WILL ANIMAL BREEDING BECOME A BIOTECHNOLOGY?

Grahame Bulfield

Roslin Institute (Edinburgh), Roslin, Midlothian EH25 9PS UK

SUMMARY

Biological science is moving very fast producing a new range of technologies capable of use in the animal breeding industry. I review the current position and, drawing on lessons from the past, try to assess the current and future implementation of the technologies by the industries and their acceptance by the public.

INTRODUCTION

Molecular biology and genetics has made the biological sciences technology-driven. The impact over the decade has been revolutionary if not cataclysmic: we are now living with an increasingly reductionist and mechanistic science. Farm animal science was among the last of the biological disciplines to feel this particular wind of change; we are now, rather belatedly, in the middle of this revolution. While the storm is raging around us, it is very difficult to tell if it will pass with little effect or wipe the ground clean for a total rebuilding. I am going to take the opportunity of this plenary paper to pose (and try to answer) the question . . . "Will Animal Breeding become a Biotechnology?"

THE PAST

If it is difficult to assess the future, a good rule is to see if there are any lessons to draw from the past. Indeed even a quick look at the 1950s will show that the structure of the animal breeding industry today was technology-driven. The widespread introduction of mathematical and statistical techniques into biology after the 2nd World War not only affected a generation of biologists but also the animal production industry: in the US through J.L. Lush's book and in the UK through Alan Robertson's popularising of complex ideas. Alan Robertson's realisation that Artificial Insemination (AI) formed a route to genetical improvement of the dispersed dairy cattle population was a key step. It was however not in that most respectable of farm species - the dairy cow - that the major advances were made, but in the lowly broiler chicken. It is hard to realise that in the 1950s the chicken was a luxury item costing around £20 ($30) at today's prices; Harry S Truman won the 1947 US Presidential election - with the slogan "a chicken in every pot".

It was not however the "science of ideas" that brought about the revolution. In the UK, at least, it was the training of practical animal breeders by the Edinburgh School of Geneticists and individuals (what we would now call entrepreneurs) capable of putting the ideas into practice. Foremost among these in the 50s and 60s was Cyril Thomber; although his endeavours were not without problems, his realisation as a commercial breeder of the power of the new technology has parallels for the future.

Today in the UK we have the world leading pig breeding company (PIC), broiler breeding company (Ross Breeders) and have increasing strengths in dairy cattle breeding (Genus and Cogent). These companies can be traced back not only to the revolutionary science of quantitative genetics but to individuals whose vision, leadership and organisation led their success.

I will therefore summarise the lessons I draw from the past:

1. The science has to present significant opportunities not possible previously . . . . but this is not enough!
2. People with practical capabilities have to be trained in the new science so they can adapt it.
3. Entrepreneurs, companies and investors have to be fired by the science and discover how it can be put into practice. The organisation and leadership are as important as the vision - a totally new structure for the industry might be necessary.

THE PRESENT

I would like to assess the current situation by separating: (1) the state of the science itself from, (2) how the industry and the public are responding.

The key issues for animal breeding are of course: (a) almost all commercially relevant traits are physiologically complex and controlled by several/many genes of medium/small effect and (b) the relative low value per unit of the product (compared with, for example, pharmaceuticals).

(1) The Science. Two partially converging areas of research are now seen as having a potential impact on animal breeding: genomics and embryology.

Genomics. Although it has not caught the media and public imagination as much as transgenics and cloning, genomics will, I believe, have just as great a long-term impact. Because of the availability of information from genetically well researched species (humans and mice), genomics in farm animals has been established in an atypical way. We can now see it as progressing in four phases. (i) Making a broad sweep map ($\simeq$ 20cM) with both highly informative (microsatellite) and evolutionarilly conserved (gene) markers. (ii) Using the *informative* markers to identify regions of chromosomes containing Quantitative Trait Loci (QTL) controlling commercially important traits. This requires complex pedigrees or crosses between phenotypically and genetically divergent strains. (iii) Progressing from the *informative* markers into the QTL and identifying the trait-gene(s) themselves either by complex pedigrees and backcrossing experiments, and/or using the *conserved* markers to identify candidate genes from their position in the gene-rich species. (iv) Functional analysis of the trait-genes to link the genome through physiology to the trait - the 'phenotype gap'.

As the details of genomics is the topic of many papers in this Congress I just want here to make the following general points:

- Farm animal genomics programmes have now substantially completed phase (i) and are in Phase (ii) and tooling up for Phase (iii).
- Information from Phase (ii) - QTL - can be patented and can and is being used by Marker Assisted Selection in commercial breeding programmes. Sophisticated statistical techniques have been developed both to identify and to use QTL.
- Both the apparently good conserved synteny and order of genes between farm animals (including chickens) and man will greatly facilitate Phase (iii).
- Enhanced transgenic technology needed to make full use of Phase (iii).
- Functional genomics (Phase iv) of Farm Animals has received little attention. Complex interaction between gene products will require the use of new tools such as control theory.

Embryology. In 1982 the first transgenic mouse was produced by microinjection of DNA into the fertilised single cell oocyte. By 1985, transgenics has been produced in pigs, sheep and cattle with chickens (by a variety of routes) following a little later. The first transgenic technology has limitations: less than 1% of embryos injected and 10% of animals born are transgenics; genes can only be added, not replaced or deleted; because multiple copies are inserted at random, correct regulation of gene expression is difficult.

To overcome these problems in the mouse, embryonic stem cells (ES cells) have been developed. These cells can be grown stably in culture for many passages and transformed with gene constructs. The constructs not only permit transformed cells to be selected but also gene targetting to be accomplished. Transformed cells are introduced into the blastocoel cavity of an embryo, produce a mosaic (chimaeric) animal and contribute to the germline. After one generation this will produce a germline transgenic animal. This technique, in principle, produces 100% transgenic animals and, by gene targetting a much wider variation of genetic modifications (such as gene knock-outs). For many years, several labs world wide have tried to produce ES cells in farm animals; although some success has been claimed, no robust and repeatable method has been published Indeed, ES cells can only be produced even in mice from a limited number of inbred strains.

In Roslin, Ian Wilmut, Keith Campbell and their colleagues have been trying a different approach. They initially took partly differentiated embryo cells and found conditions (quiescence) that reprogrammed the nuclei rendering them totipotent for nuclear transfer to unfertilised oocytes (Campbell et *al.* 1996). More recently (Wilmut *et al.* 1997) nuclear transfer, producing live lambs, has been achieved from a further embryo cell line, a foetal fibroblast line and an adult mammary epithelial line ("Dolly"). This research now opens up opportunities on two fronts: (i) gene targetting in cell culture followed by nuclear transfer and (ii) 'cloning' of animals from adults.

(2) **Industry and the Public.** The key to the implementation of the new biotechnology is the response of the industry and the attitude of the public.

While acknowledging the sustained and continuing impact of quantitative genetics on animal

breeding, there are significant new opportunities presented by the new technologies. Examples include traits that are currently difficult to improve.

- Traits which require complex and expensive measurements on individual animals: such as carcass traits.
- Traits where ascertainment is difficult under field conditions. Establishing markers for disease resistance and immune competence are examples.
- Traits with low he&abilities but with significant non-additional genetic variation such as fertility and viability.
- In addition, there is the possibility of creating new products such as nutraceuticals in milk.
- The impact of cloning on rapid dissemination of genetic progress from a nucleus herd.

At present it is possible to discern significant uptake of the new technologies, especially marker assisted selection, by companies in the pig and cattle breeding industry but not the poultry breeding industry. The difference could simply lie in the fact that the short generation interval of poultry (and low cost per unit animal) enables quantitative genetics to be applied both more forcibly and to a more complex array of traits (for example those associated with animal welfare).

Where industry is understandably cautious is in embracing transgenic technology. On the other hand this technology is now fully integrated into the medical biotechnology industry with several important products in clinical trials. Even in biomedicine, in the late 1980s, the existing pharmaceutical companies would not accept transgenic technology; this market-gap was filled with new biotechnology companies such as PPL Therapeutics in Roslin.

The public has also, generally, accepted the case of transgenics in biomedicine - producing products to treat intractable diseases such as cystic fibrosis. It is far more cautious about the use of transgenics in animal breeding. The main concerns are:

- playing God and integrity of the species
- animal welfare
- environmental protection
- patenting life
- biodiversity
- the plight of small farmers

Many of these concerns, although sincerely felt, arise from misunderstandings. Humans have 'played God' with domestication and animal breeding from 4000 years and had an enormous impact on the phenotype and diversity of farm animals (especially in the last 40 years through AI). Animal welfare issues are often a red herring as depend on the impact on the animal than on the technology itself - in the UK the Belgian Blue breed could not be used in practice if produced by transgenesis and the same would apply to some strains of broilers with leg abnormalities. Patenting does not give the right to market a technology only to prevent others from commercialising your intellectual property - animals themselves are not usually patented but rather the technique or the use of a particular gene construct is.

These public concerns do, however, require our urgent attention if the use of biotechnology in animal breeding is not to be stillborn. A significant contribution would be the production of a transgenic line with altered characteristics (such as disease resistance) which scientists, industry and most of the public could see as of advantage to both the industry and the animal itself.

THE FUTURE

Will Animal Breeding become a Biotechnology? Or will it be relegated to an interesting academic oddity (such as enzyme polymorphisms in the 1960s)? Or will public reaction kill it?

Although I think there are major scientific, implementation and public relations obstacles to be overcome, I am much more optimistic today than at our last Congress four years ago.

It is now clear to me that there are an increasing number of specific examples of traits that are being improved with the use of MAS either for QTL or genes, which would have been difficult or impossible using quantitative genetics. These examples are, more importantly, convincing at least some companies in the industry that biotechnology is commercially viable. Four years ago I believed that if the technology was to make an impact, new biotech companies would have to be established. This does not now seem likely (the jury is out on the poultry breeding industry).

As more difficult traits are tackled and resolved using genomics (such as disease resistance, carcass quality, fertility and viability), the commercial credibility of the new technology will become confirmed.

New techniques, such as gene targetting and cloning from adult cells, if established as robust and efficient for all farm species, will hugely widen the range of opportunities available.

We have the privilege of living through the most exciting time so far in the biological sciences. I am also now optimistic that the new technologies will be of use to the animal breeding industry and, more importantly, it is taking them up. I also believe that the tide is turning in public opinion as researchers realise the importance of not leaving the public relations field to the animal welfare and environmentalist lobbies.

It now seems that Animal Breeding could well become a Biotechnology!

ACKNOWLEDGEMENTS

Although the ideas in this paper are my responsibility, many colleagues in Roslin, the University of Edinburgh and the Animal Breeding Industry have helped me critically refine them.

REFERENCES

Campbell, K.H.S., McWhir, J., Ritchie, W.A. & Wilmut, I. (1996) Nature **380:**64-66.

Wilmut, I., Schnieke, A.E., McWhir, J., Kind, A. J. & Campbell, K.H.S. (1997) *Nature* **385:**810-*813.*