

# GENETICALLY ENGINEERED ANIMALS: AN OVERVIEW

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## What is a genetically engineered animal?

A genetically engineered or “transgenic” animal is an animal that carries a known sequence of recombinant DNA in its cells, and which passes that DNA onto its offspring. Recombinant DNA refers to DNA fragments that have been joined together in a laboratory. The resultant recombinant DNA “construct” is usually designed to express the protein(s) that are encoded by the gene(s) included in the construct, when present in the genome of a transgenic animal. Because the genetic code for all organisms is made up of the same four nucleotide building blocks, this means that a gene makes the same protein whether it is made in an animal, a plant or a microbe. Some examples of proteins that have been expressed in transgenic animals include therapeutic proteins for the treatment of human diseases<sup>1-4</sup>, proteins that enable animals to better resist disease<sup>5-7</sup>, and proteins that result in the production of more healthful animal products (milk, eggs or meat) for consumers<sup>8,9</sup>.

## Are there any genetically engineered animals on the market?

As of August 2008, no genetically engineered food animals had been approved for sale in the United States. [UPDATE NOTE: The **AquAdvantage® Salmon** was approved for sale in the U.S in 2015. See the story about **AquAdvantage® Salmon** here.] Growth-enhanced fish are the transgenic animal application closest to commercialization for food purposes, and several different species are currently going through regulatory review in three different countries. Since 1999, Aqua Bounty (Aqua Bounty Technologies, Inc., Waltham, MA) has been seeking U.S. regulatory approval for the commercialization of its growth-enhanced *AquAdvantage™* Atlantic salmon. This transgenic salmon is capable of growing



**Figure 1.** Genetically engineered zebrafish. Picture taken from [www.glofish.com](http://www.glofish.com)

faster, but not larger, than standard salmon grown under the same conditions<sup>10,11</sup>. Transgenic lines of growth-enhanced tilapia and carp are also under regulatory review in Cuba and China, respectively<sup>12</sup>. The only genetically engineered animal to reach the market in the United States is an ornamental fluorescent zebrafish (*Danio rerio*) called GloFish (Yorktown Technologies, Austin, TX). The U.S. Food and Drug Administration (FDA) determined not to formally regulate GloFish on the basis that tropical zebrafish pose no threat to the food supply, and the fact that there is no evidence that these genetically engineered zebrafish pose any greater threat to the environment than their widely sold unmodified counterparts<sup>13</sup>

[UPDATE NOTE: The glofish which is now sold in all 50 US states and is in 10% of home freshwater aquariums.]

One product of genetic engineering that is currently being used in animal agriculture is recombinant bovine somatotropin (rBST) derived from genetically engineered bacteria. This protein, which results in an increase in milk production when administered to lactating cows, is widely used throughout the U.S. dairy industry. rBST was approved by the FDA in 1993 because extensive testing had revealed no concerns regarding the safety of milk derived from cows treated with rBST<sup>14</sup>. It should be noted that administering this protein does not modify the DNA of the cow, and they do not become genetically engineered. People with diabetes similarly administer themselves with insulin derived from genetically engineered bacteria, and the genetic makeup of these patients is likewise unaltered by the administration of a recombinant protein.

## Why are animals being genetically engineered?

Genetic engineering is a useful technology because it enables animals to produce useful novel proteins. Conventional animal breeding is constrained to selection based on naturally-occurring variations in the proteins that are present in a species, and this limits the range and extent of genetic improvement that can be achieved. Genetically-engineered animals are being produced for two distinct applications: human medicine and agriculture.

Most commercial transgenic animal research is in the field of human medicine. Many therapeutic proteins for the treatment of human disease require animal-cell specific modifications to be effective, and at the present time they are almost all produced in mammalian cell-based bioreactors. A new cell culture-based manufacturing facility for one therapeutic protein can cost upwards of \$US500 million. The manufacturing capacity for therapeutic proteins cannot keep pace with the rapid progress in drug discovery and development, and this has resulted in unmet needs and dramatically rising costs. Genetically engineered animals may provide an important source of these protein drugs in the future because the production of recombinant proteins in the milk, blood or eggs of transgenic animals presents a less-expensive approach to producing therapeutic proteins in animal cells. In 2006, the first human therapeutic protein, Antithrombin III (ATryn®, GTC Biotherapeutics, Framingham, MA), derived from the milk of genetically engineered goats was approved by the European Commission for the treatment of patients with hereditary antithrombin deficiency<sup>15,16</sup>.



Transgenic animals are also being used to produce serum biopharmaceutical products such as antibodies that can be used for the treatment of infections, cancer, organ transplant rejections, and autoimmune diseases such as rheumatoid arthritis<sup>17-19</sup>. The current production system for such blood products is donated human blood, and this is limiting because of disease concerns (e.g. HIV/AIDS), lack of qualified donors, and regulatory issues. Genetically engineered animals, such as cattle carrying human antibody genes which are able to produce human polyclonal antibodies<sup>17</sup>, have the potential to provide a steady supply of polyclonal antibodies for the treatment of a variety of infectious and other diseases. **[UPDATE NOTE: As of 2016, in the U.S., there are now three approved pharmaceutical products on the market.]**

**Figure 2.** Genetically engineered cows producing human immunoglobulins (Hematech, Sioux Falls, S.D.) may provide an important source of polyclonal antibodies for the treatment of a variety of medical conditions including organ transplant rejection, cancer, and autoimmune diseases, such as rheumatoid arthritis. (Photo by Alison Van Eenennaam / University of California, Davis)

Transgenic mice have also become increasingly important for biological and biomedical research and have generated a vast amount of vital information about human diseases. Other transgenic animals, including livestock species, are being produced specifically as biomedical research models for various human afflictions including Alzheimer's disease, eye disease, and the possible xenotransplantation of cells, tissues and organs from genetically engineered animals into human organ-transplantation patients<sup>20,21</sup>. Transgenic animals are also being used to study animal diseases such as "mad cow" disease (BSE, Bovine Spongiform Encephalopathy)<sup>6,22</sup>, and infection of the udder (mastitis)<sup>5,7</sup>.

Although researchers have developed transgenic livestock for agricultural applications, including some with enhanced production traits<sup>23,24</sup>, environmental benefits<sup>25</sup>, and disease resistance attributes<sup>5-7</sup>, no company with the exception of Aqua Bounty has announced its intent to pursue the commercialization of these agricultural applications. There is a much higher economic incentive associated with the production of genetically engineered animals for human medicine applications, than for agricultural applications. Commercialization of agricultural applications is being slowed by concerns about the cost and timelines associated with the regulatory process, and consumer acceptance issues. Potential investors are wary because public acceptance of agricultural applications of genetic engineering has generally been lower than that associated with medical applications of this technology (e.g. recombinant insulin), and public acceptance may be even more of an issue when considering animal agricultural applications of this technology.

### **How is the genetic engineering of animals regulated?**

The U.S. Food and Drug Administration (FDA) is the lead agency responsible for the regulation of genetically engineered food animals, and it plans to regulate transgenic animals under the “new animal drug” provisions of the Food, Drug, and Cosmetic Act (FDCA). The fundamental focus of the new animal drug rubric is 1) Is the new animal drug safe for the animal?, 2) Is the new animal drug effective, and 3) If the drug is for a food-producing animal, is the resulting food safe to eat? Although premarket regulatory review of genetically engineered animals is mandatory, the FDA has not yet issued a formal guidance detailing what information will be required for this regulatory review, and at the current time the regulatory path to commercialization of genetically engineered animals remains ill-defined<sup>26</sup>.

However, transgenic animal research is subject to existing regulations governing animal research. All entities receiving or applying for federal funding to carry out research using animals are required by The Animal Welfare Act, a federal law which was passed in 1966, to have a program overseen by a committee identified as the Institutional Animal Care and Use Committee (IACUC) to review research protocols involving dogs, cats, rabbits, guinea pigs, hamsters, gerbils, nonhuman primates, marine mammals, captive wildlife, and domestic livestock species used in nonagricultural research and teaching. The Animal Welfare Act also requires that research institutions: 1) have a veterinary care program be in place, 2) all personnel using or caring for live animals are qualified to do so, and 3) a mechanism be in place for reporting of concerns regarding animal care and use at the institution. The Animal Welfare Act is administered through the United States Department of Agriculture (USDA) and is enforced through unannounced inspections by a USDA Veterinary Medical Officer. On an international level, the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC), oversees the voluntary accreditation and assessment of research institutions committed to responsible animal care and use.

### **Does genetic engineering hurt animals?**

A variety of techniques have been used to produce transgenic livestock with varying degrees of success<sup>17,27-29</sup>. Microinjection of foreign DNA into newly fertilized eggs has been the predominant method used for the generation of transgenic livestock over the past 20 years. This technology is inefficient (3-5% of animals born carry the transgene) and this results in an animal welfare concern because it requires the use of many more animals than would be needed if success rates were higher. Additionally, this technique results in random integration and variable expression levels of the target gene in the transgenic offspring. This poorly controlled expression of the introduced gene can result in animal welfare concerns. For example, various growth abnormalities have been observed in genetically engineered animals expressing growth hormone transgenes at varying levels<sup>30,31</sup>. Newer methods of making transgenic animals have been developed that employ somatic cell nuclear transfer cloning<sup>24,32,33</sup>, the cloning process first made famous by Dolly the sheep<sup>34</sup>.

Cloning offers the opportunity to produce 100% transgenic offspring from cell lines that are known to contain the transgene, and further also allows gene targeting whereby researchers are able to integrate the foreign DNA at a specific location in the genome, and thereby have more control over the expression level of the transgene.

Animal welfare concerns may also be associated with the breeding objectives underlying the reasons behind making a given genetically engineered animal in the first place<sup>35</sup>. For example, if genetic engineering makes farm animals more productive, this may have the effect of boosting productivity to a level that results in a welfare concern. This concern depends upon the effect of the specific transgene that is being investigated, and is not a concern that is unique to genetic engineering. Any genetic improvement program directed exclusively towards high production efficiency has the potential to cause animal welfare concerns, irrespective of the techniques used to obtain that goal. Conversely, it might also be that genetic engineering could be used to improve traits such as disease resistance, which could have the effect of decreasing animal suffering or mortality. As a result of varying personal belief systems, some people oppose the human use of animals for any purpose, and these people are unlikely to accept transgenic livestock production systems, irrespective of any potential benefits they may provide to the animals.

### What about the ethical aspects of genetically engineering animals?

Public opinion surveys have reported that some people are ethically uncomfortable with the idea of



genetically engineering animals. There are two central ethical concerns associated with the genetic engineering of animals. The first has to do with breaching species barriers or playing God. Proponents of this view suggest that life should not be regarded solely as if it were a chemical product subject to genetic alteration and patentable for economic benefit. The second major ethical concern is that the genetic engineering of animals interferes with the integrity or telos of the animal. Telos is defined as “the set of needs and interests which are genetically based, and environmentally expressed, and which collectively constitute or define the form of life or way of living exhibited by that animal, and whose fulfillment or thwarting matter to that animal”<sup>36</sup>. It has been argued that such concerns are not unique to genetic engineering, and that traditional breeding and selection practices can change animals in similar ways<sup>37</sup>. For example, cows from the Belgian Blue cattle breed (Figure 3) require the systematic use of Caesarean sections to deliver their calves, as a result of selection for increased birth weight resulting from the naturally-occurring “double-muscle” trait, and reduced width of the cow’s pelvic passageway<sup>38</sup>.

**Figure 3.** Belgian Blue Bull.

There is no obvious setting for addressing ethical concerns relating to genetically engineered animals in the United States<sup>37</sup>. A 2005 survey found that the majority (63%) of Americans believe governmental agencies should consider moral and ethical factors, in addition to scientific evaluation of risks and benefits, when making regulatory decisions about cloning or genetically modifying animals. However, the FDA’s risk-based regulatory approach focuses on science-based questions related to health and safety<sup>26</sup>. As such social, ethical, religious and trade issues are outside the scope of the FDA’s mandate, and regulatory decisions cannot be based on ethical grounds if no health or safety considerations exist. At the current time it is unclear how, or in what venue, these ethical concerns should be addressed. Even in the absence of incorporating ethical concerns into regulations governing genetically engineered animals, or some may argue because of this absence, no products of genetically engineered food animals are currently on the U.S. market. It is yet to be seen whether the development and associated regulatory costs, and the market acceptance issues associated with this technology ultimately result in a commercially-viable industry for products derived from genetically engineered animals.

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