GM animals – another GM crops?

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Abstract

As new biotechnologies are developed, the parallels with GM crops are often drawn. In this paper, I consider GM animals and contrast them with GM crops. I use a systems of innovation perspective to consider innovation, product markets and regulatory systems and suggest that whilst there are some parallels between GM crops and animals there are also clear differences. There are differences in the techniques used, the availability of single genes useful for transfer and the acceptability of 'failures'. Existing animal breeding techniques are competitive with GM technologies and dissemination of GM animals into a population is difficult and time consuming. The structure of the industry is different between crops and livestock with large multinational companies largely absent in the production of farm livestock for breeding. Additionally animal welfare and ethical aspects are widely recognised as important in the context of GM animals, but the likely impacts of welfare and ethics-based regulation on any GM animal production is not clear. All these differences are potentially important for the future trajectory of the technology. I also suggest that at present, the development of GM animals is being pulled in different directions by the opening up of technological possibilities and the emphasis on animal welfare and notions of animal integrity.

Introduction

At the turn of 2006, the US Food and Drugs Administration released their long-awaited draft risk assessment on food from cloned cattle, pigs, sheep and goats to the accompaniment of protesting cow-costumed marchers to Capitol Hill.[2] At the same time, the UK press announced the birth of a calf, Dundee Paradise, imported to the UK as a frozen embryo and the offspring of a cloned bull[3] apparently without the knowledge of the regulatory authorities.

The parallels with GM crops were clearly drawn, with references made to 'Frankenstein Farming'. Cloning and genetically modified (GM) animals, while technically different, are frequently brought together in discussions around the application of biotechnology to animals. In this paper, I will analyse GM animal technology based on an approach developed by Joyce Tait[4] that takes a systems of innovation perspective on life science innovations that she used for comparing GM crops, pharmaco-genetics and stem cells. I will suggest that whilst the innovation processes embodied in GM animals have some parallels with GM crops there are also clear differences, and that these differences are important for the future trajectory of the technology. The techniques used to produce GM animals have been less effective, there have been fewer single genes available that are useful for transfer, and 'failures' in the production of GM animals are less acceptable than in crops. Existing animal

breeding techniques using genetic markers and full-genome scans are competitive with GM technologies such that a GM application would need to provide considerable advantage over 'traditional' technologies or provide other benefits. The dissemination of GM animals into a farm population is difficult and time consuming and finally, the structure of the industry is different between crops and livestock with large multinational companies largely absent in the production of farm livestock for breeding. Animal welfare and integrity questions are recognised in the context of GM animals but the regulatory approach to these questions is not yet clear. I will also suggest that at present, the development of GM animals is being pulled in different directions by the opening up of technological possibilities and the emphasis on animal welfare and notions of animal integrity.

This analysis is based partly on research on the prospects for GM and cloned animals for a study co-ordinated by the EC Joint Research Centre, Institute for Prospective Technological Studies[5] and part-time employment as scientific administrator at a genetics research institute (Roslin Institute, the birthplace of Dolly the cloned sheep), after a decade of experience in an international animal breeding company.

I will use a three-fold conceptual approach: considering GM animals from an innovation perspective; a product market perspective; and finally from a regulatory system perspective. This three-pronged approach provides a richer picture of the technology and the context in which it is being developed than considering the technology alone. In the final section I will bring these three strands together.

Innovation systems

The concept of genetically modifying animals for human benefit is not new. In the 17th Century Francis Bacon described, in his utopian island 'the New Atlantis', manipulation of animal performance and appearance including production of animals that were hybrids between species.

> "*We have also parks and inclosures of all sorts of beasts and birds…We make them greater or taller than their kind is; and contrariwise dwarf them, and stay their growth: we make them more fruitful and bearing than their kind is; and contrariwise barren and not generative. Also we make them differ in colour, shape, activity, many ways. **We find means to make commixtures and copulations of different kinds**; which have produced many new kinds, and them not barren, as the general opinion is…Neither do we this by chance, but we know beforehand of what matter and commixture what kind of those creatures will arise*"[6] (p. 482, my emphasis)

In the 1980s, as recombinant DNA techniques were developed, genetic modification of animals became reality.
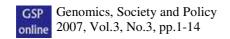
The main initial method to produce GM animals depended on injecting DNA into the nucleus of a fertilised egg in the hope that some of this 'novel' DNA would be

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incorporated into the genome of the resulting embryo. However, this technique proved to be technically difficult and inefficient, with only around 1% of the treated embryos resulting in a live, genetically modified animal. Even among these few animals, the expression of the gene could vary enormously because the technique could not target a precise location in the genome where the gene would be introduced nor could the number of genes introduced be controlled.

Nuclear transfer technology (cloning) was developed in order to try and overcome some of the difficulties with the injection technique of producing GM animals. The idea was to genetically modify cells in culture, identify cells that had been successfully genetically modified and use these to 'regrow' into genetically modified animals. The first such animals (cloned but not genetically modified), the sheep Megan and Morag, were produced in 1995 from cells obtained from foetuses[7]. The subsequent year, a range of cell-types were used to produce cloned animals using the same technique. The most remarkable and well-known of these was Dolly the sheep, derived from an adult cell (by a technique now known as somatic cell nuclear transfer or SCNT).[8] Whilst the arrival of Dolly stimulated a wide-ranging debate on the use of cloning technology for humans, in the animal world the focus on genetic modification continued with the first genetically modified animal produced using SCNT technology duly arriving in 1998 (a sheep which following the now established naming tradition was known as Polly).[9] However, the use of SCNT and genetic modification has not been extensively used as it is technically demanding and expensive. More recently, de-activated viruses similar to those used in human gene therapy have been used experimentally to produce GM animals and have opened up a new route for genetic modification that does not require cloning and is much more efficient than either cloning or the injection route.[10] This technique is of particular interest in genetically modifying chickens where previous techniques have not been useable.

In the initial rush of optimism in the late 1980s and 1990s all manner of potential applications for GM animals were mooted.

The production of therapeutic proteins in milk and eggs of various species (eg, sheep, goats, cattle, pigs, rabbits, chickens) as an alternative production method to the use of cell culture vats has been considered. The prospect of using transgenic animals to produce pharmaceuticals received a boost during a period of shortage of biomanufacturing capacity during late 1990s to 2004,[11] when for example, a recombinant treatment for arthritis (Enbrel) had to be rationed. Production in transgenic animals is also expected to have cost advantages, although the extent of these is contested. Transgenic animals are also said to have advantages over bacterial and plant-based systems in being able to produce complex proteins that are difficult to produce in cell culture.[12] The prospect of pharmaceuticals derived from animal milk became reality in August 2006 when the first such product (ATryn, an anticoagulant produced by GTC Biotherapeutics in goat milk) was approved by the European Medicines Agency for use to prevent blood clotting during surgery for patients with a

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particular hereditary condition.[13] A recent survey[14] identified 5-10 pharmaceutical compounds produced in GM animals that are progressing through clinical trials.
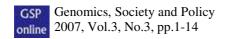
Other applications of GM animals were also identified in the survey, including genetically modified pet fish that are an unusual colour that have been commercially available in the USA since 2003. The use of GM animals to provide organs for human transplants have been discussed over a long period of time and various degrees of optimism have been expressed about the prospects of these becoming reality. However, the same survey suggested that majority opinion held that it will be at least ten years before such organs become available. Because the medical, pharmaceutical and pet industries differ considerably from agriculture, the rest of this article focuses only on the agricultural applications as it would not be possible to do justice to all the different innovation systems here.

Back on the farm, there appear to be no genetically modified animal products about to appear on European farms and food markets. The survey found no companies in the EU developing GM animals for food and the general opinion that it was very unlikely that any GM animals would be in general use before 2010. The lead genetically modified product appears to be faster-growing salmon developed in North America and awaiting regulatory approval. Therefore, the prospect of products from genetically modified animals flooding into European food markets in the near future appears rather remote.

The relatively weak uptake of GM technology in animal agriculture has been attributed by some scientists to a number of technical issues. The techniques for genetic modification have been very inefficient in terms of the number of animals required in order to successfully obtain a genetically modified animal, and this makes the technique expensive. Suitable target genes for transfer are not immediately obvious as it is not clear what new traits it would be possible and desirable to introduce. Exceptions include pigs produced in Canada that produce less environmental pollution.[15] These GM pigs produce an enzyme in their saliva that allows them to digest phosphorus from cereals thus, it is claimed, reducing phosphorus content of manure by up to 60%.

There may be more complex pressures on GM animal research. For example, experiment length (due to the lifecycle of farm mammals) may not fit easily into three year grants or PhD studentships. Animal welfare concerns may mean that individual scientists or funding bodies are reluctant to take up certain experiments or that licences are not available from the regulatory authorities, such as the Home Office in the UK. These, and other reasons must remain in the realm of speculation however, as no data are available.

A further aspect that should be considered is that of alternative technologies to genetic modification. If not GM animals then what competitive innovation is taking place?

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Brief considerations of the history of how decisions are made regarding which animals are selected to breed the next generation suggest the following simplistic pattern.

Animals were initially selected on their appearance. As statistical techniques and an understanding of genetics developed, calculations were made to attempt to identify what is inherited and what is not. Did this animal grow fast because it was genetically predisposed to do so or because it was well fed? Another step was to start using data from larger numbers of family members to make this distinction between genetics and environment more discerning (since families resemble each other).

Of course, humans have been interested in changing more than one characteristic at the same time, so methods were developed to provide a means of deciding which animals to keep depending on a portfolio of characteristics rather than just one characteristic. This involves making decisions on how much weight to give each of the different characteristics (eg, the number of eggs produced and the quality of the egg shells).

Another challenge was to be able to make decisions on which animals to keep based on characteristics that are desired but cannot be measured in the animal itself (eg, milk yield of male cattle or meat quality). Genetic markers were increasingly suggested as a way in which information about the genetic pre-disposition of animals to characteristics could be evaluated without having to measure performance in that characteristic. However, the relationship between genetic markers and characteristics can break down and finding the gene that causes the relationship with the characteristic has proved to be difficult and time consuming.

With increasing realisation of the complexity of gene interactions, the reduction in costs of genotyping and increasing computing power, it is suggested that the next stage in genetic selection will be to scan the whole genome and look for 20,000 or so differences in the DNA that are implicated in a particular characteristic. I suggest that much of animal genetics for food production is moving more and more away from what might be perceived as a reductionist approach of looking at single genes and manipulating these, and more toward treating the genome as a 'black box' the contents of which are very complex but do not require disentangling in order to achieve the pragmatic needs of selecting animals deemed to be desirable for particular purposes. The whole genome scan will therefore act as a powerful tool to allow a multiplicity of genes and their interactions to be considered simultaneously rather than focusing on a single gene and its effects. The whole organism is thus considered more as a system.

It therefore appears that technological developments in the area of genetic modification of animals are taking place but that equally, other developments in genomic technologies are highly competitive with genetic modification at least in the 'bread-and-butter' activities currently undertaken by animal breeders.

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Product markets

The livestock breeding industry, particularly of chickens, pigs and dairy cattle, is extremely well-organised internationally and has processes that are able to adopt advances in 'traditional' breeding techniques, such as increasingly sophisticated statistical analysis tools and use of genetic marker assisted selection. This is allied to a worldwide distribution network that allows any 'improvement' made in one place to be distributed to a large network. Any advantage that a genetically modified animal would have, therefore, has to be greater than the ongoing incremental change or (more likely) has to introduce a change that is not possible by 'traditional' methods. Furthermore, it takes time to introduce a new gene into a population of animals and even longer to transfer that modification into a range of current commercial populations. Unlike crops where a farmer may replace the entire crop with a new variety in one season, in farm animal production, only a percentage of the herd is replaced at any one time (although this is less true of poultry and fish). This places restrictions on the speed with which any type of GM animal could be incorporated in the population of farm livestock.

Analysis of the commercial development of GM crops[16] from the companies' perspective suggested that GM crops were developed in large part due to technology 'push' from the base of considerable public and private finance, with market 'pull' contributing to a limited extent, at least in European markets. Similarly development of GM animals also appears to be driven by technology 'push' although it has been reported that "*Funding agencies are not supporting GM livestock projects to a high level and returns for venture capital are regarded as low.*"[17]

GM crops were produced by large multinational pesticide companies who had a great deal invested in technical development. The limited amount of GM animal development for agricultural purposes that appears to be going on is primarily in small university spin-off companies. Livestock breeding is not dominated by large multinational companies and nationally run schemes are still important. Whilst a few companies dominate the pig, poultry and dairy sectors, and work internationally, they are still relatively small companies (for example, one of the largest multinational companies, Genus Plc, reported a turnover of £267.5M and an operating profit of £24M for 2005-06[18]). A possible exception was Monsanto Choice Genetics Inc, a supplier of breeding pigs which until recently was a subsidiary of Monsanto Company. Even the smaller companies have a significant impact: it is estimated that three companies provide 80-95% of Europe's egg producing market and 75% of the world market, for example, and that four companies produce 35-60% of the world markets in poultry meat.[19] However, we should note that the structure of the industry sector can change and these changes can take place very quickly.

Analysis of company strategies in developing GM crops[20] suggests a number of key features were important to the subsequent innovation trajectory. Among these was the coming together of agrochemical companies and the seed production sector (usually by the purchase of the seed producers by agrochemical companies looking for targets

for new innovation). This meant that the culture and market understanding was dominated by the agrochemical rather than the seed production sector.

The experience of GM crops in the EU appears to have made breeding companies wary of moving into GM animals. Public statements suggest that breeding organisations wish to distance themselves from GM and cloning technology, for example

> *Genus applies a unique combination of quantitative genetics and biotechnology to animal breeding and selection, which is applicable across all livestock species, and enables farmers and producers to produce higher quality and healthier non-GMO food products.*[21]

The limited data available on public attitudes to GM animals suggests that these are generally negative.[22] Attitudes to the application of GM are affected by the organism being modified. Applications to humans appear to be the most controversial, followed by animals, plants and micro-organisms. Attitudes are also affected by the aims of the modification, with medical application more acceptable than applications to food.

Context may also be important for understanding public attitudes. Ouedraogo, for example, studied public perceptions of reproductive biotechnologies in France and the UK during the period 2000-2003 using focus groups [23]. One major concern in the groups was the expectation that priority is given to economic competitiveness at the expense of sustainable development. One respondent expressed this as follows:

> "*The stakes these issues cover are far from being purely scientific. The actual problem is socio economic and it deals with the increasing influence of industrial firms in the society. Genetics represents today and especially will represent in the near future a huge economic potential that Europeans do not want to leave in American hands*"

In the UK a series of focus groups were carried out as part of a report for the Agricultural and Environmental Biotechnology Commission on GM animals.[24] These focus groups consisted of people with experience of animals in different contexts (pet owners, intensive and extensive farmers, wildlife observers and country sports enthusiasts) plus two 'control' focus groups with no pets and no acknowledged relationships with animals. Macnaghten concluded that:

> "*people tended to accept (or at least to tolerate) the suffering of the animals concerned when there existed a genuine and authentic need, typically expressed in the need to cure life-threatening diseases. Such a need had to be justified in **human** rather than **commercial** criteria and was only seen as justified when alternatives were not available*"

Attitudes to GM animals can be expected to be strongly dependent on attitudes to animals more generally and their relationship to humans. These attitudes may well be

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contradictory and changing. The Nuffield Council on Bioethics, in its report on the ethics of animal research, identified three different types of attitudes to animals[25]:

- There is something special about humans that is present in all humans but not in non-human animals
- There is a hierarchy of moral importance with humans at the apex and invertebrates near the bottom
- There is no categorical distinction between human and non-human animals.

However, attitudes may not be as clear cut as this suggests. Budiansky has noted[26] that attitudes to animals can veer from treating the animal as a thing, as an item on a supermarket shelf, to that of a person.

Macnaghten also noted the ambivalence felt by people in the context of developing a culture of care for animals but at the same time eating them.

> "*Many people saw themselves as being 'in denial', choosing to eat meat yet at the same time distancing themselves from actively confronting the realities of modern farming; colluding with abattoirs, supermarkets, advertisers and food producers in dislocating meat from its corporeal production*"[27]

Budiansky[28] argues that domestication of farm livestock was initially more to the benefit of the animals than the humans doing the domestication. He asserts that the process of domestication was far from an exploitative imposition of human will on an innocent population of animals. Domestication was rather a process that favoured those animals that had established a degree of dependency on humans to protect them from diseases and predators and provide them with food. Whilst this argument is an important one to make, others may well point out that Budiansky himself may be failing to recognise that the benefits that accrued to animals at the early stages of domestication may no longer provide quite the same advantages when livestock become part of an industrialised, globalised production system where margins of profit are narrow and there is intense pressure to compete with the cheapest production systems in the world, and Budiansky's argument remains controversial.

In terms of the product markets, there appear to be no large multinational companies at present poised to see GM animals as an important component of their strategy (although this situation can of course always change). On the other hand, there is considerable ambivalence as to whether GM animals will be seen as generally acceptable from a public perspective.

Regulatory systems

The main pertinent regulations with respect to GM animals in the EU relate to the deliberate release of genetically modified organisms (Directive 2001/18/EC), the safety of any novel food derived from such animals (Regulation (EC) No. 258/97) and the welfare of animals produced by GM techniques (Directive 98/58/EC on the

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Protection of Animals Kept for Farming Purposes). The release of genetically modified animals into the environment is expected to have less impact than the release of GM crops (with the notable exception of GM fish). There is limited risk of escapes to the environment and then very few 'wild' relatives with which most farm animals can breed. Food safety may well be an issue, but would be evaluated on a case-by-case basis. Welfare legislation with respect to GM livestock may have an impact but it is not clear how the legislation might be applied (ie, what would be deemed unacceptable under the legislation).

It is noteworthy that the welfare of animals produced by biotechnology is treated as a 'risk' issue by some regulators. For example the US Food and Drugs Administration (FDA) has evaluated welfare aspects of cloned farm animals as a 'risk' issue.[29] A similar approach appears to be adopted by the European Food Safety Authority (EFSA) in its evaluation of cloned farm livestock.[30]

A very different approach has been adopted by the UK Department of Environment, Food and Rural Affairs (Defra) which has recently developed an animal welfare strategy.[31] In its consultation document relating to this strategy, Defra makes it explicit that it is adopting a new approach. Instead of a Government-led, top-down, command and control model that aims to prohibit and curtail certain practices, Defra appears to be adopting what might be termed a governance model.[32]

> "*success in the future will mean a move away from the traditional legislative approach, towards delivery of outcomes through other more innovative means…a greater emphasis on stakeholders and Government working together to deliver good welfare, with clarity about their respective roles and responsibilities*"[33]

Defra's expressed aim is to develop a partnership where the different constituencies state what they will do to further animal welfare, and Defra in turn states what it will be responsible for. So, for example, with the objective of gaining international recognition of animal welfare as a public good, the strategy suggests that Government has the role of promoting inter-governmental initiatives (eg, in the Council of Europe) whilst stakeholders are responsible for working through the World Society for the Protection of Animals to gain agreement on a United Nations declaration on animal welfare. The consultation document suggests that the Government's role will be to enforce baseline standards but standards above this level should be delivered by stakeholders. Instruments such as welfare standards and codes of practice together with training and dissemination of information on good practice are seen as key. Roles and responsibilities are set out for individual animal owners, stakeholder organisations as well as central and local government. There is also recognition that animal production takes place in a global economy with international legislation.

Of course it remains to be seen what the outcome of Defra's consultation will be, let alone the results of this kind of approach. However, it does seem to get away from polarized discussions and instead focuses attention on the objective (animal welfare),

even if there may well be little agreement on the way in which these objectives can be realised or even a clear definition of the end-point of animal welfare.

The implications for regulating GM animals might be to suggest that different types of instrument are more likely to achieve different ends. A risk assessment, government model may be appropriate for evaluating specific hazards (such as risks to human health from consuming products) or to adjudicate among specific acceptable practices, but a governance approach may be more appropriate for ensuring that a technology is developing in a direction that takes into account factors other than economic drivers.

Beyond any welfare aspects of genetic modification of animals, there is a realisation in the EU that there are also ethical aspects that need to be considered. Some attempts have been made within the European policymaking context to address issues around the general ethical acceptability of GM animals, notably through the Group of Advisers on the Ethical Implications of Biotechnology to the European Commission. The Group concluded that

> "*genetic modification may contribute to human wellbeing and welfare, but is acceptable only when the aims are ethically justified and when it is carried out under ethical conditions.*"[34]

In conclusion, the animal breeding industry sector is not extensively regulated, as compared to say the pharmaceutical industry. Regulation is not a barrier to entry into the animal breeding industry in the sense that it can be in the pharmaceutical sector. However, any novel foods derived from GM animals are likely to have a considerable regulatory hurdle to overcome. Animal welfare legislation is an issue with which the animal breeding industry is already familiar, but it is not clear how it is being applied in animal agriculture. Another regulatory aspect relevant to animal breeding is the issue of ethical acceptability and it is not clear how this will be resolved.

Conclusions

This paper has brought together three aspects of the system of innovation for GM animals: the innovators, the markets and the regulators. The future trajectory of GM animal technology will depend on a complex set of interactions and developments that cannot be predicted. However, I have attempted to compare GM animals with GM crops and conclude that whilst there are similarities, there are also differences. Of particular note are the following factors.

The techniques for genetically modifying animals are not as effective as those for producing GM crops and the production of organisms where the modification has not worked is much less acceptable in animals than in crops. Existing animal breeding techniques are effective in achieving change and since whole populations of farm livestock cannot be replaced in the same way as crops, a GM animal will need to be very much 'better' than a non-GM animal in order to be competitive. The structure of

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the breeding stock suppliers is different in crops and livestock, with large multinational companies largely absent in the production of breeding livestock.
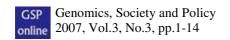
Animals raise a set of ethical issues that are widely recognised as being important. Human relationships with animals are complex and may well be in flux at the moment, and it is not clear how these will resolve. The welfare of farm animals has been an issue of note for some years but the processes for determining 'good' animal welfare seem to be underdeveloped. One regulatory approach is to treat animal welfare as a 'risk' where 'poor' animal welfare needs to be mitigated; another is to view animal welfare regulation as a process whereby progress is toward an (undefined) state of good welfare.

In considering GM animals in a wider context, there seem to be opposing forces pulling the technology in different directions. Scientific research continues to develop new techniques, new approaches and lead to new ideas on how GM technology might be used (although no data are available on the extent of funding for the development of these new technologies). In the other direction, animal welfare concerns, a desire to maintain the integrity of animals and uncertainty as to the acceptability of GM animals to the public act as restraints on developments. (I am reminded of the Pushmi-pullyou, the children's story book creature in Doctor Doolittle stories by Hugh Lofting. This Llama-like animal had two heads at the opposite ends of the body. As it tried to move, each head pulled the animal in a different direction.)

In terms of innovation systems, there are no apparent path-dependent incentives to commercial development of GM animals. Path-breaking innovations, with their more disruptive impacts on an industry sector[35] are even more difficult to envisage, given the current state of the science and of the animal breeding sector. However, both the dynamics of the industry sector and the state of the science are changeable. Additionally, there are a number of factors that could impact on future developments, such as the need to mitigate the impacts of climate change, the possibility of food shortages resulting from a combination of climate change, impact of growing biofuels and changes in global consumption patterns. Emergent animal diseases may cause production systems to be re-conceived and new zoonotic diseases which can impact on human health may provide new challenges. Any of these factors, either singly or (more likely) in combination, could have a disruptive effect on the animal breeding innovation system and the impact of GM technology in unpredictable ways.

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