Genetically Engineered Animals and their Intended Uses in Day to Day Life

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ABSTRACT
Background: Genetic engineering is an integral approach to the development of new diagnostic techniques, drugs for human and animal diseases, foods for human health, development of tissues and cells for xenotransplantation. The components of vaccine for disease control and nutraceuticals for human health by altering the food components or by introducing the health provide proteins, peptides and other components may be the integral part of human life in coming days. Genetically engineered animals also offer significant human health and environmental benefits, livestock becomes more efficient for converting feed to animal protein and reducing waste production. Finally, genetic engineering will improve the welfare of animals by imparting resistance to disease and enhancing overall health and well being. Objective: This study reviews the basics of genetic engineering and their scope in various fields of life. Conclusion: The need is to commercialize the technology by the authentication on science based formulations. The judicial approaches and validation of the technologies by removing the myths related to the technology are some other issues must be handled properly.

Key words: Genetic engineering, animals, foods, human health

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INTRODUCTION
Genetic engineering term generally refers to the use of tools of modern biotechnology and molecular biology to introduce new characteristics or traits into organisms. Scientists can use these tools to introduce new genetic material or delete or alter existing genetic material to introduce intended, new traits or characteristics. Genetic engineering enables people to introduce a much wider range of new traits into an organism than is possible by conventional breeding. It has been widely used in agriculture. The major uses of genetic engineering includes development of crops resistant to certain pests or herbicides, to develop microbes that can produce pharmaceuticals for human or animal use and in food to produce microorganisms that aid in baking, brewing and cheese-making.

Many kinds of genetic engineering animals are in development. The major use of genetic engineering is to develop the biopharm like production of milk or blood with active ingredients for the use of human or animal pharmaceuticals. Another group of GE animals are under development for xenotransplant as a source of scarce cells, tissues, or organs for transplantation into humans. Other uses of GE includes development of food for resistance of diseases and for nutritional or growth performance. Highly specific antimicrobials against human and animal pathogens i.e., E. coli 0157 or Salmonella can also be achieved by the use of genetic engineering.
GENETICALLY ENGINEERED (GE) ANIMALS VS. CONVENTIONAL ANIMALS

Phenotypically GE animals as well as conventional animals may be similar. However, scientifically GE animals necessarily contain an rDNA which is capable to develop the new trait or characteristic for example producing a pharmaceutical or growing faster. The degree of difference is solely dependent on the characteristics that GE animals actually possess. Most of the GE animals are heritable and are capable to pass their new “GE” traits on to their offspring. The initial GE animal and all of its descendants that have inherited the GE trait are called GE animals.

In general, most GE animals contain an rDNA that was introduced into early embryos or cells stage of its development. The offspring who is having constructed rDNA is heritable because they will be in every cell of the resulting animal, including those that are responsible for making sperm and egg for the next generation. However, some of the GE animals contain rDNA which is not intended to be inherited. The case is mainly reported in animals being treated with gene therapy because these rDNA constructs are not found in the germ cells. Non-heritable GE animals are very similar to conventional new animal drugs, because they may persist in the body for some time but are not passed on to the next generation.

ANIMAL CLONES VERSES GE ANIMALS

The term “animal clone,” does not include the sexually-derived offspring of animals. Actually animal cloning is a method of asexual reproduction and results in the birth of one animal that is a genetic copy of another animal. However, when animal clone becomes a parent, its children are not clones, because they will have been born through sexual reproduction. So, in explanatory way it can said that animal clone are those who can posses following qualities, (1) They are animals born as a result of asexual reproduction and (2) They have no new genes in them, that is, they are the same as the animal of which they are a copy.

So, that it may be said that genetic engineering is a method of introducing new genes into an animal’s while animal cloning is a copying of same animals with same qualities. The GE animals contain rDNA construct that gives the animal new traits and can be stably inherited in future generations while, cloning is a method of reproduction.

POTENTIAL BENEFITS OF GENETICALLY ENGINEERING ANIMALS

Potential benefits of GE animals are mainly dependant entirely on the traits that are introduced in the GE animals. Major examples of GE animals include GE cattle resistant to bovine spongiform encephalopathy, GE animals with good feed efficiency, GE animals with lower level of pollutants in their wastes, GE animals with improved fat composition and increased levels of omega-3-fatty acids for healthful nutrient profile. Now, GE animals are also use to produce certain human pharmaceuticals that are very difficult to produce in sufficient quantities by other means. These pharmaceutical GE animals are capable to reduce the diseases and ailments in humans and animals. As example, GE animals with clotting factors help in control and treatment of bleeding disorders. The detailed description of the potential benefits of GE animals may be summarized as:

- **Blood products:** The first protein drug from a genetically engineered animal was approved for medical use in the United States in year 2009 was blood products. In addition, a number of different proteins derived from the blood of transgenetic animals are in various stages of development. The vital blood products can be utilized in various forms such as clotting factors, antithrombin1-4 and human albumin5,6. Actually ‘ATryn’ was the first product approved in U.S. from a genetically engineered animal and had been granted orphan drug status by the FDA for the treatment of hereditary antithrombin deficiency. It is because it prevents excessive bleeding in patients undergoing high-risk surgical procedures or childbirth. Another drug or blood protein which is under trial in Europe for FDA approval is ‘Rhucin’, a recombinant human C1 esterase inhibitor produced in the milk of transgenic rabbits. It can treat the acute attacks of hereditary angioedema (HAE), a rare disease characterized by painful swelling of soft tissue7.

- **Protein-Based Drugs:** A number of genetically engineered animals are capable of producing complex protein-based drugs. These drugs are even available in lower cost and are more reliable and safer production means than traditional manufacturing processes8, Protein-based drugs are
mostly produced \textit{in vivo} unlikely to the protein products synthesized in the blood. The important examples of \textit{in vivo} proteins are monoclonal antibodies\textsuperscript{9}, polyclonal antibodies\textsuperscript{10, 11}, plasminogen activator\textsuperscript{12-15}, human alpha-fetoprotein\textsuperscript{16}, alpha-1-proteinase inhibitor, alpha glucosidase\textsuperscript{5, 9, 17, 18, 19} etc.

- **Vaccine components**: Novel vaccine components are the products of genetically engineered animals helps in rapid manufacturing of vaccines. These vaccines can be produced comparatively in lower cost and even are effective in viral outbreaks such as pandemic flu\textsuperscript{20-22}. The major example is malaria vaccines using genetically engineered animals

- **Xenotransplantation**: Now a day, the major use of genetically engineered animals is in production of human replacement tissues, cells or organs for human transplant. The technique of transplantation of human organs with animal-derived tissues is referred to as xenotransplantation. Pigs are the main animals used for the purpose because they are easy to breed, have anatomical and physiological characteristics compatible with humans and are well studied for several pathogens potentially transmissible to humans\textsuperscript{23}. It is also due to disease free status of piglets 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. Piglets act as potent sources for replacement of tissues including heart valves, skin and orthopedic tissues. With the advent of nuclear transfer technology\textsuperscript{24} and the successful production of alpha 1,3 galactosyltransferase knockout (GT-KO) pigs\textsuperscript{25}, now it is possible to overcome the critical barrier of organ rejection caused by pre-formed anti-pig (anti-Gal) antibodies

- **Nutrition and public health**: Now, it is 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. 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

- **Reproductive performance and fecundity improvement**: There are several genes has been identified to improve the reproduction performance of human and animals such as estrogen receptor (ESR) and the Boroola fecundity (FECB) genes. The ESR gene is associated with 1.4 more pigs born per litter\textsuperscript{26}. Introduction of a mutated or polymorphic ESR gene could increase litter size in a number of diverse breeds of pigs\textsuperscript{27}. A single major gene for fecundity, the FECB gene, which allows for increased ovulation rate, has been identified in Merino sheep. Some 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

- **Improvement in hair and fiber quality**: Today transgenic methods are being used to assess the quality, color, length, fineness and crimp of the wool and hair fiber from sheep and goats. Transgenic methods will also allow improvements to fiber elasticity and strength. A novel approach to produce useful fiber has been recently accomplished using the milk of transgenic goats\textsuperscript{28}.

**REGULATORY PROCESSES RELATED TO GE ANIMALS**

The guidance documents of FDA on Genetically Engineered (GE) animals and their products is intended to help industry understand the existing statutory and regulatory requirements apply to GE animals and their products and to inform the public about the process FDA is using to regulate them. Actually, FDA regulates GE animals under the new animal drug provisions of the
Federal Food, Drug and Cosmetic Act (FFDCA) and FDA’s regulations for new animal drugs. New animal drug approval process can be categorized into seven broad categories:

- Under the product definition category, a broad statement characterizing the GE animal and claims are being settled under this category
- The developed rDNA construct and its resemblance is assessed under molecular characterization of the construct category
- The procedure by which a particular rDNA construct was introduced into the animal and its stability maintenance over time is evaluated under molecular characterization of the GE animal lineage
- A comprehensive data on the characteristics of the GE animal and its health is generally assessed under phenotypic characterization of the GE animal category
- Modifications stability and its continual effect for over time are generally evaluated under the durability plan category
- The assessment of environmental impacts of GE animals and if modification is done for food then the safety of food to the human beings is assessed under environmental and food/feed safety category
- If all the categories validate the GE animals then claim validation is done

A product that meets the definition of a new animal drug is generally required by statute and regulation to have an FDA-approved New Animal Drug Application prior to marketing. In order for FDA to approve such an application, the FFDCA requires that the sponsor demonstrate that its product is safe and effective. In case of clones, the agency first needed to determine whether food from clones posed any additional risks compared with food from more conventionally bred animals. Following the completion of a comprehensive risk assessment, the agency was able to determine that cloning fell on the continuum of assisted reproductive technologies and that cloning poses no new risks to the health of animals involved in the cloning process or to food from cattle, swine, or goat clones or the progeny of clones of any species traditionally consumed as food. Additionally, clones are not different from non-clones with respect to their DNA; only the method by which they are produced is different. Therefore, FDA determined that no additional regulatory oversight was necessary.

Most of the food safety issues for both GE plants and animals are the same. However, all animals, including GE animals, can cause zoonotic diseases. It is possible to genetically engineer animals using viruses or segments of DNA that can recombine and possibly transfer to humans or other animals and cause disease. So there are some specific issues that must be evaluated in GE animals that are not relevant in GE plants.

**GENETICALLY ENGINEERED (GE) ANIMALS AS A HUMAN FOOD**

FDA has not approved any GE animals for food and there are strong statutory and regulatory prohibitions against unreported movement of GE animals as well as against their disposal in the food supply unless explicitly approved by the FDA. However, GE animals are being developed actively in many countries for both food and biopharmaceutical uses. In New Zealand, dairy researchers are looking to rDNA technology to affect the relative level of certain proteins in cows’ milk to make it more suitable for cheese-making. China has a major agricultural program that employs rDNA technology to make more animal-based food available and scientists from African countries are collaborating with aquaculturists in the US to develop GE tilapia that will grow quickly. Growth enhanced fish are also being developed in Cuba. Scientists at the Roslin Institute in Scotland are developing GE chickens to produce pharmaceuticals in their eggs as are other scientists in Korea. With respect to commercialization, many GE laboratory animals are in use in research laboratories around the world, including those GE laboratory animals that are sold to laboratories to perform various kinds of testing. US is an active participant in a number of international organizations that address GE animals or their products, including Codex Alimentarius and OIE (the World Organization for Animal Health).

**Milk quality and quantity enhancement:** With the advent of recombinant DNA technology, scientists are able to improve the composition of milk and are capable to produce entirely novel proteins in milk. These changes may add value to, as well as increase, the potential uses of milk. 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-) and lactoferrin. Now, it is also 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 a-lactalbumin, lysozyme, lysostaphin or other antimicrobial peptides.

**Improvement in growth rates and carcass composition:** 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. The typical examples are transgenic livestock and fish with exogenous GH gene, porcine-produced GH for enhanced growth and feed efficiency in pigs. The increased growth rate and ultimately increased rate of protein production can be achieved via genetic engineering.

**SAFETY ISSUES OF GE ANIMALS**

At present there is not a clear cut criterion whether all constructs and the resulting GE animals will be “safe” or “not safe”. Actually, the safety issues are set of conditions in which animals are rearing and used for traits development. For example, fast growing salmon to be grown in contained environments pose a different set of risks from cattle engineered to be resistant to a disease such as mastitis. So, the safety considerations by FDA are solemnly dependant on the potential environmental effects on a case-by-case basis. The guidance for meat and other foods are almost remaining same as proposed by FDA and Codex Alimentarious commission. However, animals or edible products from them containing unapproved new animal drugs may not be put into the food or feed supply without prior FDA authorization during the investigational phase of development. As part of the approval process, FDA will make clear whether edible products from particular GE animals are suitable to enter the food or feed streams. The FDA will enforce these decisions with regard to GE animals the same way it enforces them with animals treated with conventional new animal drugs. At this time, based on the kinds of animals currently under development and apart from restrictions pertaining to use in food or feed, FDA does not anticipate that it would have any reason to impose special disposal limitations on GE animals, carcasses or parts.

**GENETICALLY ENGINEERED (GE) ANIMALS AND ANIMAL WELFARE WITH SPECIAL CONCERN OF ETHICAL ISSUES**

A variety of techniques have been used produce transgenic livestock with varying degrees of success. Among all, 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. The following concerns are important as for as animal welfare is concerned:

- The technology is a lab level and for commercialization of the techniques large number of animals may be exposed for the adaptability and trials.
- 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.
- Animal welfare concerns may also be associated with the breeding objectives underlying the reasons behind making a given genetically engineered animal. 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.
- 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 patent able 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”.

CONCLUSION

Genetic engineering if executed judiciously may provide practical benefits to mankind, as we have seen from other fundamental advances in life science. These benefits may be in terms of improvement in human health through production of novel replacement proteins, drugs, vaccines, research models and tissues for the treatment and prevention of human disease, genetically engineered animals for improvement of environment and human health, improved in food production traits enabling them to help meet the global demand for more efficient, higher quality and lower-cost sources of food. It may also be beneficial to the animal health, well-being and animal welfare and some beneficial high-value industrial products can also be produced such as spider silk used for medical and defense purposes. However, practical benefits of this technology have not yet reached to the consumers due to broader gap between myths and reality of genetic engineering technology. So, there is an urgent need to formulate the regulatory framework with predictable, rigorous, science-based monitoring and authentication of the technology to deliver practical benefits through the science of genetic engineering.

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