The Future of Livestock Genomics

Report on a workshop held in Brussels
17-18 July 2006

Editors
Peter Burfening
John Claxton
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Chris Warkup

Under the auspices of the
EC-US TASK FORCE ON BIOTECHNOLOGY RESEARCH

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PREFACE

With the publication of the Animal Genomics Blueprint by USDA, and the development of a strategic research agenda for Farm Animal Breeding and Reproduction in the EU, this workshop comes at an important time for farm animal genomics. Animal genomics is prioritised as part of the theme "Food, Agriculture and Biotechnology" within the EU's Seventh Framework Programme for Research (2007-2013) and, in the US, the President's American Competitiveness Initiative (2008) stresses the importance of targeting "...investments toward the development of deeper understanding of complex biological systems...". Farm animal genomics clearly has an important role, not just in supporting agriculture as a source of food, but as a tool that directly affects human wellbeing – either, by producing healthier foods from animals, as a resource of comparative data, or as a means of generating new medical breakthroughs. To fulfil its role, it needs to have access to the right tools for research and application, and many of these will come from collaboration between researchers. This workshop has highlighted some of the key issues, the tools that are needed, and the advantages of US-EC collaboration. Exchange of information on funding available on both sides of the Atlantic will also be important to developing this collaboration.

This initiative forms one of a broad range of initiatives taken by the EC-US Task Force on biotechnology research, and we look forward to future developments in the field.

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More information about the Task Force is available on
http://ec.europa.eu/research/biotechnology/ec-us/index_en.html
The views expressed in this document are those of the workshop participants, and do not necessarily reflect the views of the sponsors or governments.

KEY POINTS AND AREAS FOR COLLABORATION

Key points from the final discussions of the workshop are summarised below:

- Many of the challenges for animal genomics are similar to those that have been addressed by human genomics – "we have been here before". However, there is a critical difference in that animal breeders aim to deliberately change the frequency of alleles for improving farm species and this intervention has repercussions on the priority of the challenges, the tools that need to be developed and in some cases raises societal issues.

- While comparative genomics will benefit strongly from data on animal genomes, work on animal genomes is important also for human genomics. Farm animal genomics as a resource for helping to understand human genomics should not be overlooked.

- There is strong concordance between the USDA "Animal Genomics Blueprint" and the developing strategic research agenda of the European Technology Platform on "Sustainable farm animal breeding and reproduction"[1], pointing to many existing opportunities for transatlantic collaboration.

- While there is much public concern about cloned animals and genetically modified animals, there is a much more positive opinion of other animal biotechnologies, such as using genomics for improving selection. Researchers should be specific about which technology is referred to when speaking on biotechnologies. Risk analyses, including ethical considerations, being realistic, using trusted information sources, and including the risk of not intervening (as opposed to simply the risk of intervening), will allow the public to make an informed decision on these technologies.

- Collaboration between US and EU researchers can provide strong synergies where it is possible do things better, cheaper or sooner than working alone. Significant informal international collaborations have been necessary to bring about the current livestock genomics infrastructure and should be built upon in the immediate future. In particular this applies to the development of:

  - Tools and resources, specifically:
    - genome sequencing;
    - curation and annotation of genomes;
    - development of SNP (single nucleotide polymorphism) panels enabling whole genome selection;
    - development of phenotype databases linked to pedigree information, DNA and, if possible, other biological materials.
  - Mobility of researchers across the Atlantic.
  - Genomics of microbial communities, including the interactions of pathogens, and their livestock hosts.

- Current mechanisms for collaboration exist and should be exploited further and expanded:
  - topics for cooperation and fellowships in the seventh Framework Programme of the EC;
  - cooperation programmes, with open access, following models like the Human Frontiers Science Programme.

- A platform for information exchange between EU and US research funders would be helpful to address these needs.

(1) www.fabretp.org

SUMMARY

Genomics technologies in farmed animals present a major opportunity to address the responsibilities of agricultural production to society at large. Whether as a source of healthier human foods, contributing to environmental sustainability, or as a potential source of human medicines, the use of animals is an important resource. The human genome field has led the way both in terms of completeness of data and in developing tools and applications. Animal genomics broadly follows a similar route, but there is a major difference in that animals are selected to express (or repress) specific traits, and in fact have been deliberately selected over several thousand years. This means that they also form a unique resource for comparative genomics with other species, including humans. In addition, the use of selection and quantitative genetics in animals is well advanced and this gives the discipline of systems biology at the animal, or population, level a leading edge over the human field. Not only, therefore, does farm animal genomics have the potential to improve sustainable agricultural production, but in key areas it is a tool for developing human genomics research.

While the use of genomics for genetic selection and for understanding the underlying mechanisms of genes, their function and their ultimate expression into a specific phenotype is considered broadly acceptable, technologies such as cloning and genetic modification are currently still controversial. In both the USA and the EU these technologies raise significant ethical and moral issues. These, however, depend to some extent on the practical benefits that might accrue from the use of such technologies. In general their use (especially the use of genetic modification) for agricultural production is not interpreted by society at large as highly advantageous. Still, they offer major possibilities as research tools and will contribute to a significant improvement in our understanding of the molecular complexity of genome functions. In addition, they have implications for fields other than purely agricultural production, such as for 'pharming' where pharmacologically active proteins might be produced for human use through transgenic animals, or through the control of zoonotic disease by enhancing resistance.

Advances, however, need the right tools, and although costs continue to fall for generating tools and genetic resources, overall they are significant. To some extent this means that collaboration is needed to develop the tools for properly exploiting farm animal genomics – all current sequencing projects for farm animals are funded through collaborations. Key targets now include the development of more sequence data, SNP panels and, with care, phenotype databases (the "phenome"). The phenotype databases necessarily need to be based on large populations and this, together with massive phenotypic diversity, means that they are expensive and will need careful planning to maximise their utility. In addition, the long-term annotation and curation of the genomics data to make sure that it remains up-to-date, reliable, and available, needs to be addressed with some urgency. A permanent platform for information exchange between EU and US research funders would be helpful to address these needs.

BACKGROUND

In the context of the "EC-US Task Force on Biotechnology Research", a satellite workshop was held on 17 and 18 July 2006 in Brussels on the subject of "The future of livestock genomics" with the objective of anticipating the next stages in the development of animal (livestock, poultry and farmed aquatic species) genomics and looking at opportunities for cooperation between the USA and Europe. The workshop was attended by leading researchers representing a broad spectrum of the research communities. The meeting was structured around a number of presentations and discussions on the potential of animal genomics, the state-of-the-art of genomics research, and societal and ethical issues related to the field.

THE POTENTIAL OF ANIMAL GENOMICS

In an overview to the potential of animal genomics **Michel Georges** highlighted three strengths of livestock genomics:

- the value of biodiversity;
- the leading edge of quantitative genetics; and
- the genetic engineering of livestock.

The value of biodiversity

There is clearly a linkage between the genotype and the phenotype of animals, yet the link between the two remains obscure in many cases. This lack of knowledge, the "phenotype gap", is being addressed in mouse models by mutagenesis screens aimed at linking mutated genotypes to specific phenotypes. While this mutagenesis-driven selection is being carried out in the laboratory, livestock populations represent an unprecedented resource of individuals selected for over 10,000 years. Domestication has created as much, or more, within species variation as natural selection has generated between species, and as a result of the specific selection, the background noise in the genome is smaller than in wild populations. Although not a livestock species, this is most strikingly apparent in the domestic dog, where the phenotypes – the different breeds – of *Canis canis* are markedly different compared to its common carnivore relatives. Effectively, the inbreeding reveals homozygous, recessive alleles, while reducing heterogeneity of the individual traits.

Information from the genome, and the effect of its variation on phenotype, will help to clarify the molecular basis of adaptation within populations that have been under selection pressures for 10,000 years. This will help:

- clarify the structure of genes (how many Quantitative Trait Loci – QTL – for each trait; how many genes for each QTL; how many alleles for each gene; how distribution of alleles affects the gene);
- explain the nature of the mutation: protein coding, regulatory or structural mutations, ancestral or recent mutations, variations in sequence or "epimutations";
- clarify the nature of the networks of interactions within or between loci.

The result is that the biodiversity of domesticated animals represents a significant resource in explaining and exploiting gene function. It cannot, however, be fully exploited without sufficient genome and genetic tools and, as such, it remains to date an undervalued resource.

At the forefront of quantitative genetics

Inbreeding within animal populations reduces heterogeneity, and means that the linkage disequilibria generated by selection within breeds are significantly higher than they are between breeds and are also significantly higher than occurs in humans. This, in turn, means that in comparative genomics the potential of this disequilibrium can be used to isolate functional sequences of the genome and identify the position of genes in other species,

including humans. Additionally, it is possible to resolve multigenic traits into a series of monogenic ones and, thus, clarify the link between phenotype and genotype. However, to do this satisfactorily requires that the genome sequence and an adequate SNP panel of the animal model being used are available, and this is not yet the case for most domesticated livestock. Indeed, the visibility of livestock genomics when it comes to attracting funds for such tools is low.

Quantitative genetics has been used for many years in selecting animals for higher production (growth, yield, efficiency) and has had remarkable results over the years (for example, the kilograms of feed needed to produce a kilogram of pig meat is estimated to have been halved between the 1960s and the present day [2]). This has been possible because these traits have been both measurable and highly heritable. As a result, livestock genomics will have a significant impact on developments in quantitative genetics. Molecular genetics and genomics now enable other traits, such as disease resistance and robustness, to be targeted for selection. Ironically, the small gains made and extremely stringent thresholds for ensuring that the false discovery rate is low mean that some private companies are now questioning the economic sense of molecular-driven quantitative genetics through classical QTL-assisted selection. Comprehensive SNP panels and genome sequences for domesticated animals would reduce the difficulties and, with the right statistical analysis, maximise the efficiency of selection based on genome-wide approaches.

Genetic engineering

Finally, the genetic engineering of livestock opens up many possibilities, though it has significant issues of public acceptability. As well as human health-related uses such as 'pharming' (producing medicines in animals) and xenotransplantation (producing tissues in animals with lower rejection risks for use in humans), there are clear possibilities also for agricultural use. For example, "designer milk" (increased casein content for cheese production, or lactose-free milk); resistance to infectious disease in animals (ruminants with the prion gene knocked out); animals that have lower impact on the environment (phytase positive pigs which increase phosphate availability and, thus, reduce excretion into the environment); or increased productivity in targeted animals (male-specific double-muscling). The possibilities, including the use of genetic engineering as a powerful research tool, are enormous, but there are many technological issues to be overcome, and societal issues to be addressed.

THE STATE-OF-THE-ART

Overview

Agriculture is charged with the unique responsibility to human health and social stability of feeding an expanding world population while minimising environmental and ecological risks. This responsibility, described by **Jim Womack**, goes beyond the industrialised world but has significant potential in the developing world (for example, by making use of the trypanotolerance of some African ruminants). The principle of exploiting livestock genomics is that it can contribute to this responsibility. In addition, livestock genomics can contribute to human health and wellbeing through the possibility of using animals to produce medicines or organs for human medicine. Although potentially contributing to human medicine, livestock genomics rides on the wave of the human genome project, and there have been massive advances in the field in the last 10 years. A relative lack of resources in the livestock field, however, means that major international collaborations are needed to drive the area forward.

Livestock genomics can be sub-divided into:

- *structural genomics* (the genome sequence and its variations);
- *comparative genomics* (the differences between different organisms); and
- *functional genomics* (how the sequence is expressed).

(2) From Steen, Prall and Plastow. (2005) Journal of Animal Science 83:E1-E8.

Following the human genome project, the National Institutes of Health (NIH), USA, called in 2002 for proposals on which organisms to sequence subsequently as model organisms. Although an increasing number of animals and pathogens are being sequenced, as yet the only livestock species genomes available are the chicken and the cow, with the pig and horse on their way. There is also some additional sequencing ongoing at a lower level, for example in some aquaculture species.

Following the sequencing efforts, work concentrating on gene mutations (assisted by the selection process of livestock species) and on gene transcription at the level of mRNA production associated with phenotype is underway, exploiting the major advances in high-throughput laboratory and computational techniques.

Structural genomics

Building on the overview, **Gary Rohrer** examined the genomics resources available for different species. Unsurprisingly, those for the human and the mouse, as a research model, far outnumber any available for livestock.

Species		EST Sequences	Reference SNP clusters
Human	*H. sapiens*	7,888,000	12,137,000
Mouse	*M. musculus*	4,719,000	6,491,000
Chicken	*G. gallus*	599,000	3,296,000
Cattle	*B. taurus*	1,039,000	26,000
Pig	*S. scrofa*	585,000	2,000

Data: Gary Rohrer

Chicken

The chicken genome sequence has a 6.6-fold shotgun and a 0.9-fold targeted coverage, funded principally by the US-NIH, and the US Department of Agriculture (USDA), and to a great extent sequenced primarily as a model organism rather than an agricultural animal. There is a wide SNP panel available that is currently being validated, plus many commercial projects funded by industry.

Cow

The bovine genome sequence has a 6-fold shotgun and a 1.2-fold BAC coverage. It has been funded by the US-NIH and USDA, plus the State of Texas, Genome Canada, US cattle producer groups, New Zealand and Australia. Identification of SNPs is ongoing, with a goal of identifying 100,000 SNPs and evaluating 40,000 in commercial lines. Gene prediction and annotation phases of the project are now underway.

Pig

The porcine sequencing project has just begun, aiming at a 3-fold BAC-skim and 3-fold shotgun coverage. Funding of the BAC-skim portion of the project is in place from USDA, while funding for the shotgun sequence is not yet complete, but includes a number of sources including the EU and US industry funding. There is a target to identify 100,000 SNPs.

Both the bovine and porcine sequencing projects were built upon the foundation of highly successful international collaborations to build physical BAC maps. These collaborations were followed by contributions from international

partners to fund the actual sequencing projects that then used a minimum tiling path of BAC clones to improve the coverage and quality of the sequence assemblies.

Equine

Recently, the US-NIH launched the sequencing of the equine genome. The project is nearing completion of a 6-fold shotgun sequence assembly and also has a component that will lead to development of genome-wide SNPs from a variety of breeds.

Next stages need to include the "finishing" of these genomes, and completion of annotation. In addition, there is a need to address what additional species should be sequenced: these might include salmonids, catfish, shrimp, oyster, turkey, quail, sheep, goat, rabbit and buffalo. There is an informal International Sheep Genome Consortium with US and EU contributors to an Australian-led project. The consortium has already sourced funds to build a BAC minimum tiling path and produce SNP resources, but wishes to progress to full sequencing of the sheep. Low level sequencing, and subsequent comparison with current genome data, would improve both current data and provide information on these additional species. As sequencing becomes ever cheaper, sequencing new species will be easier, but the long-term reduction in cost needs to be balanced against the potential benefits that may accrue from earlier sequencing. The construction of additional sequences, however, raises questions of who should maintain the data and control access. Curation and annotation of genome sequence is not a trivial cost and will need to be funded on a continuous basis.

High throughput SNP analysis and low-cost, high-quality arrays are important tools needed to finish and exploit the sequence data. In addition, a more holistic approach to the production of phenotype banks would make the next steps more effective. As the costs of genotyping and transcriptomics continue to fall, the limiting step to understanding the more complex traits such as disease resistance will be access to well phenotyped populations. To be effective, however, the populations need to be large and collecting phenotype data will be expensive, making collaboration desirable.

Comparative genomics

Building on the underlying structure, **Martien Groenen** described the lessons to be learned from comparative genomics. The utility of comparing genomes is based on three concepts:

- that selection purifies the target sequence; and, as a result,
- that important functional elements are conserved during evolution; and, therefore,
- that with increased evolutionary distance, the identification of conserved sequence to non-conserved sequence becomes more specific (higher signal-to-noise ratio), although at the cost of a loss in sensitivity.

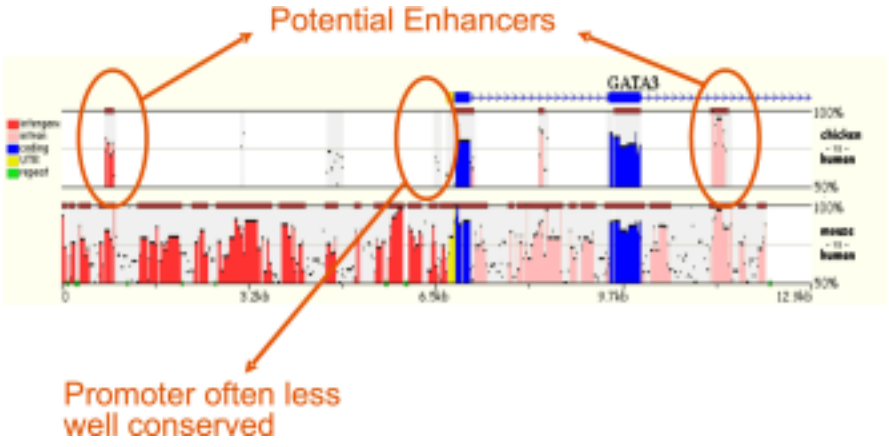


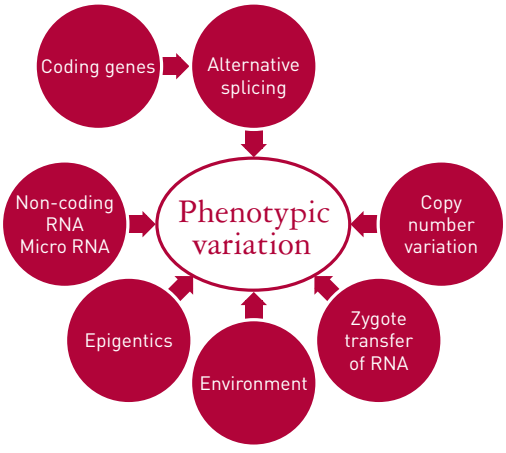
Figure 1:
Comparison of genome sequences: human-mouse and human-chicken. The greater the evolutionary distance, the greater the specificity. Courtesy Martien Groenen.

Importantly, not only are known functional elements conserved, but some apparently non-functional elements are conserved across different genomes. Why this is the case needs to be explained. Indeed, it is important to look at the correlation of all aspects of the sequence, whether structural, regulatory or simply unknown. Comparative genomics works both ways: rich sources of genome information from (for example) human and mouse can be used to help annotate livestock genomes, while information from livestock genomes can be of assistance in identifying functional elements of the human genome. The use of data from information-rich species will enable livestock genomicists to improve maps and identify genes. Identifying functional sequences in livestock genomes will help in predicting genes and regulatory elements in biological pathways in all species, including humans.

Comparing species with greater evolutionary distance will improve specificity. In Figure 1, comparing the two mammalian sequences for human and mouse (lower part of Figure) identifies many possible sequences of interest but the background makes the functional sequences (upper part of Figure) difficult to differentiate. The background can be reduced by comparing human with chicken sequences, which highlights two areas of coding sequence with other areas of conservation that might be predicted as acting as a regulatory element. The apparent lack of conservation of promoter regions is now thought to be the result of gradual changes (mutations) of the transcription factor binding sites during evolution, which is tolerated because of the high redundancy of both the sequence and location of these binding sites. The loss of specific binding sites is compensated by the gain of other binding sites at other locations within the promoters. Many of the same regulatory motifs are present across species but their order and number within a promoter region seem highly variable. Progressive changes in the genome between species assist also in the study of the evolution of genomes and to the identification of alleles, and their origin, thus contributing to genetic and population studies.

Functional genomics

With the decoding of the genome there was an assumption that organisms of a higher evolutionary level would have many more genes than less evolved species – i.e. the number of genes would be proportional to some function of the complexity of the organism. Clearly this is now known not to be the case. **Daniel Pomp** described how early estimates in the 1980s predicted that the human genome would consist of around 100,000 genes, current estimates are barely a fifth of this. The original premise that a gene was linked directly to phenotypic variation, or more accurately, each phenotypic variant was linked directly to a gene, has had to be revised. It has also led to the notion that the definition of a gene might need broadening.



It has become clear that phenotypic variation does not only rely on the gene, or even on some variation in the way that gene is translated, but on a whole range of external factors. This is evidenced by the fact that a specific phenotype might be associated with a large number of QTLs, but only a few genes. The result is that phenotypic variation is much more diverse than is genotypic variation. Attempting to put all these factors together in a system leads to the discipline of systems

Figure 2:
Factors affecting phenotypic variation.
Courtesy: Daniel Pomp

biology, which effectively brings the field back full circle to quantitative genetics – i.e. measurement of the final outcome rather than at the molecular level of the gene.

One method of analysing data is to compare, from microarray experiments, the positions of QTL that explain variation in a specific phenotype with the location on the chromosome of the related genes. In its simplest form, the QTL may relate directly to a gene ("cis-acting" QTL). Alternatively, one QTL may relate to a number of genes (a "master regulator"). As a third possibility, a QTL may, apparently, not be linked to a gene (so-called "trans-acting" QTL).

Dissecting complex traits

Many QTLs have been identified in different livestock species, but relatively few have been related to changes in specific nucleotides (QTN), according to **Jerry Taylor**. One reason for this, in cattle at least, is that selection for important QTLs has, typically, preceded domestication and is often not, therefore, breed-specific. These traits, even where useful, which is not always going to be the case, are effectively fixed across breeds. As a result, looking for changes across breeds is unlikely to be productive as they are likely to have the same, or similar, QTL. It would, therefore, be more productive to look for specific changes in half-sibs within different families. Using the half-sibs effectively filters out different QTLs, but this approach would need sufficient sequence data for individual animals to be compared at a level of sufficiently high resolution to identify the specific changes at the sequence level for every trait under consideration. Current high-throughput techniques, and reducing costs, begin to make this approach practical, but it would help to assemble databases of populations with important phenotypes. The same high-density genome information (such as panels of tens of thousands of SNPs) needed for such studies in well structured populations, also has potential for dissecting complex traits with genome-wide association studies in real-world populations that lack pre-existing pedigree information. Some drivers for such work are the economic benefits, making it attractive for industry support. This approach, then, raises the question of balancing the competitive nature of carrying out economically important work with the risk of repeating potentially expensive work held confidential under intellectual property protection.

Epigenetics

A rapidly developing field, described by **Jean-Paul Renard**, on how non-coding modifications can affect phenotypic variation, is the study of epigenetics. Although somatic cells in an organism all have the same genes, the phenotype of the cell can vary immensely (compare for example a liver cell and a neuron) depending on which genes are expressed and which are repressed. If the mechanisms for these non-gene coded alterations are heritable through mitosis, then they are termed epigenetic mechanisms; when stably inherited through meiosis they are called epimutations. Epigenetic states can be stable, but are potentially reversible during embryonic development in the germ line, in somatic cells (e.g. stem cell differentiation), in disease (e.g. epimutations in cancer) or during nuclear cloning. Mammalian genomes contain an additional layer of epigenetic information referred to as parental imprinting, where imprints are erased and reset normally in the germ line and passed on to offspring. One of the best known examples of an epigenetic effect is the inactivation of alleles on the X-chromosome leading to, for example, the tortoiseshell coat colour of female cats (where either the black or orange coat colour is expressed in different lines of cells within the same individual). As well as occurring in the germ line, resetting of the epigenetic effects can be seen in somatic cell nuclear transfer (SCNT) cloning.

Further examples, of agricultural relevance, are the callipyge muscle hypertrophy phenotype in sheep, where hypertrophic muscling is uniquely associated with the heterozygous animal

when the trait is inherited from the paternal line, and the IGF2 mutation in pigs where the 'lean' allele is silenced when inherited from the dam.

There is a range of known mechanisms by which non-coding modifications may affect expression, including changes in heritable chromatin; DNA methylation; histone modifications and variants, and their interactions with the highly conserved polycomb complex for the maintenance of gene expression states; asynchronous replication and nuclear compartmentalisation. Epigenetics is likely to play an important part in some traits of economic importance, and an array of tools and models will be needed to fully evaluate its role and, therefore, exploit its potential. An important research tool to help understand epigenetics, and its contribution to phenotype, is the ability to produce animals with the same DNA sequence, i.e. SCNT clones.

Genetic and genomic selection

One of the most economically important aspects of genome data is the possibility to use it for improving selective breeding. In comparison to traditional methods of selection – which are based on selecting for quantitative traits using breeding value estimates calculated from measured traits, genetic covariances among traits, and the pedigree relationships in populations – selection using genome information supplements phenotypic data with knowledge of the genotype of individuals in the population for known relevant gene variants (alleles). Gene-assisted selection is potentially more rapid. It also can be more easily applied to traits where the heritability is low and genetic change is slow, and traits that are difficult to measure. This presupposes, however, that the data on the trait and the QTL or the genes it links to are known. In turn, this means we need more data on genetic markers, particularly on SNPs.

Using genome data means that animals can be genotyped at birth. **Curt Van Tassell** described how this can be of help in selection. The breeding value of animals is normally estimated based on the characteristics of the parents (the parental breeding value, PBV). Enhancing this estimate using genomic information (the genome-enhanced PBV or GEPBV) means that traits that are not normally visible until later in life or are expressed in only one sex (e.g. milk production) can be estimated at birth. In addition, the GEPBV can be used to estimate traits not normally recorded, such as efficiency of nutrient utilisation and various animal behaviours.

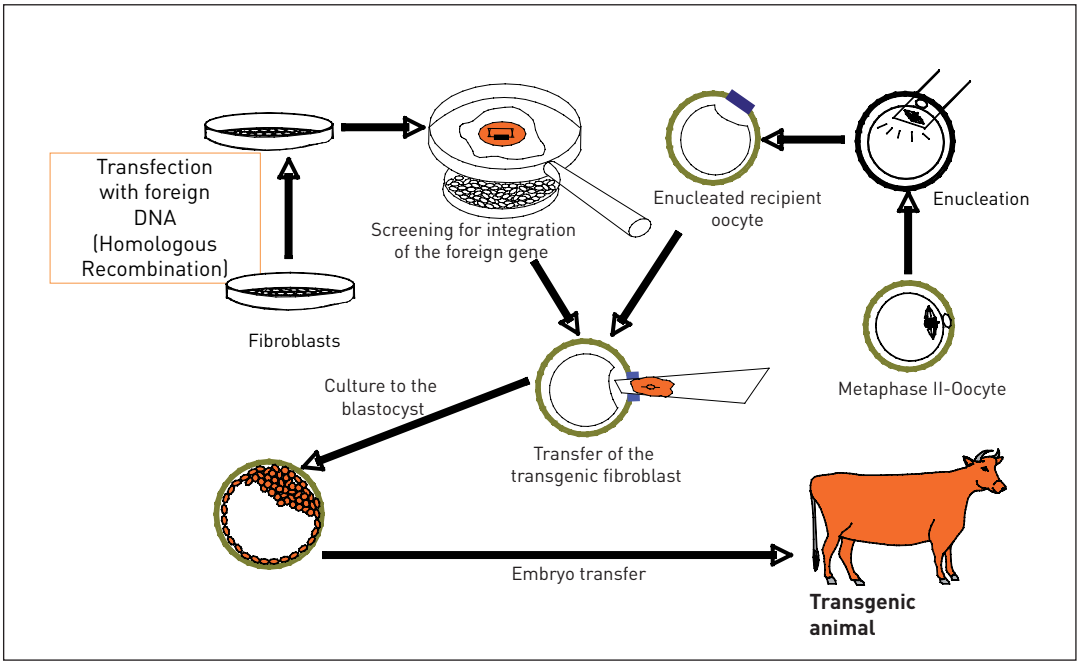
Going a step further, **Theo Meuwissen** described how breeding value could be estimated from summing the chromosome segment effects – that is summing along a chromosome the effects of SNPs (or sequence if available) on a particular trait. Theoretically errors should cancel out across the genome. The result from this 'genome-wide' selection is an EBV, of comparable robustness to a conventional EBV based on analysis of pedigree and phenotype data. Once the associations between chromosome segments and phenotypes are established, it should be possible to select without phenotypic information for a number of generations. This type of approach is particularly attractive for expensive-to-measure traits, or traits measured later in life. The most likely first application of this approach will be in dairy cattle where, in principle, bulls could be selected on the basis of genomic information alone and used for mating long before their progeny test results would be known – considerably reducing generation interval and accelerating progress.

Host-pathogen interactions

The importance of animal disease, and the complexity of the interaction of host and pathogen, was described by **Marie-Hélène Pinard van der Laan**. Pathogens react differently in different hosts, not just at a species level but also at an individual level, and the interaction of factors for resistance in the host and factors for virulence in the pathogen can lead to a wide variety of infection and disease states. QTLs for resistance and virulence require genomics information from the host and pathogen, respectively. The identification of resistance-based QTL will lead to the identification of breeding targets, and data on specific genes will further focus these targets. Bioinformatics developments will be crucial to realising the full potential of host-pathogen genomics. In addition, building on current collaborations, and on a defined set of hosts and pathogens, should deliver key results at as early a stage as possible. **Paul Coussens** used the example of Johne's disease (*Mycobacterium avium paratuberculosis*, MAP, infection) as an example of how the genomics of host-pathogen interactions can be used. The basis of the infection is that the organism infects, but is not killed by, macrophages. Using macrophages derived from monocytes (MDM), it has been shown that infection with MAP has profound effects on gene expression in the host, effectively preventing the macrophage from killing the bacterium, and that this expression varies between individuals. In this case, the molecular basis of the response is critical to understanding the process – unchallenged MDM isolated from blood shows as much overall variation as occurs between challenged and unchallenged cells. Not only does research like this lead to better understanding of the disease, it also opens up the possibility of selecting more resistant lines based on the gene expression of more resistant animals. It additionally provides the possibility of developing a more effective test for MAP.

Genetic modification

An exciting, though controversial, consequence of the knowledge of the genome sequence, is the possibility of manipulating genomes to enhance particular phenotypes. **Heiner Niemann** reviewed some of the possibilities. There are a number of methods of modifying the nuclear material within an animal, but the most common experimental method in livestock has been microinjection, whereby DNA-constructs are injected into zygotes. However, the results are not predictable, efficiency is low (of the order of 1-4%), the construct inserts randomly, and as its expression will be affected by where it inserts, this may be associated with variability in the effect of the transfer. As a result, efforts are now focusing on somatic cell nuclear transfer (SCNT) as a tool to make transgenic manipulation more reliable. SCNT has become more efficient over time, and is particularly so in pigs and cattle, where the proportion of successful transfers with live-born calves can reach as high as 25-30%. Very recently, significant



Source: Professor Dr. Heiner Niemann

progress has been reported for porcine SCNT: pregnancy rates after transfer of cloned embryos reach 70-80% with average litter size close to normal. Instead of trying to transfect a zygote, the process involves transfecting, a somatic cell. If a whole series of cells, e.g. fibroblasts in culture, are transfected, the most suitable (in terms of expression of the transgene) can be selected and then replicated using SCNT cloning. A main advantage of SCNT is that a specific gene locus can be targeted and the specific gene knocked out and/or a transgene inserted and, thus, expressed from this site. Thus, although SCNT cloning does not itself modify the nucleus, it is a technique that improves the production of transgenic animals in a significant manner. There are a wide range of potential applications of such technology. For example, agricultural (e.g. improved growth and development, wool production, disease resistance, reproductive performance, reduced environmental impact); biomedical ('pharming', bioreactors, blood replacements, xenotransplantation, disease models), and as a tool for basic research. Recently, the first recombinant product, Antithrombin III (ATryn® from GTC Biotherapeutics), derived from the mammary gland of genetically modified goats, has received regulatory approval for medical use, and is an example of the use of genetic modification for 'pharming'.

Bob Wall described work in transgenic cattle that indicated that incorporating the transgene for lysostaphin could reduce the frequency of infection of the udder with *Staphylococcus* spp., thus reducing the risk of mastitis. He also described some of the difficulties resulting from the use of transgenic animals for other processes. For example, while using animals as bioreactors to produce different products is technologically feasible, purification of the resulting product remains a problem. Similarly, xenotransplantation may not offer the prospect of permanent replacement organs – at least for solid tissues – but will more likely be able to supply "temporary" organs to prevent deaths of people while awaiting human tissues. It should be noted, however, that the highest demand for organ transplants is for vascular tissues which have less rejection problems. Finally, the complexity of the regulatory framework obscures the field and is in need of clarification if full potential is to be realised.

SOCIETY AND ETHICS

Societies' views from the USA and the European Union

Although surveys suggest that the public opposes the use of "animal biotechnology", the studies show that the question needs to be specified in more detail. Of the wide range of biotechnologies most, such as reproductive technologies (e.g. artificial insemination) and artificial selection, are actually relatively well accepted by the public. The two technologies that pose significant challenges, however, are cloning and genetic modification. **Alison Van Eenennaam**'s first point was, therefore, that the research community should be specific about what it means and, in particular, should not conceal the controversial technologies within the broader remit of "animal biotechnology", as this was likely to undermine all biotechnologies. Further the community of scientists working in this area needs to be very careful to differentiate between cloning and genetic modification of animals. There is a great difference in the US on the acceptance of cloning when well described as opposed to being generally included in the broad terminology of genetic modification of animals. It was also noted that providing increased information about biotechnologies does not necessarily mean increased acceptance of those biotechnologies.

Using an example of the difference in response of two counties in California to ballot initiative proposals to ban the use of GM crops, she drew some further lessons: where local producers, especially "family farmers" saw a specific advantage in the use of the GM product, it received more support, and the initiative was kept local – i.e. big business was kept out. In addition, making time available for discussion and being realistic about the advantages were seen as positive by the public for acceptance of the GM technology in plants. However, the use of GM animals has less support than GM crops, and the majority of people oppose the use of GM

animals (though with some support for use in producing human health products). The additional opposition of using GM technology in animals, and to some extent cloning, is primarily on moral and ethical grounds, values which vary widely, and the question is how to take account of these in decision making. For example, when an objection is a moral one not shared by all, how important is individual freedom of choice? Most scientists also agree, for example, that there are moral and ethical issues in cloning and GM technologies in animals, but their response to these issues is different from the public at large.

The results of some studies of public perceptions suggest substantial similarities between Europe and the USA: genetic manipulation in animals raises more concerns than it does in plants, and medical applications are more acceptable than food-related applications. In Europe, there is significant scepticism about the benefits of science but, as in the USA, the response depends very much on the question being asked and systematic comparison between the views of US and European citizens is needed to substantiate such views. In addition, people make a judgement about perceived advantage, benefit or need, and trade these off against the perceived risks, unnaturalness or ethical considerations. For example, use of genetic modification for pharmacological reasons is generally perceived to be more acceptable than applying genetic manipulation to animals to change meat composition. How people make trade-offs between risk and benefit depends on individual attitudes, the magnitude of the perceived risk and the benefit associated with a specific application, the information available and the level of trust in the information source. A societal perception that the "truth is being hidden" from the public at large is associated with distrust, indicating the need to increase transparency in regulation. It is also important to communicate uncertainty and population-level variability associated with different potential hazards and benefits. An additional factor of relevance relates to how effectively the risks, and indeed benefits, of specific technological applications are perceived to be managed. For example, there is evidence that communication about proactive risk management and mitigation approaches creates consumer confidence in risk governance and regulation. **Lynn Frewer** discussed these issues in the European context, and suggested that socioeconomic factors associated with risk and benefits and ethical issues should be added to the normal risk assessment for new technologies. In that context, it is important to balance the risks of not doing something with those of doing it. In general, when a personal advantage is perceived to result from a new application, it may outweigh the perceived risks. However, when these risks are seen as very high, they may override any perceived benefits.

Animal cloning and genetic modification

Ilias Papatryfon described a project to map research and commercial activities worldwide for animal cloning and genetic modification. The project [3] aimed to identify technical and commercial drivers and barriers and to address policy and socio-economic implications raised by animal cloning and genetic modification. The number of published papers on cloning increased over the decade 1990-2000 but this has since levelled off. Most of the work was done in the USA, with Europe coming third (after the Far East). The work concentrated on technical aspects and was mostly publicly funded. The number of published papers on animal GM increased over the period 1985-1998 and then levelled off, with most coming from the EU, followed by the USA. Most of the key research identified as important related to basic mechanisms of embryo development, large offspring syndrome, gene manipulation technology and deriving embryonic stem cells – and only after these key areas was animal breeding identified as a "priority". Most commercial research in the field appears to be for 'pharming'. Within the EU, there seems to be no commercial activity at all in relation to using the technologies for food applications, but elsewhere in the world (including the USA) there is such work. However, while safety is a key driver in the food sector, there appears little consensus on what to measure in relation to making risk assessments for GM animals. The commercialisation of GM fish in North America is likely to raise the profile of the issue in the near future. Meanwhile, the commercial use of cloning for agricultural production would seem to be restricted in the short term to cloning bulls and maybe boars – with commercialisation of the offspring.

(3) Animal cloning and genetic modification. A prospective study JRC IPTS. European Commission, Seville. In preparation.

Lessons from the agronomy industry

Emphasising the need to ensure a connection with public attitudes, **Simon Barber** described some of the problems that had occurred in Europe with the (non-)acceptance of plant biotechnology as a disconnect between plant breeders and consumers and, to some extent, between plant breeders and retailers/processors. In contrast, links between plant breeders and producers remained strong. Reiterating the notion of trust, in relation to GM crops, the consumer appeared to trust NGO and press sources more than industry, underlining the need for industry to develop better links with consumers. It was also apparent that the precautionary principle where, in the absence of hard data, policy is developed on the basis of extra caution, was rarely used objectively, but rather to support a pre-defined opinion (either for or against).

APPENDIX I
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APPENDIX II
Abstracts of presentations

The Potential of Genomics Technologies

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Domestic animals form a unique genomics resource as a result of their remarkable phenotypic diversity and of their population structures which make them particularly suited for positional cloning (identifying genes through their position on the chromosome rather than through their function). Recent progress in characterising the genomes of domestic animals, including the identification of large numbers of single nucleotide polymorphisms (SNPs), will have a major impact on our ability to identify genes and mutations underlying this phenotypic diversity, including morphology, behaviour, disease susceptibility and – last but not least – traits of agronomic importance. Moreover, advances in cost-effective SNP genotyping technology combined with novel statistical-genetics procedures, paves the way towards 'genomic selection' (GS). GS is anticipated to provide a major boost to 'marker assisted selection' of livestock in the very near future. Finally, the availability of whole genome sequences, improved understanding of gene function, and advances in gene targeting and cloning should provide novel opportunities for the genetic engineering of useful strains of livestock.

The State of the Art of Livestock Genomics: An Overview

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Agricultural science has the unique responsibility to human health and social stability of feeding an expanding world population while minimising environmental and ecological risks. The foundation of livestock genomics was a promise that it could play a significant role in meeting this global challenge.

Domestic animal genomics has followed closely in the footsteps of the human genome initiative, adopting both its successful strategies and technologies to advance our understanding of livestock genomes with meager budgets relative to the resources available for human and medical research. Early attempts to construct whole genome maps of livestock species were based on the two technologies underlying the first human genome maps: somatic cell genetics and *in situ* hybridization. These early maps defined synteny

(genes on the same chromosome but not necessarily linked) and cytogenetic locations of sequences hybridising specific DNA probes. These strategies proved extremely important to early comparative mapping because the mapped markers were generally genes or gene products, highly conserved across mammalian genomes. Linkage mapping, however, lagged behind, awaiting the development of highly polymorphic markers with sufficient density in the genomes of outbred animal populations to efficiently map traits using whole genome approaches. Beckmann and Soller, inspired by advances in human genetics, were early proponents of the use of DNA level markers for building maps and mapping traits in livestock species. Several international workshops in the early 1990s resulted in cooperation in the development of linkage maps and other tools that were important to the initiation of our current genome sequencing projects. These early linkage maps have been refined and expanded and have become effective tools for mapping loci that influence biologically and economically important traits, including quantitative trait loci (QTL). Unfortunately, a substantial backlog of QTL is developing in all the livestock species with only a very few specific mutations underlying the QTL having been identified.

Genome sequencing, database development, expression arrays and SNP maps with automated genotyping are rapidly becoming components of our genomic toolbox, providing promise for genome mining and gene discovery. Gene sequencing and SNP discovery in our domestic animal species will soon give us information about linkage disequilibrium over large genomic regions and the identification of haplotype blocks in various populations and breeds of livestock. RNA interference is already a tool for experimental modification of gene expression in animals and may soon find its way into animal improvement, probably in conjunction with cloning from modified somatic cells. The future has never been brighter for livestock genomics. Our resources are still meager, however, relative to those targeted to human medicine. Hopefully, we will not abandon the spirit of international cooperation that has been so important in getting us to where we are with a fraction of the fiscal outlay for other genomics programs.

Livestock Genomics Architectures

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Livestock animals have provided a high-quality, readily accessible protein source for human consumption since their domestication. In addition, man has continuously modified the genomes of these species through a variety of selective breeding practices for traits ranging from growth, composition, color and disposition. The results have provided populations of pedigree animals with detailed phenotypic information that have tremendous potential for unlocking the secrets hidden in the billions of bases that make up an organism's genome. Unfortunately, livestock genomics has to retro-fit genomic tools developed for human and mouse genomics in order to conduct state-of-the-art research. Recent developments have provided (or will provide) the genomic sequence for the chicken, cow and pig and it is imperative that this research be continued so as to develop the additional tools necessary for capturing the value from our investment into these populations and genome sequencing projects. The numbers of expressed sequence tags for livestock species in GenBank (range from 0.6-1.0 million submissions) are dwarfed by the 4.7 and 7.7 million submissions for mouse and human respectively. Only recently have there been enough sequence data to develop nearly comprehensive species-specific gene chips for these farm animals. A more dramatic trend, with the exception of the chicken, is observed for SNPs in dbSNP of GenBank. Total submissions for human (28,828 k), mouse (8,751 k) and chicken (3,642 k) are several orders larger than for cattle (21 k) and pig (6 k). Definite needs for the genomics community include collection of near-finished sequence for these three important species, species-specific annotation to prevent the "humanisation" of the annotated genome and SNP development to permit genome-wide association studies in the valuable existing populations. Once these tools are developed it is imperative that continued funding is available for scientists to use them to answer important biological questions.

Livestock Genomics: Lessons from Comparative Genomics

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In livestock species, comparative genomics has played a major role in the transfer of information from information-rich species such as human and mouse to the less well studied livestock species. The high degree of conservation of synteny and gene order in animals enables the prediction of genes within regions of the genomes of farm animals where QTLs have already been localised. The successful identification of the causative mutations underlying some of the QTL has been based on the use of this conserved synteny. Recently, the number of species whose genome has been sequenced has increased enormously and the genomes of several livestock species are now available (chicken, cow) or will become available in the near future (pig). The use of comparative genomics for the identification of genes underlying QTL, however, is still relevant for those species whose genomes have not (yet) been sequenced (turkey, sheep, duck, salmon).

With the increasing number of animal genomes being sequenced, the classical use of comparative genomics as a tool to transfer information across species is no longer its major application. Instead comparative genomics has become an extremely powerful tool for the identification of conserved non-coding elements in vertebrates and in our understanding of the molecular mechanisms underlying genome dynamics and the evolution of the different species. This will open up a whole range of possibilities for understanding the gene content in relation to species of an organism. Likewise, the availability of the genome sequence of closely related species (e.g. human vs. chimpanzee) is extremely useful for the identification of ancestral alleles and recent selective sweeps. In this case, comparative genomics focuses on the differences rather then on the similarities between the genomes and for many livestock closely related species are available that allow the same approach to be taken (e.g different pig species such as *S.scrofa, S. barbatus, S.verrucoses, S. celebensis*).

Currently, one of the most powerful uses of comparative genomics is the genome-wide identification of conserved regulatory elements in vertebrates. It is estimated that although only 1% of a typical mammalian genome directly codes for proteins, more the 5% of its genome consists of conserved functional elements, most of which are thought to be involved in the regulation of gene expression. Vertebrate genomes contain a variety of regulatory elements differing in their functions and their degree of evolutionary conservation. The highest degree of sequence conservation is observed in the so-called ultra-conserved elements which are often found as clusters in the vicinity of genes coding for transcription factors active during the development of the embryo. Because of the excellent signal to noise ratio, bird (chicken)-mammal comparison is an extremely powerful tool for the identification of such non-coding, conserved regulatory elements. Despite conservation of the regulation of expression of related genes, promoter regions often lack clear overall sequence conservation. Most of these elements consist of multiple binding sites for a variety of transcription factors characterised by a high degree of degeneracy. Although, these binding sites are more difficult to predict, new bioinformatics tools are being developed that increasingly enable the identification of such binding sites even in the absence of clear overall sequence conservation. Recently it has become clear that, in addition to this form of gene regulation, genes are also being regulated through the action of so-called microRNAs (miRNA). These miRNA are short RNAs of only 22 nucleotides that are complementary to sequences in the 3'end of the mRNA of protein coding genes. They are thought to regulate gene expression through sequence-specific base pairing with their target RNAs. It is estimated that vertebrate genomes may contain as many as 500 to 1,000 of these miRNA. Approximately one-third of the miRNA genes are highly conserved even between distant species and thus can be easily identified by comparative genomics.

Functional Genomics – So Much Variation from a Few Thousand Genes

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Thousands of genetic disorders exhibiting Mendelian inheritance have been described in animals and humans, and the molecular basis for many of these has been identified. In contrast, most economically relevant traits in animal agriculture, and most common human maladies such as obesity, exhibit continuous phenotypic variation and a predominantly multifactorial and polygenic basis. While certain rare mutations have been identified, accounting for a small minority of extreme phenotypes, the actual nature and identity of genes segregating and contributing to common phenotypes in populations is essentially unknown. As an example, over 300 QTL have been reported for growth and body composition traits in the mouse, likely representing at least 100 distinct genes, but only a handful of these have been localised at the gene level. These gaps in knowledge and capability between the ease of QTL mapping and the difficulty in identifying the underlying genes dramatically limit the ability to harness the promise of genomics for the betterment of food production and human health.

Systems biology is the study of an animal viewed as an interactive network of many genes, proteins, mechanisms and the animal's external environment, combining to determine an individual's complex phenotype. When viewed in this manner, systems biology can be considered as the legacy of traditional quantitative genetics, which focused on the end phenotype as the substrate for genetic improvement. It is now hopeful that the tremendous power of functional genomics will enable this legacy to be fulfilled by facilitating the discovery of the genes and the functional genetic variations that underlie economically and biomedically important traits.

The use of microarrays for global phenotyping of gene expression is the primary method of functional genomics. While microarray analysis has a plethora of uses across nearly all areas of biological research, one particularly powerful application is to synergistically harness the powers of recombination and functional analyses in a method known as 'Genetical Genomics', or expression QTL (eQTL) mapping. This paradigm treats gene expression levels of any particular transcript measured across different individuals in a segregating population as a complex sub-phenotype that in principle reflects part of the underlying genetic variation of a trait being studied. eQTL mapping has been highlighted as a powerful mechanism to dissect complex traits and make the selection of candidate genes underlying QTL more efficient, with early successful implementation in many species including yeast, Drosophila, Eucalyptus, humans, rats and mice.

The knowledge being harnessed by functional genomics and eQTL mapping on the nature of complex trait variation opens up new avenues for understanding gene regulation. For example, variation in the expression (and potentially the function) of some genes is regulated in cis – where a polymorphism within or near the gene itself self-regulates its mRNA abundance. Other genes are regulated in trans – where one or more polymorphisms that are unlinked to the gene itself explain variation in the gene's mRNA abundance. And fascinating findings based on eQTL mapping suggest the presence of 'master regulators' of quantitative trait variation, whereby polymorphisms at a single locus may help regulate variation in gene expression for thousands of other genes.

What is emerging from functional genomics studies in animals is that the genome, although represented by a relatively finite number of expressed genes, has the potential to generate an essentially unlimited amount of phenotypic variation. Furthermore, such phenotypic variation can have tremendously complex underpinnings. And finally, the nature of the genes that harbor variation controlling complex traits can be extremely unpredictable.

Dissecting the Genetics of Complex Traits

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In 1990, three research groups initiated mapping projects to discover genes that were responsible for variation in growth and meat quality traits of beef cattle. All three used crosses among *Bos taurus* and *Bos indicus* cattle to maximise the likelihood of detecting quantitative trait loci (QTL) of "large effect" on phenotype – assuming that these QTL existed. This hypothesis was proven correct and all three projects identified chromosomes harboring numerous QTL. Sixteen years later, following a great deal of work worldwide, the majority of the QTL themselves remain unidentified and tests are commercially available for mutations in only 6 genes (GDF8, CAST, CAPN1, TG, RARG and LEP) putatively associated with beef production traits. Our inability to identify the causal mutations underlying QTLs has made it impossible to implement marker-assisted selection in commercial populations, since allele phase relationships for linked markers are generally unknown. There are several reasons for the low rate of QTL and quantitative trait nucleotide (QTN) identification in beef cattle. Possibly paramount has been the misconception of the importance of mapping within subspecific crosses rather than in commercially relevant populations. Not only is this approach resource-intensive, but the parental breeds have fixed nucleotide differences about every 2-kb which guarantees that any causal QTN will be unidentifiable against the background of subspecific genetic differences. Second has been the small number of studies that have been performed in large mapping populations, primarily due to the cost and logistical difficulty of scoring whole genome (WG) marker maps in a large number of samples. Third has been the lack of a WG sequence for cattle for evaluating positional candidate genes and the sequencing of these candidate genes to identify potential QTN, whether they lie in coding or regulatory regions. Fourth has been our inability to rapidly identify and screen mutations within a QTL-critical region and identify which is the causal QTN. With the release of the third assembly of the bovine WG sequence, the availability of highly multiplexed and high-throughput single nucleotide polymorphism (SNP) genotyping, and the imminent availability of low-cost whole-genome resequencing technologies, most of the limitations to QTN identification will soon be overcome. Using these technologies, we have designed a strategy for massive, parallel QTN identification as follows: 1) we have assembled 15,000 DNA samples on commercially produced cattle with pedigree and phenotype or expected progeny difference (EPD) data; 2) we are designing a low-cost custom assay which produces genotypes for up to 60,000 SNPs in a single assay; 3) we shall use this assay to map QTL in a large group of half-sib families and will simultaneously identify the location of QTL and the segregation status of each of the sires for each QTL; and 4) we shall resequence the whole genome of the sires of these families in order to identify all mutations within QTL regions that are concordant with the QTL segregation status of the sires. The number of families that are genotyped influences the power for QTL detection via the number of families that segregate for each QTL which, in turn, is a function of allele frequency. The number of families also influences the power for QTN identification via the number of animals that will have concordant genotypes for the QTL and detected mutations. The number of individuals within each family also influences the power for both QTL and QTN detection via the number of sires for which segregation status at a QTL can correctly be identified. This strategy does not require a functional analysis of each detected mutation to infer causality and support its utility for marker-assisted selection programs.

Epigenetics

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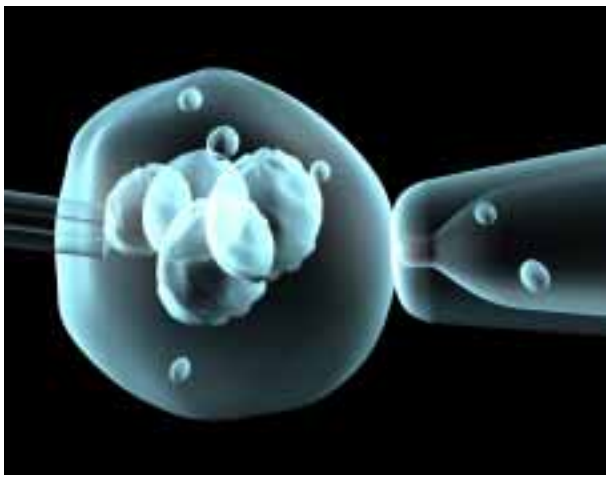
Epigenetics describes the study of heritable changes in genome function that occur without a change in DNA sequence. This includes the study of how patterns of gene expression are passed from one cell to its descendants, how gene expression changes during the differentiation of one cell type into another, and how environmental factors can change the way genes are expressed.

The idea that epigenetic mechanisms have a significantly more important role than previously thought in the production traits of livestock is supported by two different lines of evidence.



First, the identification of epigenetic sources of variation at specific loci controlling tissue development and function. This new understanding of the genetics of complex traits is exemplified by the two paradigmatic cases of the callipyge (double muscle-like) phenotype in the sheep and the control of the IGF2 gene and its receptor in the pig. Second, cloning experiments which led to the generation of healthy and fertile adults has extended our view on the importance of epigenetics in the functional plasticity of the genome. Although these clones represent only a few percent of the reconstructed embryos, they demonstrate that gene activities can be fully reprogrammed during embryonic and fetal development without alteration to the genome-contained DNA sequences.

Chromatin changes are closely associated with epigenetics. The discovery that enzymes such as methyltransferases and acetylases can (re)organise chromatin into configurations accessible or inaccessible to the regulators of gene expression has led to the view that one genome can generate several 'epigenomes' as the fertilised egg progresses through embryonic and foetal development. The effect of these enzymes provides support at a molecular level to the complex mechanisms that lead to persistent effects of maternal nutrition or transient postnatal dietary challenge on the physiology of the offspring when adult. The best known epigenetic modification is DNA methylation reflected by changes in the methylation of cytosine residues in CpG dinucleotides, often present as repeats (also termed islands) in the genome. An important step in livestock species with a fully sequenced genome would be to identify all these CpG islands to provide a screening tool (array) for the analysis of differentially methylated regions. When applied to sets of adult clones with the same initial genotype, this tool would contribute to defining the genomics of the key physiological functions of an organism. Since patterns of DNA methylation are determinants for the correct functioning of non-imprinted genes involved in the development of the lymphoid system or of the glucocorticoid response, this tool would provide a sensitive readout of the epigenetic status of the genome of livestock for the combined use of molecular genetic testing and epigenetic analysis. This would permit the improvement of traits such as immune competency, disease and stress resistance, which are of low heritability.

The extension of this approach to other epigenetic modifications (histone acetylation) will offer new opportunities for the selection of traits that contribute to the robustness of animals, i.e. their ability to maintain their economic potential when exposed during pregnancy to unpredictable environmental and genetic effects. As such, epigenetics will contribute not only to more economic livestock production, but also to the study of the ontogeny of key physiological functions and their interaction in health and disease.

Use of Genomics Information in Selection

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Genetic improvement of dairy cattle has proceeded rapidly for milk yield, even approaching theoretical maximums based on population genetics principles. Current technologies result in over 200 pounds (90kg) of genetic improvement in milk yield per year and approximately 7 pounds (3kg) of genetic gain in fat and protein yield per year. The rate of genetic improvement for traits other than production and conformation, particularly those related to fitness, has

been far less successful, however. For example, there has been a consistent genetic deterioration in fertility as measured by daughter pregnancy rate over the last 40 years. The U.S. national herd is comprised of approximately 9 million dairy cows, and about 95% of those cows are Holsteins. Each year the artificial insemination (AI) organisations progeny test about 1,200 Holstein dairy bulls at a combined cost of $30 million. Even a marginal reduction in cost of progeny testing, or a modest increase in genetic enhancement, will have enormous impact on the profitability. Bovine genomics has entered a new era and is being transformed with the availability of the whole genome sequence. A white paper proposing shotgun sequencing of the cow was submitted in 2002. The shotgun sequence component of the bovine genome project has been based exclusively on an extensively in-bred Hereford cow, L1 Dominette 01449. The first draft was released in October 2004. The bovine genome project is expected to deliver a high-resolution sequence assembly in the very near future. Identification of potential single nucleotide polymorphisms (SNP) across breeds was made possible through genome sequence derived from cows of six additional breeds. While the promise of genomics is starting to impact genetic improvement in dairy cattle, the utilisation of this technology in livestock has been limited because quantitative trait locus (QTL) and causative mutation, or quantitative trait nucleotide (QTN) identification, has been slow and expensive. With the availability of high throughput SNP genotyping, the application of genome-wide selection seems tantalisingly close. However, hurdles must be cleared before this technology can move forward. First, a reduced set of SNPs needs to be identified that makes application by industry partners feasible and integration of genomics into the genetic evaluation system tractable. Second, algorithms need to be developed or modified to infer haplotypes in a broad sampling of variously related Holstein bulls. Finally, and most importantly, implementation of genome-wide selection is needed. This integration will send a clear message to industry partners that genomics has become an integral part of the estimation of genetic merit in the post-genome sequence era.

Genomics of Host-Pathogen Interactions: General Aspects

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The production of healthy animals is a major demand from breeders and consumers, both for economic reasons and because of increasing concern about food safety and animal welfare. Disease development is the result of complex interactions between host genetic factors, pathogen genetic factors and environmental factors. While traditionally disease control has been relying on the use of intensive treatment, new opportunities for control arise from the potential development of host-pathogen interaction genomics research. New technologies such as new therapeutics and vaccines, improved diagnostics or selective breeding for resistance are expected to be developed from a genomics approach.

Research and further application in genomics of host-pathogen interactions require advanced knowledge in: 1) the genome structure of hosts (ex. genes, regulatory sequences ...) and pathogens (ex. virulence factors...); 2) the genetic variation explaining the observed differences for host responses to diseases and pathogen virulence; and 3) ultimately the biological immune mechanisms underlying the interactions between the host and the pathogen. While significant progress has been made recently in analysing host and pathogen genomes, thanks mainly to international collaborations (eg. sequencing programmes), deciphering the underlying mechanisms still requires significant effort.

Clearly, studying genomics of host-pathogen interaction requires integration between different disciplines: immunology, parasitology, pathology, epidemiology, structural genomics, population genetics, functional genomics, bioinformatics and so on. While most studies to date

on host genomics have mainly concentrated on the genetic variability to diseases and QTL searches and some practical applications, very promising and complementary approaches are now becoming widely applied using transcriptomics. Well defined disease phenotypes in specific animal populations are necessary tools for functional genomic studies. For example, comparing gene expression in susceptible or resistant animals may be of great benefit in identifying genes involved in resistance and in predicting and testing gene function.

In conclusion, genomics provides valuable tools to develop improved disease control in animals. But these applications remain very scarce, due particularly to fragmentation of research across the different countries and the different fields of expertise needed. To confront this issue in Europe a European Network of Excellence, EADGENE (European Animal Disease Genomics Network of Excellence for Animal Health and Food Safety – www.eadgene.org) has been initiated (2004-2009). Gathering 13 partners from 10 countries, it brings knowledge, animal and genomic resources, coordinates research in order to apply genomics as a tool to improve animal health by linking research and industry. On a broader level, for example between the USA and the EC, such international cooperation needs to be developed and strengthened.

The Use of Functional Genomics to Decipher Complex Host-Pathogen Interactions: Bovine Paratuberculosis

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Johne's disease, a fatal wasting syndrome in cattle and other ruminants, is caused by *Mycobacterium avium* subspecies *paratuberculosis* (MAP), an intracellular bacterium that resides in host macrophages. A related bacterium, *Mycobacterium avium* subspecies *avium* (MAA), is not pathogenic in cattle and is readily destroyed in bovine macrophages. There is a controversial link between MAP and human Crohn's disease, and MAA causes pulmonary infections in immune-compromised humans. Given the importance of these organisms to domestic animal agriculture and the biomedical community, our research has focused on understanding three main issues: 1) why MAP and MAA are not destroyed by host macrophages; 2) why the appropriate and effective Th1-like immune response to MAP wanes during infection, and 3) if a long-term chronic infection, such as MAP, has a detectable effect on host peripheral leukocyte gene expression patterns.

To more fully understand why MAP is not efficiently killed by host macrophages, we have used gene expression profiling to compare the response of monocyte-derived macrophages (MDMs) to both MAP and MAA. Statistical analysis of microarray data revealed significant differences in expression of 30 genes in MDMs infected with MAP or MAA. Expression of selected genes was validated in MDMs isolated from five healthy cows by Q-RT-PCR. Our data support the notion that MAA is a stronger activator of MDMs, particularly with regard to Fas-ligand and TIMP 1. It also appears that MDMs from different donor cattle sort into two groups of high and low responders in expression of IL-6 mRNA, possibly signifying genetic differences. IL-6 gene expression is regulated via the MAPK pathway, and we have begun exploring potential differential activation of this pathway by MAA and MAP in MDM cells.

Our numerous functional genomic studies of cattle naturally infected with MAP have led to a proposal that regulatory T cells may be an important factor in progression of MAP infection. Regulatory T cells producing IL-10 could be responsible for the apparent loss of a Th1-like response and would thus allow MAP to proliferate inside host macrophages in an uncontrolled manner. We have used various methods to determine if regulatory T cells arise during MAP infections in cattle, and data from these preliminary studies will be presented.

In analysing data from over 20 microarrays comparing gene expression patterns in total leukocytes from cattle naturally infected with MAP to those from uninfected control cattle, we had observed numerous differences that seemed to correlate well with infection status. Significant among these gene expression differences were genes encoding GATA-3, p-Selectin, and CD30. Together, these studies suggested that gene expression patterns in total

leukocytes might be specific enough to form the basis of a new diagnostic method for long-term chronic infections. To evaluate this, we have isolated mRNA from total leukocytes of 100 cattle naturally infected with MAP and from 50 healthy control cattle. We are currently analyzing expression of 45 genes, suggested to be differentially expressed by microarray experiments, using a high throughput Q-RT-PCR procedure.

Engineering change – Genetic modification of farm animals

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The first transgenic livestock were produced almost 20 years ago by microinjection of foreign DNA into the pronuclei of zygotes. Until recently, pronuclear microinjection of DNA was the standard method for producing transgenic animals. This technique is now being replaced by more efficient protocols based on somatic nuclear transfer which also permit targeted genetic modifications. To date, somatic nuclear transfer has been successful in 11 species, albeit at low efficiency. Lentiviral vectors and siRNA technology are also becoming important tools for transgenesis. Further qualitative improvements may be derived from technologies already known in mice that allow precise modifications of the genome, including targeted chromosomal integration by site-specific DNA recombinases, such as Cre or FLP, or methods that allow temporally and/or spatially controlled transgene expression. The genomes of the first domestic animals (cattle, chicken, dog) have been sequenced and annotated recently. Thus, after 12,000 years of domestic animal selection based on the random mutations caused by radiation and oxidative injury to the genome, technology is now available to introduce or remove known genes with known functions.

Transgenic farm animals are likely to be important in human medicine as sources of biologically active proteins (gene 'pharming'), pigs may serve as organ donors in xenotransplantation, and for research in cell and gene therapy. The first recombinant protein (human antithrombin III, ATryn®) produced in the mammary gland of transgenic goats has recently been approved by the European drug supervisory agency (EMEA). Typical agricultural applications include improved carcass composition, lactational performance, and wool production, as well as enhanced disease resistance and reduced environmental impact. Product safety can be ensured by standardisation of procedures and monitored by PCR and array technology. As sequence information and genomic maps of farm animals are refined, it becomes increasingly practical to remove or modify individual genes. This approach to animal breeding will be instrumental in meeting global challenges in agricultural production in the future.

Transgenic Livestock – Still an Immerging Technology

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Transgenic livestock have been oversold. They have not met the promise of revolutionising the pharmaceutical industry by producing drugs inexpensively while shrinking product development time. Neither have they met the promise of enhancing livestock production efficiency by improving carcass composition, increasing food safety or boosting animal wellbeing. They have failed to achieve their promises for a mixture of technical and sociological reasons. Now that the initial irrational exuberance has subsided, it is time to

consider strategic options that will advance the potential of this technology in a more reasoned fashion. One of the most powerful aspects of transgenic technology is its ability to move genetic information across species barriers. An example of this approach, designed to enhance animal wellbeing and increase profitability, is in the dairy sector. Mastitis is a disease of the mammary gland caused by both contagious and environmental pathogens that find their way onto every dairy farm. These mammary gland infections cost the US dairy industry approximately $2 billion dollars annually and have a similar impact in Europe. In the absence of effective treatments or breeding strategies to enhance mastitis resistance, we have genetically engineered dairy cows, with the aid of somatic cell nuclear transfer, to carry a sequence for lysostaphin fashioned after a gene from *Staphylococcus simulans*. Lysostaphin is a highly specific antimicrobial peptide that targets *Staphylococcus aureus*, the most tenacious of the mastitis-causing pathogens. Milk from these transgenic cows kills *S. aureus* in a dose-dependent manner and the cattle resist mammary gland infections. The presence of this new antimicrobial in the milk does not appear to alter the structure or processing properties of milk. This first step in protecting cattle against mastitis will be followed by introduction of other genes to deal with potential resistance issues and other mastitis-causing organisms. Care will be taken to avoid altering milk's nutritional and manufacturing properties. Multi-cistronic constructs will be required to achieve our goals as will other strategies such as gene targeting technology. This work demonstrates the possibility of using transgenic technology to address disease problems in agriculturally important species.

Animal Cloning and Genetic Modification: a Prospective Study

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Technical developments in animal cloning and genetic modification (GM) seem to be on the verge of commercialisation, starting to attract public attention and raise new policy issues. While the two technologies are often discussed together, as they are considered part of the same group of modern biotechnologies, they are distinct by nature and therefore present different technical, ethical and regulatory challenges. Further complications arise as these technologies may be applied simultaneously to the same animal to benefit from the advantages that each has to offer. Both technologies may find different applications, mainly in food production, production of pharmaceuticals or other novel compounds through molecular 'pharming', xenotransplantation, pets, sporting animals and endangered species, while providing at the same time powerful tools with which to investigate biology as well as a focus for public debate on science and society.

To address these issues, the JRC/IPTS embarked on a prospective study on animal cloning and genetic modification with the following objectives: to map research and commercial activities worldwide, to identify and analyse the drivers and barriers for future development and adoption, and to address current and future policy and socio-economic implications raised by the adoption of the two technologies. The study was carried out through the European Science and Technology Observatory (ESTO) and with the collaboration of leading experts in the relevant fields, namely Innogen (the ESRC Centre for Social and Economic Research on Innovation in Genomics), UK; the Roslin Institute, UK; the Genesis Faraday Partnership, UK; the AHRC Centre for Studies in Intellectual Property and Technology Law of the University of Edinburgh, UK; and the Future Technologies Division of the German Association of Engineers (VDI TZ).

The timeliness of undertaking this activity seems to be justified as results point out that cloned livestock are expected to be used within the food chain somewhere in the world before 2010, while GM salmon are awaiting regulatory approval in North America, Asia and South America. Meanwhile, ATryn® (GTC Biotherapeutics, Inc.), a human antithrombin product produced in the milk of genetically modified goats, is the first molecular 'pharming' product from animals, having received a positive opinion for market authorisation (June 2, 2006) from the European Medicines Evaluation Agency's (EMEA) Committee for Medicinal Products for Human Use. It awaits final market authorisation by the European Commission in the following

months. Moreover, a few new products are estimated to be at or near market and are likely to be commercially available within the next five years, on the basis of evaluation by the commercial companies themselves. Roadmaps were created to assess the factors that will be crucial/influential in the future adoption of the technologies by various commercial sectors, as well as to shed some light into the possible impacts and implications this may have for society, including issues of international relevance such as research and trade.

The Views of Society on the Medical and Agrifood Uses of Animal Livestock Biotechnology – The U.S. Perspective

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Many polls have concluded that the majority of Americans are opposed to animal biotechnology. However, biotechnology encompasses a broad range of techniques for the genetic improvement of domesticated animal species and included in such polls is the finding that 50% of Americans find traditional animal crossbreeding practices morally wrong. Given the sketchy knowledge many people have regarding animal production practices, it becomes essential to explain and distinguish between the different applications of animal biotechnology when addressing lay audiences. This is a really important lesson for the future of livestock genomics because the public is more favorably disposed towards the concept of genomics (53%) than genetic engineering (39%) or cloning (15%). Although some surveys have indicated that individuals with a moderate knowledge of science are more inclined to approve of biotechnology in general, this paradigm does not necessarily hold true for the genetic engineering and cloning of animals, where support for the use of these technologies tends to be limited to those with a very high level of scientific knowledge. Attempting to convey a high level of knowledge about a scientifically complex topic like animal biotechnology to a largely urban public presents a considerable hurdle for agrifood and medical uses of genetically engineered animals.

Perhaps even more challenging is the recent finding that a strong majority (63%) of Americans believe governmental agencies should consider moral and ethical factors, in addition to scientific evaluation of risks and benefits, when making regulatory decisions about cloning or genetically modifying animals, with 53% feeling that way strongly. Support for incorporating moral and ethical standards into the equation was shared by both religious and non-religious Americans. California provides an interesting microcosm to examine the factors shaping societal attitudes towards biotechnology, and provides some insight into the problems that may be encountered as the products of animal biotechnology move towards commercialisation. Six California counties have held ballot initiatives to prohibit the propagation of genetically modified organisms during the past three years, and these initiatives met with varying degrees of success. It is instructive to examine the factors that resulted in the call for such initiatives in the different counties, and to determine the factors that influenced how people voted, ultimately resulting in the contrasting fates of these initiatives. California is also home to a state agency decision that considered ethical factors when making a decision to ban the only genetically engineered animal that has ever been commercialised in the United States. In 2003, California's Fish and Game Commission made a decision to prohibit the possession of GloFish, a genetically engineered fluorescent red zebrafish. This decision was not founded on science-based evidence of environmental risk, being that zebrafish is a tropical species that is not sufficiently cold-tolerant to reproduce in California waters, but rather was based on ethical grounds. In summarising his decision one of the Commissioners stated that after consultation with his religious adviser, "I became convinced to vote no on this issue, even though there is not much of a risk here to California's environment. The question became an ethical question". He went on to conclude that, "at the end of the day, I don't think it's right to produce a new organism just to be a pet." This example highlights some of the issues that medical and agrifood uses of animal biotechnology may face if moral and ethical considerations are incorporated into the regulatory process, an outcome that is seen as highly desirous by a strong majority of Americans. It is difficult to

know what weight such considerations should carry in the decision making process, and perhaps most problematically, whose morals and ethics should be used to decide the acceptable uses of animal biotechnology.

The Views of Society on the Medical and Agrifood Uses of Animal Livestock Biotechnology – The European Perspective

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Traditional models of risk analysis have assumed that risk communication follows on from risk management, which, in turn, is the outcome of risk assessment. More recent frameworks have assumed greater integration between these three elements of risk analysis, in part a response to evidence of a decline in public confidence in risk analysis practices (for example, within the biotechnology sector). However, each area of application of biotechnology (and indeed specific applications) may be associated with differing public attitudes (relating both to perceived risk and benefit) as well as ethical concerns. Very generally, there is evidence to suggest that public acceptance of technologies, including biotechnologies, frequently varies with the nature of the application, not whether a specific technological process *per se* has been used. As a consequence, it is important to conduct research to understand consumer attitudes towards the new, both the technology and its applications.

In the case of animal biotechnology, the research literature would suggest that some broad differences between different types of application in terms of acceptance can be identified. Some broad conclusions regarding consumer acceptance of different biotechnology applications can be made. For example, medical applications are more acceptable than those which are food-related. Biotechnology applications involving animals are generally less acceptable than those involving plants or micro-organisms. However, people are not homogeneous with respect to their attitudes, and individual differences can also be identified across different countries, demographic sectors, life stages and other relevant factors. It is also important to understand how people make cognitive 'trade-offs' between perceptions of risk, cost and benefit associated with specific applications of biotechnology. For example, many people will be more willing to accept a medical application of animal biotechnology if the condition being treated is perceived to be severe. Against this, people may not accept even a plant-related application if the condition to be treated is not considered severe, particularly if delivery is via food (for example, the genetically modified low allergen apple).

Why have public concerns about technologies arisen in the first place? Much public negativity associated with the way risks are managed and regulated has been the result of risk managers, assessors and other key actors in the process of risk analysis failing to take account of the actual concerns of the public when assessing, managing and communicating about risks. In turn, this has had a negative impact on public perceptions regarding the motives of regulators, science and industry in taking decisions or actions in relation to risk assessment priorities, resource allocation and risk mitigation activities. In part, this is the result of communication about risk being based on scientific risk assessments alone, which has failed to incorporate public concerns, values, preferences for specific benefits, and fears into the broader societal debate. It is arguable that greater public inclusion in the process of policy development, specifically focusing on the argument that more extensive public consultation and participation in risk management and other science and technology issues would restore public confidence in institutions with responsibility for technology policy. Increased public consultation appears to play a limited role in increasing public confidence, because there is little evidence that the output of the consultation exercise influences the policy process, and because there is scant evidence that institutional responses to broader consultations are able to tolerate lack of consensus in public opinion.

In conclusion, public acceptance of plant and animal biotechnology will depend upon understanding consumer perceptions of benefit and risk associated with specific applications, and developing a communication strategy which addresses consumer concerns and values as well as technical risk assessment.

Lessons Learned from the Agronomy Biotech Industry

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Lessons around what? The resounding success of modern agricultural biotechnology and its rapid adoption around the world, or the resounding failure to convince European (and other) citizens and consumers of the benefits of applying modern biotechnology to plant breeding and food, feed and fibre production? Within the EU numerous polls show that citizens are not convinced of the benefits of plant biotechnology and many state that they would not buy the products (labelled under EU law) in which these materials are ingredients. Yet there are products on the shelves of EU supermarkets suggesting that consumers do buy them. Consumer/citizen adoption of innovative technologies is a very complex issue, but there is no doubt that their perceptions and expressed views have a major influence on the EU's three policy and lawmaking institutions (the Council, Parliament and Commission), as indeed they should. The EU has a very "rigorous" approval process for agricultural biotechnology products and it is still not functioning in a predictable way. One lesson learned from the plant biotechnology 'affair' in the EU might be that real dialogue between the innovators, integrators and users of the technology and the end-consumer is fragile – but this is probably true of any innovative technology. Nonetheless, establishing good links with consumers and their representatives to develop a real dialogue at the very earliest stages of innovation can only help.

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