What is the future of animal biotechnology?

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Abstract

Animal biotechnology encompasses a broad range of techniques for the genetic improvement of domesticated animal species, although the term is increasingly associated with the more controversial technologies of cloning and genetic engineering. Despite the many potential applications of these two biotechnologies, no public or private entity has yet delivered a genetically engineered food-animal product to the global market, and the sale of milk or meat from cloned animals and their offspring is currently subject to a voluntary moratorium in the United States. The animal biotechnology industry faces a variety of scientific, regulatory, ethical and public acceptance issues. Effective and responsible communication among scientific, community, industry and government stakeholders will be required to reach a societal consensus on the acceptable uses of animal cloning and genetic engineering.

Keywords: transgenic animal, genetically engineered animal, genetically modified animal, clone, animal biotechnology

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Animal biotechnology encompasses a broad range of techniques for the genetic improvement of domesticated animal species, although the term is increasingly associated with the more controversial technologies of cloning and genetic engineering. Despite the many potential applications of these two biotechnologies, no public or private entity has yet delivered a genetically engineered food-animal product to the global market, and the sale of milk or meat from cloned animals and their offspring is currently subject to a voluntary moratorium in the United States. The animal biotechnology industry faces a variety of scientific, regulatory, ethical and public acceptance issues. Effective and responsible communication among scientific, community, industry and government stakeholders will be required to reach a societal consensus on the acceptable uses of animal cloning and genetic engineering.

An article published in California Agriculture entitled “Genetic engineering and cloning may improve milk, livestock production” (Murray and Anderson 2000) detailed potential uses of these biotechnologies and optimistically concluded that “by midcentury most agricultural animals will be genetically engineered to be more efficient and healthier than current stock, producing healthy products for human consumption in an environmentally friendly system.” While these technologies undoubtedly have the potential to deliver such benefits, no genetically engineered food animals are currently on the market, and the U.S. Food and Drug Administration (FDA) continues to call for a voluntary prohibition on the marketing of milk or meat from clones and their offspring. This review examines the scientific, regulatory, ethical and public acceptance issues faced by the animal biotechnology industry, and discusses the implications of the current climate on the future of animal biotechnology.

Biotechnology is defined as technology based on biology. From this definition it is obvious that livestock breeders have been practicing animal biotechnology for many years. For example, traditional selection techniques involve using observations about the physical attributes and biological characteristics of an animal to select the parents of the next generation. One needs only to look at the amazing variety of dog breeds to realize the influence that breeders can have on the appearance and characteristics of animals from a single species. Genetic improvement through selection, based on an increased understanding of population genetics and statistics, has
been an important contributor to dramatic advances in agricultural productivity (Dekkers and Hospital 2002).

Many different biotechnologies have been incorporated into livestock breeding programs to accelerate the rate of genetic improvement. These include artificial insemination (AI), sire-testing programs using data collected from thousands of offspring, synchronization of estrus, embryo transfer, cryopreservation of gametes and embryos, and DNA-based marker-assisted selection of genetically superior animals. Prior to their eventual widespread adoption, some of these new technologies were controversial, and their introduction met with some resistance (NRC 2002). Initially, artificial insemination was seen to be “against the laws of God, a repugnant practice that would lead to abnormal outcomes” (NRC 2002). Today this technology is widely used in agriculture, in addition to both veterinary and human medicine. Genetic improvements using traditional breeding techniques have not come without a price, and there are some health and welfare concerns associated with highly productive animals, such as gait abnormalities in broiler chickens and fertility problems in high-yielding dairy cattle. A comparable legacy has arisen from the selective breeding of domesticated dogs, which are now afflicted with more than 200 diseases of genetic origin.

Animal cloning

When most people hear the term animal biotechnology, they think of Dolly the sheep, the first mammal ever cloned or duplicated from an adult cell. The hype that surrounded Dolly in 1997 rapidly became entangled with the debate over human cloning, and the ensuing discussion failed to elaborate on the reasons for, or even differentiate between, cloning versus the genetic engineering of animals.

Cloning had actually been practiced for a long time before the appearance of Dolly. Splitting or bisecting embryos to make identical twins, a process in which the cells of a developing embryo are split in half and transferred into different recipient mothers, was introduced into livestock breeding programs in the 1980s. Identical twins are technically identical to black fur. To orange fur while others give rise inactivated, some skin cells give rise to black fur.

Reprogramming involves changes at the epigenetic level. Epigenetic changes refer to alterations in gene expression resulting from modifications of the genome that do not include changes in the base sequence of DNA. Two key areas of epigenetic control are chromatin remodeling and DNA methylation. Epigenetic changes may also include imprinting, the switching off of maternal or paternal copies of certain genes.

With clones the reprogramming of somatic cell modifications is sometimes incomplete, leading to inappropriate patterns of DNA methylation, chromatin modification and X-chromosome inactivation in the developing clone. This can result in aberrant gene-expression patterns and correspondingly high rates of pregnancy loss, congenital abnormalities and postnatal mortality.

— A.L. Van Eenennaam

GLOSSARY

Chromosome: A self-replicating DNA sequence found in the cell nucleus that bears a linear array of genes.

Cytoplasm: The cellular substance outside the nucleus in which the cell’s organelles, such as mitochondria, are suspended.

Genetic engineering: The transfer of recombinant DNA sequences into the genome of a living organism.

Genome: The total DNA in a single cell, representing all of the genetic information of the organism. The normal human genome consists of 46 chromosomes, 23 from each parent.

Mitochondria: Components in cells that serve as primary energy sources for all cellular functions. Mitochondria have their own genome, present in only one copy, which does not recombine in reproduction.

Nucleus: A separate compartment in the cell that contains 6 feet of DNA packed into 23 pairs of chromosomes.

Recombinant DNA: The laboratory manipulation of DNA in which DNA, or fragments of DNA from different sources, are cut and recombined using enzymes.

A CLOSER LOOK

How animals are cloned and why problems sometimes occur

Cloning by nuclear transfer is a two-part process. First, scientists remove the nucleus from an egg, and then they fuse it with a somatic cell containing the nucleus and genetic material from another cell by the application of an electrical charge. The fused egg is then placed in a laboratory dish with the appropriate nutrients. Eventually the resulting embryo, which is a genetic copy of the animal that produced the somatic cell and not the egg, is transplanted into a surrogate mother.

The successful production of normal clones from differentiated somatic cells suggests that adult nuclear DNA retains the ability to direct the correct pattern of gene expression for embryogenesis. The process of resetting adult nuclear DNA to the embryonic pattern of gene expression is known as reprogramming and likely involves switching off certain genes and turning on others. Errors in reprogramming may lead to abnormalities in gene expression in cloned animals and affect the health and longevity of the animal.

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clones, but the term is now more commonly used to refer to an individual that results from the transplantation of the DNA contained in a single somatic (non-egg) cell derived from an adult organism, into an enucleated oocyte (an egg that has had its own DNA removed). This process is called somatic cell nuclear transfer (SCNT) cloning, and it has been successfully performed in many livestock species (e.g., sheep, cattle, pigs and goats). From an animal breeding perspective, the importance of the SCNT procedure is that it allows the replication of adult animals with demonstrated superior performance attributes. Commercial companies providing fee-for-service cattle cloning have recently emerged, offering producers guaranteed-live cloned offspring for $10,000 to $20,000 per calf.

Agricultural uses. There are probably only a few prospective uses for cloned animals in commercial agricultural operations. They may provide a genetic insurance policy in the case of extremely valuable animals, or produce several identical sires in production environments where artificial insemination is not a feasible option. Theoretically, clones could also be used to reproduce a genotype that is particularly well suited to a given environment. The advantage of this approach is that a genotype that is proven to do especially well in a particular location could be maintained indefinitely, without the genetic shuffle that normally occurs every generation with conventional reproduction.

However, the disadvantage of this approach is that it freezes genetic progress toward desirable attributes, such as milk production or disease resistance, at one point in time. Since there is no genetic variability in a population of clones, within-herd selection no longer offers an opportunity for genetic improvement. Additionally, the lack of genetic variability could render the herd or flock vulnerable to a catastrophic disease outbreak or singularly ill-suited to changes that may occur in the environment.

Although clones carry exactly the same genetic information in their chromosomal DNA, they may still differ from each other, in much the same way that identical twins do not look or behave in exactly the same way. Clones do not share the same cytoplasmic inheritance of mitochondria from the donor egg, nor often the same gestational environment, since they are frequently borne and raised by different animals. In fact, a recent study showed that SCNT clones differ more from each other than do contemporary half-siblings (Lee et al. 2004).

Efficiency and problems. The cloning procedure is currently inefficient, with only 1% to 3% of the nucleated egg cells developing into live offspring. High rates of pregnancy loss have been observed at various times after placement of the eggs containing the adult cell nuclei into recipient animals. However, these problems are not seen universally in SCNT-cloned cattle, and there are reports of apparently healthy cloned cattle that have gone on to conceive and have healthy calves (Lanza et al. 2001; Pace et al. 2002).

Abnormalities have also been observed in cloned animals subsequent to birth, with frequencies that are at least partially dependent upon the type of tissue from which the transferred nucleus was derived. These abnormalities include defects in cardiovascular, musculoskeletal and neurological systems, as well as susceptibility to infections and digestive disorders. Many of these problems appear to result from incorrect reprogramming of the transferred nuclear DNA as it transitions from directing the cellular activities of a somatic cell to directing the complex developmental pathway required to develop into an entirely new embryo. Researchers have documented abnormal gene expression patterns in cloned offspring and errors in both imprinting and X-chromosome inactivation (Thibault 2003).

Food safety. The main underlying food-safety concern with SCNT clones is whether the nuclear reprogramming
that occurs during the cloning process has any influence on the composition of animal food products. There is no fundamental reason to suspect that animals derived via SCNT would produce novel toxins or allergens. Studies comparing the performance of SCNT clones and other types of dairy cattle clones to their full siblings found that there were no obvious differences in performance or milk composition (Takahashi and Ito 2004; Norman and Walsh 2004; Walsh et al. 2003; Tome et al. 2004; Tian et al. 2005).

The FDA Center for Veterinary Medicine has been developing a risk assessment to identify hazards and characterize food consumption risks that may result from cloning (Rudenko et al. 2004). Their report on livestock cloning states, “the current weight of evidence suggests that there are no biological reasons, either based on underlying scientific assumptions or empirical studies, to indicate that consumption of edible products from clones of cattle, pigs, sheep or goats poses a greater risk than consumption of those products from their nonclone counterparts” (FDA 2003). Despite these findings, the marketing of milk or meat from SCNT clones and their offspring remains subject to a voluntary prohibition. The FDA report states, “additional data on the health status of progeny, and composition of milk and meat from clones and their progeny, would serve to further increase the confidence in these conclusions.” Several research groups are actively collecting these types of data.

**Genetic engineering**

Although cloning is not genetic engineering per se, there is a logical connection between these two technologies. Genetic engineering involves the modification of characteristics of organisms using recombinant DNA techniques, with the specific intent of altering protein expression. A transgenic organism carries DNA originally derived from an organism other than its parents in its genomic DNA. Common examples of transgenic agricultural organisms are insect-resistant corn and cotton that has DNA from the soil microorganism *Bacillus thuringiensis* (Bt) incorporated into its genome (see page 116). To be passed on to the next generation, this novel transgenic DNA must be present in the organism’s germ-line cells (egg or sperm). 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% to 5% of animals born carry the transgene) and results in random integration and variable expression levels of the target gene in the transgenic offspring.

Cloning enhances the efficiency of genetic engineering by offering the opportunity to produce 100% transgenic offspring from cell lines that are known to contain the transgene. This prospect stimulated the research that led to the development of SCNT cloning of animals, despite widespread media coverage about the highly controversial issue of human reproductive cloning. Cloning also offers the unique opportunity to produce animals from cells that have undergone precise, characterized modifications of the genome. This includes the disruption of specific endogenous genes, like those that encode the prion protein responsible for mad cow disease (bovine spongiform encephalopathy), or the allergenic proteins that cause the
rejection of animal organs in human xenotransplantation surgeries (where animal organs are transplanted into human patients) (Piedrahita and Mir 2004).

Agricultural applications. Genetic engineering was originally envisioned to have a multitude of agricultural applications. Recombinant bovine somatotropin (BST) derived from genetically engineered bacteria is one product of genetic engineering that is currently being used in animal agriculture. This protein, which increases milk production in lactating cows, is widely used throughout the U.S. dairy industry. Administering the protein rBST does not modify the DNA of the cow, and they do not become genetically engineered. BST was approved by the FDA in 1993 following extensive testing by numerous medical associations and scientific societies, which revealed no health or safety concerns for consumers (Bauman 1999).

The FDA is again 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 Federal Food, Drug, and Cosmetic Act. To date only one company has publicly announced a request for FDA approval to market a genetically engineered food animal, a salmon that is capable of growing four to six times faster than standard salmon grown under the same conditions (see page 126).

At this point it seems unlikely that genetic engineering will find widespread use for improving most livestock production traits. Agriculturally relevant traits such as growth tend to be controlled by many genes, making it difficult to select or predict how the expression of one or two recombinant proteins might influence these complex performance traits. Additionally, traditional selection techniques achieve reliable and consistent rates of genetic improvement for most livestock species and do not require the investment, risk and time involved for the production and regulatory approval of genetically engineered organisms. Enhancing the nutritional attributes or safety of food animal products in ways that are not possible through traditional selection techniques, such as the production of hypoallergenic milk or low-cholesterol eggs, is one area where the genetic engineering of agricultural animals might provide unique opportunities for value-added products in the future.
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acceptable, such as those found in con-
centrated animal-feeding operations. In
this case, genetic selection program
directed exclusively toward high
production efficiency has the poten-
tial to cause welfare concerns
for farm animals, irrespective of the
techniques used to obtain that goal.
Conversely, animal biotechnology
might also be used to improve traits
such as disease resistance, which could
have the effect of decreasing animal
suffering or mortality.

Although it is possible that genetic
engineering will be used to increase
agricultural productivity, in the short
term it seems more likely that this
technique will be used for biomed-
cal applications. In this case, genetic
manipulation is not intended to cause
changes that have physiologic effects
on the animals themselves and gener-
ally raises fewer potential animal wel-
fare concerns (NRC 2002). There are
still some unique concerns such as the
premature lactational shutdown that
has been observed in some animals ex-
pressing recombinant proteins in their
mammary gland (Shamay et al. 1992).
Additionally, the specific pathogen-free
housing requirements for animals in-
tended to produce human therapeutics
or organs for human transplantation
may compromise the behavioral needs
of the animal.

**Ethical concerns**

One genetically engineered animal, a
red fluorescent zebrafish called GloFish,
is commercially available in the United
States (see page 126). Federally, the FDA
decided not to regulate GloFish on the
basis that tropical fish 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.
However, California’s Fish and Game
Commission decided to prevent the sale
of these transgenic zebrafish to aquar-
ium hobbyists in the state. This deci-
sion was not founded on science-based
evidence of environmental risk — since
zebrafish is a tropical species that is not
sufficiently cold tolerant to reproduce in
California waters — but rather on ethi-
cal grounds. 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 engi-
neering of animals interferes with the
integrity or “telos” of the animal. Telos
is defined as “the set of needs and in-
terests 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”
(Holland and Johnson 1998).

Scientists might argue that science
does not make value or moral judg-
ments, and therefore ethics is not sci-
cifically relevant. The scientific process
places a high value on controlled
experiments as a way to obtain under-
standing. Potential, and maybe even
fanciful concerns, do not mesh well
with a process that focuses on what can
be measured, analyzed and quantified.
This proclivity to value that which is
verifiable and subject to experimental
manipulation may be at odds with the
values of other groups in society. Given
that ethics are difficult to integrate into
the scientific process, it is perhaps not
surprising that scientists often fail to
articulate the ethical issues occasioned
by their work, allowing that discus-
sion to be carried out in the press or by
those with a particular axe to grind. To
help address this disconnect, graduate
students at many universities are now
required to attend ethics courses in ad-
dition to their core curriculum.

The adoption of modern technologies is becoming increasingly important for the success of commercial livestock operations. Above, researchers at the UC Sierra Foothill Research and Extension Center use DNA tests and electronic animal identification equipment to individually track the parentage and performance of each animal and identify genetically superior breeding stock.
Public perceptions

In a survey conducted in 2005, only 6% of respondents indicated they had heard or read a lot about applying the science of biotechnology to animals, and 45% indicated they had heard “nothing at all” about the topic (IFIC 2005). A 2003 public knowledge study by Rutgers University found that 51% of respondents associated the word “cloning” with the terms “genetic engineering” and “genetic modification,” which is perhaps not surprising given that these terms are not used consistently in the media. Despite finding that the majority of people surveyed admitted to knowing “very little” (55%) or “nothing at all” (22%) about biotechnology, the Rutgers study also found that the majority of those interviewed disapproved of animal-based “genetically modified” foods (Hallman et al. 2003). As a point of reference, half of the respondents in a 2002 study by the same group had never heard about traditional livestock crossbreeding schemes, and this widely used breeding approach received only a 31% acceptance rating; at the same time, 50% of the respondents indicated that they considered the crossbreeding of animals to be morally wrong (Schilling et al. 2002).

The Rutgers studies showed that for many Americans, biotechnology remains an abstract and unfamiliar concept that, in the absence of other information or knowledge, evokes negative reactions. Many of the respondents who initially disapproved of the genetic modification of animals in an abstract sense later indicated that they approved when presented with specific examples, suggesting that opinions about genetic modification are malleable when additional information is presented. This is perhaps not surprising given the fact that most people do not consider themselves informed about biotechnology and related topics, and they generally lack knowledge about the process of livestock and food production in the United States (Hallman et al. 2003). Many people change their attitudes when presented with information on why the technology is being used, and if they view the potential benefits as important.

Communicating risks and benefits

Although to date the only genetically engineered animal available on the U.S. market (but not in California) is a glowing red aquarium fish, this technology has the potential to address other more vital societal interests. Given that the term “animal biotechnology” elicits a negative public reaction in the absence of any other information, scientists have an obligation to engage in the public discourse by articulating the science-based risks and benefits of their research, in addition to the ethical issues occasioned by their work. Polarizing the issue of genetic engineering of animals into “all is permitted” or “nothing is permitted” prevents rational social progress on the issue. Effective and responsible communication among scientific, community, industry and government stakeholders is essential to reach a societal consensus on the acceptable levels of risk for specific products of animal biotechnology, and to determine which set of values will ultimately be applied to decide the acceptable uses of animal biotechnology.

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References


