaar, R.C. Walker, J.S. Logan. (2004) Cardiac xenotransplantation: progress toward the clinic. Transplantation. 78(11): 1569-1575.

[71] Weiss, E.H., B.G. Lilienfeld, S. Muller, E. Muller, N. Herbach, B. Kessler, R. Wanke, R. Schwinzer, J.D. Seebach, E. Wolf, G. Brem. (2009) HLA-E/human beta2-microglobulin transgenic pigs: protection against xenogeneic human anti-pig natural killer cell cytotoxicity. Transplantation 87: 35-43.

with corticosteroids. [72] [73] Recent *in vitro* experimental evidence using corneas from transgenic GT-KO/CD46 pigs show considerable resistance to the human immune response.[26] With new genetic modifications being introduced, it is likely that, from an immune perspective, pig corneas will soon be comparable to human corneas. They also appear to be comparable to a human cornea from a biomechanical perspective.

In addition, the potential of pigs as sources of cells that might correct various neurodegenerative conditions is also being explored. For example, there is considerable potential for the transplantation of pig dopamine-producing cells in conditions such as Parkinson's disease.[74] Preliminary reports indicate significant improvement in motor function in monkeys in which a Parkinson-like condition has been induced, and in which cells from the ventral mesencephalon of pig embryos have been implanted. The number of patients who would benefit from this form of therapy is clearly considerable.

Similar to the large unmet need for viable human-compatible cells and organs, due to the same supply constraints, processed tissues obtained from donated human cadavers, and used to make more than a hundred different types of human-derived tissue products, are also in limited supply. As a result, processed tissues including heart valves, skin, surgical mesh (derived from small intestine submucosa or SIS), and orthopedic tissues (including bone and tendons), are currently obtained from pigs and used for human therapeutic applications. [75] The FDA regulates these tissues as medical devices, and although they have shown efficacy in their human therapeutic applications, recently it has been demonstrated that some of these non-transgenic pig-derived products (specifically heart valves and SIS) are subject to gal-mediated immune responses that result in chronic rejection and premature failure of the devices. [76] [77] The advent of transgenic Gal-free (GT-KO) pigs promises improved outcomes for like devices. Because these fall under the medical device regulatory umbrella (unlike live cell/organ xenotransplantation tissues), they provide near-term opportunities (possibly less than 3 years for those tissue devices that would follow a specific regulatory approval path) for commercial products derived from genetically engineered pigs. These products bring the promise of scale, safety, and improved efficacy for these tissue markets.

With new genetic modifications being introduced, it is likely that, from an immune perspective, pig corneas will soon be comparable to human corneas.

[72] Zhiqiang, P., S. Cun, J. Ying, W. Ningli, W. Li. (2007) WZS-pig is a potential donor alternative in corneal xenotransplantation. Xenotransplantation 14(6):603-611.

[73] Oh, J.Y., M.K. Kim, J.H. Ko, H.J. Lee, C.G. Park, S.J. Kim, W.R. Wee, J.H. Lee. (2009) Histological differences in full-thickness vs. lamellar corneal pig-to-rabbit xenotransplantation. Vet. Ophthalmol. 12(2):78-82.

[74] Badin, R.A., A. Padoan, M. Vadori, M. Boldrin, G.M. de Benedictis, F. Fante, D. Sgarabotto, C. Jan, V. Daguin, P. Naveilhan, I. Neveu, J. Soullilou, B. Banhove, M. Plat, F. Botte, F. Venturi, L. Denaro, M. Seveso, R. Manara, P. Zampieri, D. D'Avella, D. Rubello, E. Ancona, P. Hantraye, E. Cozzi. (2010) Porcine embryonic xenografts transgenic for CTLA4-Ig enable longterm recovery in Parkinsonian macaques. Am. J. Transplant. 10 (Supplement 4):208 (Abstract LB01).

[75] Laurencin, C.T., S.F. El-Amin. (2008) Xenotransplantation in orthopaedic surgery. J. Am. Acad. Orthop. Surg 16(1):4-8.

[76] Konakci, K.Z., B. Bohle, R. Blumer, W. Hoetzenecker, G. Roth, B. Moser, G. Boltz-Nitulescu, M. Gorlitzer, W. Klepetko, E. Wolner, H.J. Ankersmit. (2005) Alpha-gal on bioprostheses: xenograft immune response in cardiac surgery. Eur. J. of Clin. Invest. 35:17-33.

[77] Malcarney, H.L., F. Bonar, G.A. Murrell. (2005) Early inflammatory reactions after rotator cuff repair with porcine small intestine submucosal implant: a report of 4 cases. Am. J. of Sports Med. 33:907.

Despite the recent technology advances in this field, it is true that xenotransplantation still faces both technical and regulatory hurdles, as well as some criticism. But much of it is strongly reminiscent of the criticism leveled against human-to-human transplantation during the late 1960s and early 1970s. Yet with persistence, the field of human-to-human transplantation has proved highly successful. This success was the result of a stepwise increase in our understanding of the biology of rejection, improvements in immune suppression drug management, and experience. [78] Likewise, with respect to xenotransplantation, especially for whole organ pig xenografts like heart and kidney, where it's likely that xenotransplantation may not be universally successful until further technologic advances occur. However, exciting pre-clinical advances in cellular transplantation for treatment of diabetes, as well as for treatment of acute liver failure, either using transgenic (ie. GT-KO) pig livers as a temporary bridge to transplant, or purified pig liver cells in bioartificial liver devices, present opportunities that could be achievable. [79] Also, the application of genetically engineered animals for producing medical device products is generating significant interest from orthopedic and pharmaceutical companies and is likely to take the lead in forging the path to commercialization of safe and efficacious xenograft tissue products.

Table 1. Genetically engineered animals will enhance public health through more abundant, affordable medicines

Trait: Produce human drugs and replacement tissues

Type of Animal: cattle, chickens, fish, goats, pigs, sheep

- Blood products: antithrombin, human albumin, Factor IX
- Other protein-based drugs: monoclonal antibodies, polyclonal antibodies, plasminogen activator, human alpha-fetoprotein, alpha-1-proteinase inhibitor
- Vaccine components: antigens for any viral or bacterial disease such as pandemic flu, malaria, small pox
- Replacement tissues: pancreatic islet cells; whole organ xenografts such as liver, heart, kidney; heart valves; skin; surgical mesh from intestinal mucosa; orthopedic tissues; cellular transplants such as liver

[78] Cooper, D.K., A.M. Keogh, J. Brink, P.A. Corris, W. Klepetko, R.N. Pierson, M. Schmoeckel, R. Shirakura, L. Warner-Stevenson. (2000) Xenotransplantation Advisory Committee of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 19(12):1125-1165.

[79] Fung, J., A. Rao, T. Starzl. (1997) Clinical trials and projected future of liver xenotransplantation. World J Surg. 21(9):956-961.

Genetic Engineering Applied to the Improved Production of Animals for Agriculture: Food, Environment and Animal Welfare

There are numerous potential applications of genetic engineering of agricultural animals to develop new or altered strains of agriculturally important livestock. The future benefits of these applications are consistently as compelling as those for the biomedical applications, as they both promise to advance public health. In addition, owing to the global role of animal food products, genetic engineering promises to improve food security, production, quality and safety, while reducing the environmental footprint of livestock agriculture. In addition, the technology promises to improve animal welfare.

Enhanced Nutrition and Public Health

Human health is directly impacted in large part by the requirement for a sustainable and secure supply of healthful food. Genetic engineering of agricultural animals has the potential to provide compelling consumer benefits to public health via enhanced nutrition. For over 10,000 years, farmers and ranchers have improved the genetics of livestock and poultry to provide for nutritious, safe and economical animal protein products. It is a well-known fact that as socio-economic status of global communities rise, consumers demand more dietary animal protein as meat and milk, and that health and cognitive skills of children improve. It can be argued that the only technology that will allow such improvements in diet and health will be genetic engineering of livestock and poultry that is sustainable and available consistently worldwide.

Genetic engineering of agricultural animals has the potential to provide compelling consumer benefits to public health via enhanced nutrition.

Genetic engineering holds the promise to improve nutritional attributes of animal food products including their quantity, the quality of the whole food and specific nutritional composition. For example, increasing lean meat may be achieved by using genetic engineering to impact growth modulators, such as growth hormone and insulin-like growth factor. Another strategy is to introduce or regulate genes that mediate the formation of muscle tissue. In addition, introducing or altering proteins regulating lipid metabolism such as the hormone leptin or the enzyme fatty acid synthase could accomplish improvement in the percentage of lean meat to fat in whole foods. A new and promising area of genetic engineering is the development of livestock with modified lipid profiles, or "heart-healthy" fatty acids. This could be extended to other meat and milk producing species to improve and extend the health benefits of altering lipid composition to a wide variety of animal products. All of these potential interventions could result in more nutritious and healthful animal products used for food. Implications for public health through amelioration of pathologies (i.e. cardiovascular and cerebrovascular disease, cancer, diabetes, and obesity) associated with poor diet (high fat, low quality protein) could be monumental. The production of lower fat, more nutritious foodstuffs from meat and milk produced by genetic engineering could enable these potential improvements to public health.

Food borne diseases are a major global contributor to human morbidity/mortality, and genetically engineered animals can help manage and mitigate the causes in many ways. The public health benefits of improving food safety, via a more wholesome food supply, include production of genetically engineered animals that have inherent resistance to food borne pathogens. Early research has included development of poultry and livestock resistant to such organisms as *E. coli, campylobacter, clostridium* and *streptococcus.* Other genetic engineering could eliminate the animal's susceptibility to diseases, zoonotic and other, and their threat

to human health, such as bovine spongiform encephalopathy or "mad cow disease" or mastitis, an inflammation of the mammary gland that reduces milk quality. Improving animal health via genetic engineering also provides the added benefit of reducing the need for veterinary interventions and use of antibiotics and other medicinal treatments. The implications for public health through improving animal welfare, and increasing the animal's disease resistance are significant.

Practical applications of genetic engineering in livestock production include improved milk production and composition, increased growth rate, improved feed utilization, improved carcass composition, enhanced reproductive performance, increased prolificacy and altered cell and tissue characteristics for biomedical research [80] and manufacturing. The production of swine with a growth hormone transgene serves as an excellent example of the value of this technology. Improvement of milk composition through genetic engineering has the potential to enhance the production of certain proteins and/or growth factors deficient in milk. [81] The improvement of the nutrient or therapeutic value of milk may have a profound impact on survival and growth of newborns in both humans and animals. Other animal products, such as eggs and meat could also benefit from the use of genetic engineering. Genes could be targeted that could increase egg production in chickens and postpone reproductive senescence not only in chicken but also in other species as a result of physiologic events such as lactation, anorexia, poor nutrition and season of the year. [82]

The implications for public health through improving animal welfare, and increasing the animal's disease resistance are significant.

Table 2. Environmental impact will be reduced through genetic engineering of animals
Trait: Reduced phosphorus excretion Type of Animal: pigs
• Improve phosphorus digestion: salivary phytase
Trait: Enhancing efficiency of growth reduces total waste excreted Type of Animal: cattle, crustaceans, fish, pigs
• Enhanced growth rate: increasing growth factors, hormones, increased muscle protein synthesis or growth rate
Trait: Fluorescence in presence of polluters as an environmental indicator Type of Animal: fish
• Environmental detector of pollutants: *Zebra danio* (GloFish®)

[80] Wheeler, M.B., S.J. Choi. (1997) Embryonic stem cells and transgenics: recent advances. Arch. Fac. Vet. UFRGS 25:64-83.

[81] Bremel, R.D., H.C. Yom, G.T. Bleck.(1989) Alteration of milk composition using molecular genetics. J. Dairy. Sci. 72:2826-2833.

[82] Seidel, G.E. (1999) The future of transgenic farm animals. In: Genetically engineered animals in Agriculture (Murray, J.D., Anderson, G.B., Oberbauer, A.M., Mc Gloughlin, M.M., eds.),269-283. CABI Publishing, New York.

Reduced Environmental Impact

Livestock agriculture has been targeted by some as being harmful to the environment. However, genetic engineering of agricultural animals has the potential to significantly reduce its environmental footprint. Genetic engineering of animals could make a significant impact on protecting and improving the environment, such as decreasing phosphorous and nitrogen pollution in the Chesapeake Bay watershed or in the aquifers in hog and poultry producing areas such as Minnesota, North Carolina and Arkansas. Increasing efficiency and productivity per animal through genetic engineering will lead to a decreased burden on limited land and water resources while protecting the environment by decreasing potential pollutants from entering the soil and ground water. The protection of watersheds and ground water will become an ever more pressing issue regarding human health as populations continue to grow and expand into rural environments. Ample research and development has ensued for swine (the Enviro-Pig™) produced by genetic engineering [83] that has the ability to reduce the amount of phosphorous excreted into the environment. Increased rate of production of milk or meat will also decrease the impact on the environment by decreasing 1) the amount of manure, 2) the direct competition for human food, 3) the water requirement both for the animals and for facility hygiene and 4) the land footprint required for livestock facilities. Also improving feed conversion efficiency, reducing the pounds of feed required to produce a pound of meat or milk, could significantly reduce the environmental footprint of feedlot operations. Reducing feed inputs reduces manure outputs per unit of food produced. The AquAdvantage™ salmon produced by genetic engineering halves the time to market, improves feed efficiency and will contribute to a major reduction in the environmental footprint of aquaculture while producing a safe, healthy food.

Improved Animal Welfare

Genetic engineering of agricultural animals will improve animal welfare by producing healthier animals. Animal welfare is the top priority of anyone involved in animal husbandry and stewardship of the production of livestock. Therefore, because the technology can specifically impart resistance to a number of diseases, and improve productive characteristics, genetic engineering stands to significantly impact the health and well being of livestock. The end result of the improved health and well being from genetic engineering is to reduce frequency of veterinary interventions and use of various dietary and metabolic supplements, which have become commonly used in livestock production.

Due to the outlook for significant benefits there is ample global research and private development of genetically engineered animals that improve foods, are environmentally friendly, improve animal welfare and produce industrial products. It appears that the first food application with the U.S. FDA for genetic engineering is to enhance the growth rate of commercially valuable fish such as Atlantic salmon.[84] Other food applications are also underway. Genetic engineering may improve several aspects of livestock production including 1) milk quality, 2) meat production as growth and carcass composition, 3) animal welfare (via disease resistance), 4) reproductive performance and 5) quality of hair and fiber.

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[83] Golovan, S.P., R.G. Meidinger, A. Ajakaiye, M. Cottrill, M.Z. Wiederkehr, D.J. Barney, C. Plante, J.W. Pollard, M.Z. Fan, M.A. Hayes, J. Laursen, J.P. Hjorth, R.R. Hacker, J.P. Phillips, C.W. Forsberg. (2001) Pigs expressing salivary phytase produce low-phosphorus manure. Nature Biotechnol 19:741-745.

[84] Fletcher, G.L., M.A. Shears, E.S. Yaskowiak, M.J. King, S.V. Goddard. (2004) Gene transfer: potential to enhance the genome of Atlantic salmon for aquaculture. Australian Journal of Experimental Agriculture 44(11):1095-1100.

Table 3. Animal welfare will be improved for genetically engineered animals

Trait: Improving disease resistance

Type of Animal: cattle, chickens, fish, mollusks, pigs

- Resistance to disease: bovine spongiform encephthalopathy, avian influenza, brucellosis, mastitis, K88-positive E. coli, parasitic organisms, viral or bacterial pathogens, genetic diseases
- Self-immunization: raising antibody titers
- Natural resistance: cloning

Enhancing Milk

Advances in recombinant DNA technology have provided the opportunity either to improve the composition of milk or to produce entirely novel proteins in milk. These changes may add value to, as well as increase, the potential uses of milk.

The improvement of livestock growth or survivability through the modification of milk composition requires production of genetically engineered animals that: 1) produce a greater quantity of milk, 2) produce milk of higher nutrient content or 3) produce milk that contains a beneficial "nutriceutical" protein. The major nutrients in milk are protein, fat and lactose. By elevating any of these components, we can improve growth and health of the developing offspring that consumer the enhanced milk. In many production species such as cattle, sheep and goats, the nutrients available to the young may not be limiting. However, milk production in the sow limits piglet growth and therefore pig production. [85] Methods that increase the growth of piglets during suckling result in increased weaning weights, [86] decreased time to reach market weight and thus decreased feed requirements for the pig.

Cattle, sheep and goats used for meat production may also benefit from improved milk yield or composition. In tropical climates, *Bos indicus* cattle breeds do not produce copious quantities of milk. Increases in milk yield of as little as 2-4 liters per day may have a profound effect on weaning weights in cattle such as the Nelore breed in Brazil. Similar comparisons can be made with improving weaning weights in meat type breeds like the Texel sheep and Boer goat. This application of genetic engineering could lead to improved growth and survival of offspring.

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[85] Hartmann, P.E., I. McCauley, A.D. Gooneratne, J.L. Whitely. (1984) Inadequacies of sow lactation: survival of the fittest. Symp Zool Soc Lond 51: 301-326.

[86] Noble, M.S., S. Rodriguez-Zas, G.T. Bleck, J.S. Cook, W.L. Hurley, M.B. Wheeler. (2002) Lactational performance of first parity transgenic gilts expressing bovine ±-lactalbumin in their milk. J Anim Sci 80:1090-1096.

A second mechanism by which changing milk composition may improve animal growth is the addition or supplementation of beneficial naturally occurring hormones, growth factors or bioactive factors to the milk through the use of genetic engineering. It has been suggested that bioactive substances in milk possess important functions in the neonate with regard to regulation of growth, development and maturation of the gut, immune system and endocrine organs. [87] Transgenic alteration of milk composition has the potential to enhance the production of certain proteins and/or growth factors that are deficient in milk. [88] The increased expression of a number of these proteins in milk may improve growth, development, health and survivability of the developing offspring. Some of these factors are insulin-like growth factor 1 (IGF-I), epidermal growth factor (EGF), transforming growth factor beta (TGF-β) and lactoferrin. [89 90 91]

Other properties of milk that bear consideration for modifications are those that affect human and animal health. It has been shown that specific antibodies can be produced in genetically engineered animals. [92] It should be possible to produce antibodies in the mammary gland that are capable of preventing mastitis in cattle, sheep and goats and MMA (mastitis-metritis-agalactia) in pigs, and/or antibodies that aid in the prevention of domestic animal or human diseases. Another example is to increase proteins that have physiological roles within the mammary gland itself such as α-lactalbumin, [93] lysozyme, [94 95 96] lysostaphin [97] or other antimicrobial peptides.

Transgenic alteration of milk composition has the potential to enhance the production of certain proteins and/or growth factors that are deficient in milk.

It is important to consider the use of transgenics to increase specific components, which are already present in milk for manufacturing purposes. An example might be to increase one of the casein components in milk. This could increase the value of milk in manufacturing processes such as production of cheese or yogurt. One might also alter the physical properties of a protein such as β-casein or κ-casein. [98] By increasing the glycosylation of β-casein, [99]

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[87] Grosvenor, C.E., M.F. Picciano, C.R. Baumrucker. (1993) Hormones and growth factors in milk. Endocrinol Rev. 14(6):710-728.

[88] Wall, R.J., V.G. Pursel, A. Shamay, R.A. McKnight, C.W. Pittius, L. Henninhausen. (1991) High-level synthesis of a heterologous milk protein in the mammary glands of transgenic swine. Proc Natl Acad Sci USA 88:1696-1700.

[89] Konakci, K.Z., B. Bohle, R. Blumer, W. Hoetzenecker, G. Roth, B. Moser, G. Boltz-Nitulescu, M. Gorlitzer, W. Klepetko, E. Wolner, H.J. Ankersmit. (2005) Alpha-gal on bioprostheses: xenograft immune response in cardiac surgery. Eur. J. of Clin. Invest. 35:17-33.

[90] Malcarney, H.L., F. Bonar, G.A. Murrell. (2005) Early inflammatory reactions after rotator cuff repair with porcine small intestine submucosal implant: a report of 4 cases. Am. J. of Sports Med. 33:907.

[91] Zhang, J., L. Li, Y. Cai, X. Xu, J. Chen, Y. Wu, H. Yu, G. Yu, S. Liu, A Zhang, J. Chen, G. Cheng. (2008) Expression of active recombinant human lactoferrin in the milk of transgenic goats. Protein Expr Purif 57:127-135.

[92] Storb, U. (1987) Transgenic mice with immunoglobin genes. Annu Rev Immunol 5:151-174.

[93] Bleck, G.T., B.R. White, D.J. Miller, M.B. Wheeler. (1998) Production of bovine alpha-lactalbumin in the milk of transgenic pigs. J Anim Sci 76:3072-3078.

[94] Maga, E.A., G.B. Anderson, J.D. Murray. (1995) The effect of mammary gland expression of human lysozyme on the properties of milk from transgenic mice. J Dairy Sci 78:2645-2652.

[95] Brundige, D.R., E.A. Maga, K.C. Klasing, J.D. Murray. (2008) Lysozyme transgenic goats' milk influences gastrointestinal morphology in young pigs. J Nutr 138:921-926.

[96] Brundige, D.R., E.A. Maga, K.C. Klasing, J.D. Murray. (2010) Consumption of pasteurized human lysozyme transgenic goats' milk alters serum metabolite profile in young pigs. Transgenic Res. 19(4):563-574.

[97] Donovan, D.M., D.E. Kerr, R.J. Wall. (2005) Engineering disease resistant cattle. Transgenic Res 14:563-567.

[98] Brophy, B., G. Smolenski, T. Wheeler, D. Wells, P. L'huillier, G. Laible. (2003) Cloned transgenic cattle produce milk with higher levels of β-casein and ∫ κ-casein. Nature 21:157-162.

[99] Choi, B.K., G.T. Bleck, M.B. Wheeler, R. Jiminez-Flores. (1996) Genetic modification of bovine-casein and its expression in the milk of transgenic mice. J Agric Food Chem 44:953-960.

one could increase its solubility in milk, which would reduce the time required for rennet coagulation and whey expulsion. This would produce firmer curds that are valuable in cheese making. Changes in other physical properties could result in dairy foods with improved characteristics, such as better tasting low fat cheese. [100] It should also be possible to increase the concentration of milk components while maintaining a constant volume. This could lead to greater product yield (i.e. more protein, fat or carbohydrate from a liter of milk). This would also aid in manufacturing processes while also decreasing transportation costs for the more concentrated products in fluid milk. The end result would be more saleable product for the dairy producer and a reduced environmental footprint.

The overall result of genetic engineering to modify milk will be the creation of more uses of milk and milk products in both agriculture and medicine. [101] This is truly a *"value-added"* opportunity for animal agriculture by increasing the concentrations of existing proteins or producing entirely new proteins in milk.

The overall result of genetic engineering to modify milk will be the creation of more uses of milk and milk products in both agriculture and medicine.

Enhancing Growth Rates and Carcass Composition

The production of genetically engineered livestock has been instrumental in providing new insights into the mechanisms of gene action governing growth. [102 103 104 105 106] Using transgenic technology, it is possible to manipulate growth factors, growth factor receptors and growth modulators. Transgenic sheep and pigs have been used to examine postnatal growth of mammals. Growth hormone (GH) and IGF genes have been incorporated and expressed at various levels in genetically engineered animals. [107] Transgenic livestock and fish have been produced which contain an exogenous GH gene. This type of work enabled the study of chronic expression of these hormones on growth in mammals and fish. Results from one study have shown that an increase in porcine-produced GH as a result of a transgene leads to enhanced growth and feed efficiency in pigs. [108] In fish, dramatic increases have been shown in growth rate of transgenic Atlantic salmon using the gene promoter and growth hormone gene derived from fish species. [109] These researchers also indicate that fish used in

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[100] Bleck, G.T., R. Jiminez-Flores, M.B. Wheeler. (1995) Production of genetically engineered animals with altered milk as a tool to modify milk composition, increase animal growth and improve reproductive performance. In: Greppi GF, Enne G [ed], Animal Production & Biotechnology. Elsevier, Amsterdam 1-19.

[101] Van Berkel, P.H.C., M.M. Welling, M. Geerts, H.A. van Veen, B. Ravensbergen, M. Salajeddine, E.K.J. Pauwels, F. Pieper, J.H. Nuijens, P.H. Nibbering. (2002) Large-scale production of recombinant human lactoferin in the milk of transgenic cows. Nature 20:484-487.

[102] Ebert, K., M. Low, E. Overstrom, F. Buonoma, T.M. Roberts, A. Lee, G. Mandel, R. Goodman. (1988) A Moloney MLV-RAT somatotropin fusion gene produces biologically active somatotropin in a transgenic pig. Mol Endocrinol 2:277-283.

[103] Ebert, K.M., T.E. Smith, F.C. Buonoma, E.W. Overstrom, M.J. Low. (1990) Porcine growth hormone gene expression from viral promoters in transgenic swine. Anim Biotechnol 1:145-159.

[104] Murray, J.D., C.D. Nancarrow, J.T. Marshall, I.G. Hazelton, K.A. Ward. (1989) The production of transgenic Merino sheep by microinjection of ovine metallothionein-growth hormone fusion genes. Reprod Fertil Dev 1:147-155.

[105] Pursel, V.G., C.A. Pinkert, K.F. Miller, D.J. Bolt, R.G. Cambell, R.D. Palmiter, R.L. Brinster, R.E. Hammer. (1989) Genetic engineering of livestock. Science 244:1281-1288.

[106] Rexroad Jr, C.E., K.M. Mayo, D.J. Bolt, T.H. Elsasser, K.F. Miller, R.R. Behringer, R.D. Palmiter, R.L. Brinster. (1991) Transferrin- and albumin-directed expression of growth-related peptides in transgenic sheep. J Anim Sci 69:2995-3004.

[107] Seidel, G.E. The future of transgenic farm animals. (1999) In: Murray, J.D., G.B. Anderson, A.M. Oberbauer, M.M. McGloughlin [ed], Genetically engineered animals in Agriculture. CABI Publishing, New York, 269-283.

[108] Vise, P.D., A.E. Michalska, R. Ashuman, B. Lloyd, A.B. Stone, P. Quinn, J.R.E. Wells, R.R. Seamark. (1988) Introduction of a porcine growth hormone fusion gene into transgenic pigs promotes growth. J Cell Sci 90:295-300.

[109] Hew, C.L., G.L. Fletcher, P.L. Davies. (1995) Transgenic salmon: tailoring the genome for food production. Journal of Fish Biology 47(Suppl. A):1-19.

aquaculture would be made sterile, thus minimizing the ecological impact due to accidental escape of fish that might be raised in ocean pens. Introduction of salmonid GH constructs has resulted in a 5-11 fold increase in weight after one year of growth. [110] [111] [112] This demonstrates that increased growth rate and ultimately increased rate of protein production can be achieved via genetic engineering. In addition, the production of these growth-enhanced salmon will have vast positive environmental benefits. Cutting in half the time required to raise salmon means supply can be increased without proportionately increasing the use of farms. In addition, land-based systems become economically viable and competitive with ocean-pen systems further reducing environmental impact. The apparent increase in food conversion rates means that fewer natural resources are required to produce the fish, thus enhancing sustainability.

The Rendement Napole (RN) or acid-meat gene has been implicated in lower processing yields in lines of Hampshire and Hampshire crossbred pigs. "Knocking-out" the RN gene may provide a method to alter post-mortem pH and thereby increase meat tenderness. Other specific loci, which may affect growth patterns, are the ryanodine receptor, the *myo*-D, [113] [114] GH releasing factor, high affinity IGF binding proteins (IGFBP-1 to IGFBP-6), the sheep callipyge [115] and the myostatin (growth/differentiation factor-8, *GDF*-8) genes. [116] Based on a recent report on the mouse, the myostatin gene is an exceptionally intriguing potential locus for "knocking-out" in meat producing species. The loss of the myostatin protein results in an increase in lean muscle mass. Certainly, there are numerous potential genes related to growth, including growth factors, receptors or modulators which have not yet been used, but may be of practical importance in producing genetically engineered livestock with increased growth rates and/or feed efficiencies.

Altering the fat or cholesterol composition of the carcass is another valuable benefit that can be delivered via genetic engineering.

Altering the fat or cholesterol composition of the carcass is another valuable benefit that can be delivered via genetic engineering. By changing the metabolism or uptake of cholesterol and/or fatty acids, the content of fat and cholesterol of meats, eggs and cheeses could be lowered. There is also the possibility of introducing beneficial fats such as the omega-3 fatty acids from fish or other animals into our livestock. [117] Receptors such as the low-density lipoprotein (LDL) receptor gene and hormones like leptin are also potential targets that would decrease fat and cholesterol in animal products.

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[110] Devlin, R.H., T.Y. Yesaki, C.A Biagi, E.M. Donaldson, P. Swanson, W-K. Chan. (2002) Extraordinary salmon growth. Nature 371:209-210.

[111] Devlin, R.H., T.Y. Yesaki, E.M. Donaldson, S-J. Du, C.L. Hew. (1995) Production of germline transgenic Pacific salmonids with dramatically increased growth performance. Can J Fish Aquat Sci 52:1376-1384.

[112] Du, S.J., Z. Gong, G.L. Flecther, M.A. Schears, M.J. King, D.R. Idler, C.L. Hew. (1992) Growth enhancement in transgenic salmon by the use of an "all fish" chimeric growth hormone gene construct. Biotechnology 10:176-181.

[113] Harvey, R.P. (1991) Widespread expression of MyoD genes in Xenopus embryos is amplified in presumptive muscle as a delayed response to mesoderm induction. Proc Natl Acad Sci USA 88:9198-9202.

[114] Sorrentino, V., R. Pepperkok, R.L. Davis, W. Ansorge, L. Phillipson. (1990) Cell proliferation inhibited by MyoD1 independently of myogenic differentiation. Nature 345:813-814.

[115] Snowder, G.D., J.R. Busboom, N.E. Cockett, F. Hendrix, V.T. Mendenhall. (1994) Effect of the Callipyge gene on lamb growth and carcass characteristics. In: Proceedings of the Fifth World Congress Genet Applied to Livestock Production, Guelph, Canada 18:51-54.

[116] McPherron, A.C., A.M. Lawler, S.J. Lee. (1997) Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. Nature 387:83-90.

[117] Lai, L., J.X. Kang, R. Li, J. Wang, W.T. Witt, H.Y. Yong, Y. Hao, D.M. Wax, C.N. Murphy, A. Rieke, M. Samuel, M.L. Linville, S.W. Korte, R.W. Evans, T.E. Starzl, R.S. Prather, Y. Dai. (2006) Generation of cloned transgenic pigs rich in omega-3 fatty acids. Nat Biotechnol 24:435-436.

The use of genetic engineering to improve feed efficiency and/or appetite could profoundly impact livestock production and deliver significant benefits to producers, processors, and consumers. Increased uptake of nutrients in the digestive tract, by alteration of the enzyme profiles in the gut, could increase feed efficiency. The ability to introduce enzymes such as phytase or xylanase into the gut of species where they are not normally present, such as swine or poultry, is particularly attractive. The introduction of phytase would increase the bioavailability of phosphorus from phytic acid in corn and soy products. One group has reported the production of transgenic pigs expressing salivary phytase as early as seven days of age. [118] The salivary phytase provided essentially complete digestion of the dietary phytate phosphorus in addition to reducing phosphorus output in waste by up to 75 percent. Furthermore, transgenic pigs required almost no inorganic phosphorus supplementation to the diet to achieve normal growth. The use of phytase transgenic pigs in commercial pork production could result in significantly decreased environmental phosphorus pollution from livestock operations.

The use of genetic engineering to improve feed efficiency and/or appetite could profoundly impact livestock production and deliver significant benefits to producers, processors, and consumers.

Enhanced Animal Welfare through Improved Disease Resistance

The impact of genetic engineering on animal welfare is compelling. Genetic engineering of agricultural animals has the potential to improve disease resistance by introducing specific genes into livestock. Identification of single genes in the major histocompatibility complex (MHC), which influence the immune response, was instrumental in the recognition of the genetic basis of disease resistance/susceptibility. [119] The application of transgenic technology to specific aspects of the immune system should provide opportunities to genetically engineer livestock that are healthier and have superior disease resistance.

Many aspects of disease resistance or susceptibility in livestock that are genetically determined. [120] One specific example where transgenesis has been applied to disease resistance in livestock is the attempt to produce cattle resistant to mastitis. Mastitis is an infectious disease of the mammary gland that causes decreased milk production and lost productivity. Treatment and prevention of mastitis is costly and labor intensive. Lysostaphin is an antimicrobial peptide that protects mammary glands against *Staphylococcus aureus* infection by killing the bacteria in a dose-dependent manner. Transgenic dairy cows that secrete lysostaphin into their milk have been produced to address the mastitis issue.

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[118] Golovan, S.P., R.G. Meidinger, A. Ajakaiye, M. Cottrill, M.Z. Wiederkehr, D.J. Barney, C. Plante, J.W. Pollard, M.Z. Fan, M.A. Hayes, J. Laursen, J.P. Hjorth, R.R. Hacker, J.P. Phillips, C.W. Forsberg. (2001) Pigs expressing salivary phytase produce low-phosphorus manure. Nature Biotechnol 19:741-745.

[119] Benacerraf, B., H.O. McDevitt. (1972) Histocompatibility linked immune response genes. A new class of genes that controls the formation of species immune response has been identified. Science 175:273-279.

[120] Lewin, H.A. (1989) Disease resistance and immune response genes in cattle: strategies for their detection and evidence of their existence. J. Dairy Sci 72:1334-1348.

The application of nuclear transfer technology, or cloning, will enable the augmentation of beneficial alleles and/or the removal (via gene "knock-out") of undesirable alleles associated with disease resistance or susceptibility. An example is "knocking-out" the intestinal receptor for the K88 antigen. The absence of this antigen has been shown to confer resistance to infection of K88-positive *E. coli*. [121] Potential areas of investigation include resistance to: 1) parasitic organisms such as trypanosomes and nematodes; 2) viral or bacterial pathogens such as bovine leukemia virus, pseudorabies virus, foot and mouth virus, clostridium and streptococcus and 3) genetic diseases such as deficiency of uridine monophosphate synthase (DUMPS), mule foot and bovine leukocyte adhesion deficiency (BLAD).

The opportunity to produce animals that could self-immunize against pathogens is an exciting application of genetic engineering. Transgenes could be designed to produce antigens resulting in immunization of the genetically engineered animal to particular diseases. Transgenes will be designed that could be turned on by administering, for example, zinc in feed, or a specific antibiotic to produce antigens that could raise protective antibody titers.

Transgenes could be designed to produce antigens resulting in immunization of the genetically engineered animal to particular diseases.

Using the genetics from naturally resistant animals in cloning applications will produce animals resistant to a variety of diseases including bovine spongiform encephalopathy (BSE) and scrapie. An example of this kind of application is the production of transgenic mice expressing either the human or bovine prion protein. Each of these mouse strains was inoculated with the prions that cause BSE or with a variant of Creutzfeldt-Jakob disease (vCJD). The BSE was transmitted to the mice containing the bovine prion protein but was not transmitted to transgenic mice containing the human prion protein. [122] However, all three transgenic mouse lines containing the human prion protein showed transmission of the disease when inoculated with vCJD. Recently, cattle have been produced lacking the prion protein. [123] Analysis of these animals determined that they are in fact resistant to BSE, and this is a major step toward developing cattle that do not develop "mad-cow" disease. Another example of this potential application is the production of fetuses that are resistant to brucellosis, [124] a highly contagious bacterial disease of cattle that can be transmitted from cattle to humans and causes high fever and muscular pain. This is only a partial list of organisms or genetic diseases that, when targeted for improvement via transgenic methodologies, will increase production efficiency and enhance animal welfare.

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[121] Edfors-Lilia, I., H. Petersson, B. Gahne. (1986) Performance of pigs with or without the intestinal receptor for Escherichia Coli K88. Anim Prod 42:381-387.

[122] Bishop, M.T., P. Hart, L. Aitchison, H.N. Baybutt, C. Plinston, V. Thomson, N.L Tuzi, M.W. Head, J.W. Ironside, R.G. Will, J.C. Manson. (2006) Predicting susceptibility and incubation time of human-to-human transmission of vCJD. Lancet Neurol 5:393-398.

[123] Richt, J.A., P. Kasinathan, A.N. Hamir, J. Castilla, T. Sathiyaseelan, F. Vargas, J. Sathiyaseelan, H. Wu, H. Matsushita, J. Koster, S. Kato, I. Ishida, C. Soto, J.M. Robl, Y. Kuroiwa. (2007) Production of cattle lacking prion protein. Nat Biotechnol. 25(1):132-138.

[124] Shin, T., L.G. Adams, J.W. Templeton, M.E. Westhusin. (1999) Nuclear transfer using somatic cell line derived from a bull genetically resistance to brucellosis. Transgenic Res 8:488 abstr.

Improving Reproductive Performance and Fecundity

Several genes have been identified which may profoundly affect reproductive performance. These include the estrogen receptor (ESR) and the Boroola fecundity (FECB) genes. It has been shown that a specific form of the ESR gene is associated with 1.4 more pigs born per litter than is typical in lines of pigs that do not contain this specific ESR gene type. [125] Introduction of a mutated or polymorphic ESR gene could increase litter size in a number of diverse breeds of pigs. A single major gene for fecundity, the FECB gene, which allows for increased ovulation rate, has been identified in Merino sheep. [126] Each copy of the gene has been shown to increase ovulation rate by approximately 1.5 ova per cycle. Production of transgenic sheep containing the appropriate FECB allele could increase fecundity in a number of diverse breeds. Identification of additional genes involved in fecundity from hyperprolific breeds/strains of swine (Meishan), sheep (Finnish Landrace) and cattle (high twinning) will provide additional opportunities to improve reproductive performance. The manipulation of reproductive processes using transgenic methodologies is only beginning, and it should be a very rich area for research and livestock improvement in the future.

The manipulation of reproductive processes using transgenic methodologies is only beginning, and it should be a very rich area for research and livestock improvement in the future.

[125] Rothschild, M.F., C. Jacobson, D.A. Vaske, C.K. Tuggle, T.H. Short, S. Sasaki, G.R. Eckardt, D.G. McLaren. (1994) A major gene for litter size in pigs. In: Proceedings of the Fifth World Congress Genet Applied to Livestock Production, Guelph, Canada 21:225-228.

[126] Piper, L.E., B.M. Bindon, G.H. Davis. (1985) The single inheritance of the high litter size of the Boorola Merino. In: Land, R.B., D.W. Robinson [ed], Genetics of Reproduction in Sheep. Butterworths, London 115-125.

Table 4. Genetically engineered animals will enhance public health through healthier, high quality, and abundant food

Trait: Enhancing milk for use by animals Type of Animal: pigs
• Natural proteins fortified: α-lactalbumin, insulin-like growth factor-1, epidermal growth factor, transforming growth factor-β, lactoferrin, antibodies to mastitis, lysozyme, lysostaphin
Trait: Enhancing milk for direct use by humans Type of Animal: cattle, sheep
• Natural components fortified: β-casein, κ-casein, protein, fat, lactose
Trait: Enhancing growth rates and carcass composition Type of Animal: cattle, crustaceans, fish, pigs, sheep
• Increasing growth factors, hormones: growth hormone, insulin-like growth factors • Tenderness of meat: knock-out of acid-meat gene • Increased muscle protein synthesis or growth rate: ryanodine receptor, myo-D, growth hormone releasing factor, insulin-like growth factor binding protein-1 to insulin-like growth factor binding protein-6, sheep callipyge gene, myostatin gene • Altered fat or cholesterol in meat: omega-3 fatty acids, low-density lipoproteins, leptin hormone
Trait: Enhancement of reproductive performance Type of Animal: pigs, sheep
• Genes that increase fecundity: estrogen receptor, boroola fecundity genes
Trait: Enhancement of hair and fiber Type of Animal: sheep
• Wool: quality, length, fineness, crimp • Fiber: elasticity, strength

Improving Hair and Fiber

The control of the quality, color, yield and ease of harvest of hair, wool and fiber for fabric and yarn production has been an area of focus for genetic engineering in livestock. The manipulation of the quality, length, fineness and crimp of the wool and hair fiber from sheep and goats has been examined using transgenic methods. [127] [128] Transgenic methods will also allow improvements to fiber elasticity and strength. [129] In the future transgenic manipulation of wool will focus on the surface of the fibers. Decreasing the surface interactions between fibers could decrease shrinkage of garments made from such fibers. [130]

A novel approach to produce useful fiber has been recently accomplished using the milk of transgenic goats. [131] Spiders that produce orb-webs synthesize as many as seven different types of silk used in making these webs. Each of these silks has specific mechanical properties that make them distinct from other synthetic and natural fibers. One of the most durable varieties is dragline silk. This material can be elongated up to 35 percent and has tensile properties close to those of the synthetic fiber Kevlar®. This silk has a greater capacity to absorb energy before snapping than steel. The protein monomers that assemble to produce these spider silk fibers have been produced in the milk of transgenic goats. The numerous potential applications of these fibers include medical devices, suture, ballistic protection, aircraft, automotive composites and clothing to name a few.

Table 5. More abundant, high-value industrial proteins may be produced by genetically engineered animals

Trait: Tensile properties for biodefense or medical uses Type of Animal: goats
• Natural proteins: spider silk

[127] Hollis, D.E., R.E. Chapman, B.A. Panaretto, G.P. Moore. (1983) Morphological changes in the skin and wool fibers of Merino sheep infused with mouse epidermal growth factor. Aust J Biol Sci 36(4):419-434.

[128] Powell, B.C., S.K. Walker, C.S. Bawden, A.V. Sivaprasad, G.E. Rogers. (1994) Transgenic sheep and wool growth: possibilities and current status. Reprod Fertil Dev 6(5):615-623.

[129] Bawden, C.S., B.C. Powell, S.K. Walker, G.E. Rogers. (1998) Expression of a wool intermediate filament keratin transgene in sheep fiber alters structure. Transgenic Res 7:273-287.

[130] Bawden, C.S., S.M. Dunn, C.J. McLaughlan, A. Nesci, B.C. Powell, S.K. Walker, G.E. Rogers. (1999) Transgenesis with ovine keratin genes: expression in the sheep wool follicle for fibres with new properties. Transgenic Res 8:474 abstr.

[131] Karatzas, C.N., J.F. Zhou, Y. Huang, F. Duguay, N. Chretien, B. Bhatia, A. Bilodeau, R. Keyston, T. Tao, C.L. Keefer, B. Wang, H. Baldassare, A. Lazaris. (1999) Production of recombinant spider silk [BiosteelTM] in the milk of genetically engineered animals. Transgenic Res 8:476-477.

Science-Based Regulation of Genetically Engineered Animals

Science-based regulation of genetically engineered animals and their products ensures safety of the products and public confidence. Tremendous progress has been accomplished since 2008 in developing new regulatory guidance, both internationally and domestically. The technology involved in production of genetically engineered animals holds great promise of benefits through both biomedicine and agriculture. This scientific promise resulted in a regulatory pathway for enabling these new technologies. With continued research globally, both medical applications of genetic engineering of animals through development of new drugs, biologics and xenotransplants and agricultural applications are upon us.

International Progress on Regulatory Guidance

A significant development occurred in 2008 when the Codex Alimentarius Commission adopted an international standard for food safety risk assessment for genetically engineered animals. [132] Internationally, product developers should be familiar with and apply appropriately the 2008 Codex guidelines for rDNA animals for food safety assessment of foods derived from rDNA animals. As other international guidelines are developed for the safety of products from genetically engineered animals, product developers should stay abreast of these developments and apply the guidelines, as appropriate, depending on the species and/or research purpose.

The technology involved in production of genetically engineered animals holds great promise of benefits through both biomedicine and agriculture.

U. S. Progress on Regulatory Guidance

Science-based regulation of genetically engineered animals and their products ensures safety of the products and public confidence. Significant progress was achieved when, after many years of analysis, including public comment for a draft guidance, the U.S. FDA announced final regulatory guidance for genetically engineered animals in January 2009. [133] The U.S. federal government had set the precedent for reasonable oversight of biotechnology through the development of its genetically engineered plant regulatory framework. Comprehensive coordination for regulation that bridged the divide between food and biomedical products was required. The federal government study of the regulation of genetic engineering of plants and microbes had eclipsed animals for over two decades. Despite the Office of Science and Technology Policy's (OSTP) 1986 intensive study and publication of the coordinated framework for policy and regulation of agricultural biotechnology, which outlined agency responsibilities for regulation of genetically engineered plants, microbes *and animals,* [134] and in-depth case reviews of the regulation of various genetically engineered animals by the Council on

[132] Codex Alimentarius Commission. 2008. Joint FAO/WHO Food Standards Programme, 31st Session, Geneva, Switzerland, 30 June - 5 July 2008, Report of the Seventh Session of the Codex Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology. al31_42e[1].pdf at www.codexalimentarius.net (http://www.codexalimentarius.net/download/standards/11023/CXG_068e.pdf]

[133] Food and Drug Administration, Center for Veterinary Medicine. (2009) Guidance for Industry 187, Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs. (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf)

[134] Office of Science & Technology Policy (OSTP), Executive Office of the President (June 26, 1986) Coordinated Framework for the Regulation of Biotechnology. 51 FR 23302.

Environmental Quality [135] (CEQ), the policy environment had not moved forward in a timely manner. The OSTP analysis focused on the statutory authorities of FDA and the U.S. Department of Agriculture (USDA). Published in 2001, the CEQ case studies for both transgenic growth-enhanced salmon and transgenic goats producing a human drug indicate that the animals are subject to FDA oversight according to the Food Drug and Cosmetic Act (FDCA) because they are considered to contain a "new animal drug" as defined in the law.

The FDA Center for Veterinary Medicine claimed jurisdiction over genetically engineered animals several years ago, defined a regulatory pathway and invited parties from industry and academia to apply for an Investigational New Animal Drug (INAD), but there had been no publication of guidance documents or regulations on the process until January of 2009. Several applications were submitted by product developers to the FDA over the past decade, but no genetically engineered animals had gone beyond the INAD stage nor received approval for an animal-made pharmaceutical. In coordination with the FDA, the USDA has evaluated their authorities and role in regulation of genetically engineered animals and is coordinating with the FDA.

The New Animal Drug approach consolidates regulatory review and oversight for the animal's health, human health and the environment, affording an efficient process with regard to use of agency expertise and other resources.

The New Animal Drug approach is a mandatory process that provides an "approval." Many industry participants believed this imprimatur was necessary for successful commercialization and appropriate to the technology and products. Industry believes that this rigorous, science-based approval process will improve consumer acceptance because of the mandatory framework for approval. The New Animal Drug approach consolidates regulatory review and oversight for the animal's health, human health and the environment, affording an efficient process with regard to use of agency expertise and other resources. Industry's expectation is that the process will avoid duplicative and burdensome process steps and forge a science-based, seamless and smooth path toward approvals.

Industry Stewardship Guidance on Genetically Engineered Animals

In the future, institutions may wish to establish guidelines used in keeping with federal, state, and local government regulatory requirements. The animal biotechnology industry released guidelines for research and development with GE animals as a stewardship program for GE animals (Biotechnology Industry Organization, 2009). [136] The BIO Guidance provides information for the development and implementation of stewardship programs for all institutions and researchers that plan to engage in research and development, and possible commercialization, of GE animals. The mission of the industry stewardship initiative is to institute and promote guidelines for the development and use of GE animals which promote good animal welfare, enhance industry credibility and comply with current regulatory requirements.

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[135] OSTP-Council on Environmental Quality (2001) 'CEQ and OSTP Assessment: Case Studies of Environmental Regulations for Biotechnology.' http://www.ostp.gov/html/ceq_ostp_study1.pdf.

[136] BIO Guidance on Genetically Engineered Animal Stewardship, http://bio.org/foodag/geanimalctr/20090814_GE_Animal_Stewardship_Guidance.pdf

Enabling Both Agricultural and Biomedical Applications of Genetic Engineering

Genetically engineered animals in agriculture are poised to deliver benefits to producers, processors, the environment and individual consumers. Improvements in food production efficiency become more urgently needed in the face of projected increases in demand driven by population growth and prosperity. [137] Aside from increasing production efficiency, the examples of livestock able to resist specific diseases, and thus improving animal welfare, decreases the use of antibiotics in the food supply, clearly a consumer benefit. In addition, this technology has the potential to produce more healthful products such as meat high in omega-3 fatty acids. The increased food safety aspects of eliminating BSE or certain bacteria in milk production and dairy products clearly benefit consumers.

One of the most promising areas of research and development involves the farm animals bred to deliver environmental benefits. Consumer surveys suggest that genetic engineering directed to issues involving environmental sustainability and food safety receive meaningful support. [138] Because of its unique attributes, the Enviro-Pig™ excretes feces that contains 30 to 60 percent less phosphorus than non-transgenic pigs fed the same conventional diet. [139] As a result, 33 percent less land would be required to absorb the manure from these pigs as fertilizer. If this were combined with animal diets adjusted to decrease crude protein, even less land would be required. [140] In addition, notwithstanding the impact on the land, there will also be a direct positive impact on human health as the negative impact on environmental quality is reduced. Furthermore, any genetically engineered animal that grows more efficiently also provides a substantial positive environmental impact. The genetically engineered salmon, AquAdvantage™ salmon, that is bred to grow to a mature size more quickly, increases the efficiency of food production while providing a huge environmental benefit. The positive environmental impact will be significant in aquaculture that uses genetic engineering. [141 142 143 144 145 146]

One of the most promising areas of research and development involves the farm animals bred to deliver environmental benefits.

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[137] United Nations Food & Agriculture Organization (2002). World Agriculture: Towards 2015/2030 at http://www.fao.org/docrep/004/y3557e/y3557e00.HTM.

[138] Santerre, C.R., K.L. Machtmes. (2002) The impact of consumer food biotechnology training on knowledge and attitude. J. Am. Coll. Nutr. 21(Suppl. 3):174-177.

[139] Golovan, S.P., R.G. Meidinger, A. Ajakaiye, M. Cottrill, M.Z. Wiederkehr, D.J. Barney, C. Plante, J.W. Pollard, M.Z. Fan, M.A. Hayes, J. Laursen, J.P. Hjorth, R.R. Hacker, J.P. Phillips, C.W. Forsberg. (2001) Pigs expressing salivary phytase produce low-phosphorus manure. Nature Biotechnol 19:741-745.

[140] If transgenic phytase pigs were raised in place of conventional pigs, the land area required for spreading would be reduced by 33% before manure N would be applied in excess. It is generally recognized that for each 1% decrease in protein in the diet, there is an 8 to 10% reduction in manure (Lenis, N.P., A.W. Jongbloed. (1999) New technologies in low pollution swine diets: Diet manipulation and use of synthetic amino acids, phytase and phase feeding for reduction of nitrogen and phosphorus excretion and ammonia emission. Asian Aus. J. Anim. Sci. 12:305-327.

[141] Alestrøm, P (1995) Genetic engineering in aquaculture. In 'Sustainable fish farming'. Reinertsen, H., H. Haaland [ed.] AA Balkema: Rotterdam

[142] Berkowitz, D.B.,I. Kryspin-Sorensen (1994) Transgenic fish: safe to eat? Biol. Technology (Elmsford, N.Y.) 12:247-252.

[143] Devlin, R.H. (1997) Transgenic salmonids. In 'Transgenic animals, generation and use'. L.M. Houdebine [ed.] Harwood Academic Publishers 105-117.

[144] Devlin, R.H., E.M. Donaldson (1992) Containment of genetically altered fish with emphasis on salmonids. In 'Transgenic fish'. Hew, C.L., G.L. Fletcher [ed.] World Scientific 229-265.

[145] Fletcher, G.L., R. Alderson, E.A. Chin-Dixon, M.A. Shears, S.V. Goddard, C.L. Hew (1999) Transgenic fish for sustainable aquaculture. In 'Proceedings of the 2nd international symposium on sustainable aquaculture'. Svennevig, N., H. Reinertsen, M. New [ed.]. AA Balkema: Rotterdam 193-201.

[146] Fletcher, G.L., P.L. Davies (1991) Transgenic fish for aquaculture. In 'Genetic engineering, principles and methods'. Setlow, J.K. [ed.] (Plenum Press: New York) 331-370.

The transgenic pig and salmon embody the leading edge of various types of genetically engineered animals that will reduce the environmental footprint of animal agriculture through enhanced metabolic capabilities. Likewise, similar to environmentally-friendly agriculture, another more immediate and obvious application of genetic engineering is the development of animals that have improved food production qualities, thus creating efficiencies, cost savings, and qualitative improvements in food production that can enable farmers worldwide to extend food supplies while using fewer natural resources.

Future Challenges and Conclusion

Genetic engineering of agricultural animals has made its mark on the global stage of biotechnology. With the daunting global challenges of hunger, health and environment, genetic engineering of agricultural animals must be a tool in the 21st century tool box for humankind. A rigorous, science-based regulatory process that results in approvals will boost consumer confidence and acceptance of products from genetically engineered animals. It should be noted that following the approval by the U.S. FDA of ATryn™ there was broad positive coverage by the media, and there was literally no public concern. At the VIIth University of California-Davis International Conference on Transgenic Animals, there was excitement among the over 125 international scientists about the future of the industry. There was no doubt among those leading researchers that in the future, consumers will reap the benefits of this exciting area of biotechnology.

Genetically engineered animals can deliver substantial improvements in terms of cost, safety and availability of urgently needed drugs and treatments, thus bringing substantial public health benefits.

While the agricultural application of this science is compelling, the medical applications are groundbreaking, and the needs for both public health and food security are urgent. Genetically engineered animals promise not only safer, lower-cost proteins and drugs that could increase access and enable essential changes in medical practice but also fundamentally better medical products that can provide substantial improvements over today's medicines. The drugs that genetically engineered animals can produce—blood components, replacement proteins, antibodies, and xenotransplants—remain among the most expensive drugs to produce in the world. Genetically engineered animals can deliver substantial improvements in terms of cost, safety and availability of urgently needed drugs and treatments, thus bringing substantial public health benefits. Likewise, genetically engineered animals can also meet the growing global demand for high quality and safe animal food products in a sustainable, environmentally safe and positive animal welfare manner.

Both the biomedical and the agricultural applications of genetic engineering of agricultural animals are immediate research and development opportunities, bolstered by the presence of a clear regulatory framework. However, many challenges remain for the animal biotechnology product developers in industry and academia. First, the FDA must continue timely issuance of additional approvals in order to maintain the viability of the small biotechnology companies and public institutions involved in this research. These groups have been deprived of investor funding to a large degree as the regulatory process was emerging. Now there is an expectation that approvals can be realized, which will enhance the flow of investment into the industry. Second, international harmonization of the regulation of genetically engineered animals must be a goal. Global research and development may be more active and better funded than in the U.S. In order to avoid trade disruption and consumer backlash against the technology, it is essential that countries adopt the science-based guidelines set forth by Codex and develop regulations for animal biotechnology. Third, proactive adoption of stewardship guidelines by all product developers in both industry and academia will be essential to gaining public acceptance. Finally, the most important priority of those working with genetically engineered animals is that the public accepts the technology and is confident in purchasing and using the products.

The challenges ahead are not simple but if we follow the lead of the science, rigorous regulatory approval will portend compelling consumer benefits.

The human health benefits will now be realized based on the science-based regulatory framework for governing how these animals will provide biomedical, food and agricultural benefits. We have embraced the human health aspects of genetically engineered animals as well as the food and agricultural aspects. The challenges ahead are not simple but if we follow the lead of the science, rigorous regulatory approval will portend compelling consumer benefits. The industry, academia and the U.S. FDA have worked together closely, and mapped the road forward with a rigorous science-based framework.

Scott Gottlieb, *a physician and Resident Fellow at the American Enterprise Institute was Deputy Commissioner for Medical and Scientific Affairs of the Food and Drug Administration from 2005 to 2007.*

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Notes

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