



Report of the ESF Exploratory Workshop on

Large Animal Models for Biomedicine

Freising, Germany, 25-26th September 2008

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SCIENTIFIC REPORT

12th November 2008

Executive Summary

The main objectives of the workshop were to bring leading animal scientists together with clinicians, ethicists and representatives of industry to discuss the potential of large animal models of human disease for translational research and to identify particular areas where such models are required. Experts in genetic engineering of large animals met with specialists in high-end phenotyping techniques such as imaging and metabolic profiling. The pig was the major species discussed, but clinical cases of dog diseases were also shown to be excellent models for the development of certain clinical diagnostic and therapeutic procedures. Metabolic diseases, tumorigenesis, immune-related diseases and regenerative medicine were identified as areas where large animal models are urgently required.

The workshop made clear that there is an urgent need for standardised phenotyping assays for large animal disease models. There is excellent expertise in individual labs, but phenotypic tests need to be harmonised and standardised to facilitate comparison of results obtained in different labs. A future European pig clinic as a decentralised phenotyping centre was discussed as a potential FP7 project. In addition, the setup of smaller collaborative projects focussed on certain disease areas was discussed, with a view to obtaining ESF funding. A task force was established to pursue these goals.

The workshop revealed that a number of large animal models have already been, or are currently being established. Large animals offer a link between the classical rodent models and application in the clinic and new models are likely to catalyse the development of drugs and a variety of new medical technologies, devices and interventions. However, it also became clear that extensive validation of the models according to industry standards would be necessary before they are adopted by the pharmaceutical industry. Most likely this validation work will require public funding, but would provide a significant competitive advantage for the European pharmaceutical and biotechnology industry as a whole.

Both pig and dog are appropriate species in which to raise models of human disease, for different reasons. Spontaneous diseases in dogs can be used to bring established diagnostic and therapeutic principles to the clinic, providing information for both veterinary and human medicine. Pigs can be genetically modified to mimic a particular molecular defect that underlies a human disease. Thus, genetically modified pigs are important models for the development of novel diagnostic and therapeutic principles and for the development of biomarkers (companion diagnostics) to evaluate their safety and efficacy.

From the outset, it was recognised that this is a potentially controversial area of biomedical research. There are general reservations about genetic engineering amongst the public, but at the same time, a high level of positive expectations about science and trust in scientific institutions. It seems likely that the public will accept the use of animals where there is a serious and urgent clinical need, but extending animal models into larger species nevertheless carries risks in terms of public perception. There is a need to ensure that clear medical benefit is derived from work in this area and that this is properly communicated. Mishandling of public perception, or failure to maintain high ethical standards especially regarding animal suffering, would be a serious failing and trigger strong public resistance.

The overall impression of the participants was that the Workshop was very worthwhile and that there should be a follow-up meeting in 2009 to pursue the agreed aims. This could possibly be held in Spain.

Scientific Content

Session 1. Clinical needs, technical strategies, commercial issues

In the first session, Jan Motlik and David Argyle introduced the various large animal species that are currently being used to model human diseases, with a contribution from Lars Bolund. These were companion animals such as cats and dogs and livestock species such as pigs and sheep (see models for respiratory disease).

Companion animals live in a similar environment to humans, often suffer from similar diseases which may be either inherited, arise spontaneously or be a result of lifestyle factors (e.g. diabetes). For example, cancer is extremely prevalent in both dogs (~30%) and cats (~25%). Canine tumours are mainly of mesenchymal origin and are therefore an excellent model for human osteosarcomas. Importantly, as these are companion animals there is a clear public interest in the development of treatment regimes, many of which might also be relevant to humans, e.g. vaccine

Diseases in cats and dogs
Canine/feline diabetes
Canine XSCID (X-linked severe combined immunodeficiency)
Canine atopic dermatitis
Canine muscular dystrophy
Canine asthma (rare)
Cats and dogs cancer

development for melanomas, radiation precision for anti-cancer treatment. The dog is of particular interest because of the phenotypic variation brought about by years of selective breeding and the insight this could bring to human disease

predispositions. Several hundred canine genetic diseases orthologous to human conditions have been described. The sequence of the canine genome has recently been determined and is being used to genetically define these diseases, a process termed “mining the dog genome”. This work is very interesting, although still at an early stage. Transgenic techniques in dogs and cats are not yet well developed.

Pigs are the most important animal for mammalian meat production and also an excellent model for medical research and the testing of new methods and drugs for disease prevention and treatment. A genome survey revealed that the pig is genetically more similar to man than conventional laboratory animals - in agreement with the similarities in organ development, physiology and metabolism. The finished sequence of the pig genome can be expected in the middle of 2009 through the work of the international Swine Genome Sequencing Consortium, which includes the Beijing Genomics Institute. cDNA and genomic sequencing efforts have already revealed a large number of DNA markers (mainly SNPs) that have been very valuable in the mapping of QTLs in large and well phenotyped pig family materials. Loci associated with disease resistance in production pigs can already be used for genotype assisted breeding to obtain healthier animals. Comparative genomics of different pig breeds (with extreme phenotypes) can be related to human medical genetics and contribute to the understanding of the genetic background of complex traits and diseases. Various porcine breeds are available, of particular interest are the mini-pig breeds, these are closed well-characterised herds, with short generation times and large litters. Methods for the production of genetically defined models are well established.

Genetic engineering in livestock - state of art and emerging technologies.

Bruce Whitelaw gave a brief overview of this area. Transgenic technologies have been established in livestock since the mid 1980s. Since then many techniques have been developed. Some are based on transgene integration in the egg or zygote and benefit from ease of use and robustness, but lack precision. Some are efficient, e.g. lentiviral vectors, but most are still relatively inefficient. Alternative transgene delivery methods are based on using cells grown in culture as the first step. These methods, e.g. nuclear transfer (cloning), offer precision but remain technically demanding. Although recently a cost-efficient technology for pig nuclear transfer "Hand Made Cloning" without the use of micromanipulation was reported. New methods are being developed that aim to combine precision with efficiency. At present, the generation of transgenic animals, although expensive, is a robust application of modern genetics. Current technologies allow for both small and large transgenes to be transferred. There is no conceptual limitation on sequence source or combination. The time is right to exploit this technology to develop more appropriate and beneficial models of human disease. The first examples including diabetes, cystic fibrosis, neuropathologies, and cancer are being evaluated within the research community now.

Commercial aspects.

The question whether there is commercial interest from pig breeders in the commercialisation of large animal models for biomedicine was covered in a talk by John Dobrinsky from Minitube International USA. This company has considerable experience in this area, including dealings with the FDA.

Animal models serve to study fundamental biological systems and diseases in a way that cannot be studied in humans, allowing specific hypotheses and experimental approaches to be tested in an ethically acceptable manner. US Law states that "animal studies must precede human trials when requesting approval for sale of a biomedical drug or device".

Although some animal models for genetic diseases have arisen spontaneously, transgenics and gene targeting have revolutionised the field. In mice, mutant strains are available for almost every gene in the genome. Some mutant mice exhibit a phenotype similar to that in humans, e.g. chronic granulomatous disease, haemophilia A, spinocerebellar ataxia. Some mutant mice do not, e.g. hypoxanthine phosphoribosyl transferase deficiency and cystic fibrosis transmembrane receptor inactivation. It is therefore clear that single gene manipulations in rodents may not always provide a suitable model.

Several important factors that affect the usefulness of rodent models include their short life span. The study of disorders that occur late in life are difficult to model in short-lived species. Differences in heart and metabolic rates, anatomical size also influence drug clearance rates. Also, unlike most laboratory mouse strains humans are outbred.

Current FDA requirements are for pre-clinical trials to use at least two different animal models, rodent and non-rodent. Nevertheless there have been some striking failures, e.g. the anti-inflammatory drug TGN1412. Treatment in rabbits and monkeys

showed no serious side effects, but six human volunteers suffered multiple organ failure. The rate of success for a new medical compound entering Phase I of clinical testing and making it to market is <8%. Inadequate models are the biggest hurdle.

Swine Biomedical Models. The pig is an omnivore and thus prone to many of the same dietary health problems as humans. Pig physiology is similar to humans. The digestive tract anatomy is similar to humans, infant pig and human nutritional needs are comparable. Pigs can suffer from obesity, hypertension, hypercholesterolemia, dyslipidemia, insulin resistance, atherosclerosis and gastric ulcers. Genetic analysis of pigs and humans shows mutations in similar genes affecting these metabolic disorders

Pigs as models for human diseases
Heart physiology: atherosclerosis, myocardial infarction Reproductive function: sperm, embryo development, maternal-fetal interactions Transplantation: cell and organs; xenotransplantation Skin physiology: melanoma, dermatitis Brain: stroke, dementia, Parkinson's disease, Alzheimer's disease Gut physiology and nutrition: infants, obesity, allergies Biomechanical models: injury, stem cells Tissue engineering: cartilage, spinal fusion, polymer scaffolds Respiratory function: artificial lung, asthma Infectious disease: therapeutics

Diverse pig phenotypes are available as a result of selective breeding. These differ in body size, metabolism, fecundity, disease resistance and in the products they produce for humans.

The pig genome is similar in size, complexity and chromosomal organisation to the human genome. Comparative maps indicate that the porcine and human genomes are more similarly organised than when either is compared to mouse. Rodent genomes are evolving faster than other representative genomes. From genomic basis to physiology and size, organ development and anatomy and disease progression, the pig is an ideal model or candidate for studying the human condition.

Regarding regulatory aspects, the FDA-CVM Guidance for Industry was published on 18 September, 2008. If commercialisation is the aim, then the following points must be considered:

- Size of "colonies", centralised facilities vs. farms
- Feed, husbandry and management: specialised
- Biosecurity of swine farms; barrier facilities
- Domestic pigs vs. minipigs vs. micropigs
- Animal husbandry: Breeding, breeding animal management; breeding and growing animal facilities, gestation management, farrowing management, neonatal care, nursery management
- Per diem: rodents vs. domestic swine vs. miniature swine
- Inbred vs. outbred populations: Sachs Inbred 94
- Transgenic herd expansion: heterozygotes, homozygotes

- Founder line management and inbreeding; multiplier farm systems
- International movement of live animals vs. germ plasm
- Assisted Reproductive Technologies (ART): AI, Cloning, ET

Clinical needs.

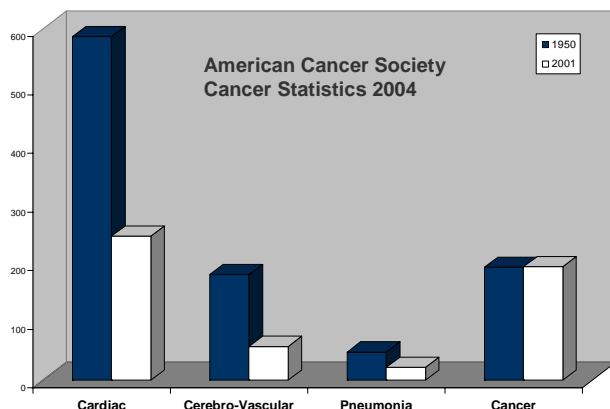
Here Dieter Sauer first gave a general overview, followed by some specific examples in the area of gastrointestinal oncology.

Large animals have been used for many years in biomedical research to develop new techniques and strategies in order to improve early detection, prevention and treatment of various diseases. Examples are pioneering developments such as endoscopic retrograde cholangio-pancreaticography (ERCP) to treat biliary and pancreatic disorders endoscopically or the intramedullary nail for surgical osteosynthesis of bone fractures. To date, most studies have used healthy large animals or induced diseases (chemical diabetes induction, artificial bone fractures etc.) for pre-clinical evaluation of novel diagnostic procedures and treatment regimes. However, using healthy animals or induced diseases limits the usefulness of large animal models substantially. Most of the great challenging human diseases like cancer cannot be recapitulated accurately in such models.

Genetically engineered mouse models that permit conditional expression or inactivation of genes have dramatically improved our basic understanding of gene function in vivo. Especially genetically defined mouse models of human cancer are valuable tools to investigate the molecular and cellular mechanisms of carcinogenesis and are now widely used to validate novel treatment strategies pre-clinically as a proof of principle. However, the usefulness of such small animal models of human disease for pre-clinical research is limited by several key factors. Rodents differ considerably from humans in gene function, drug metabolism, anatomy, physiology, diet and lifespan. For example, the small body size of rodents precludes the evaluation of new surgical techniques or radiation therapies. In addition, molecular endoscopic imaging for early detection of cancer and minimal invasive endoscopic interventions are not possible in small animal rodent models.

Since large animal models of human diseases provide therefore significant advantages over rodent models, a new generation of genetically engineered large animal models is urgently needed from the clinical point of view.

Oncology: While in some disease areas considerable progress has been achieved in the last 50 years (see insert), there is little improvement in the cancer statistics.



Novel diagnostic technologies are urgently needed. The development of diagnostic and minimal invasive endoscopic procedures in the field of gastrointestinal oncology critically depend on large animal models. Precursor lesions and early cancer in the human gastrointestinal tract are endoscopically often indistinct from normal mucosa and thus are not

visible by standard white light endoscopy. Consequently, they are often missed during routine endoscopic examination since no highly sensitive and specific endoscopic techniques are available to date. Dr. Saur's group and his collaborators have developed techniques for highly sensitive and specific early detection of cancer in genetically engineered small animal models by using optical molecular imaging techniques. To further develop these techniques to molecular endoscopic imaging in humans there is a clear need for "humanised" novel large animal models of human cancer that can be examined with endoscopes used in humans. In addition, examples were shown of novel minimal invasive endoscopic cancer resection techniques like sub-mucosal endoscopy. Using healthy pigs, they demonstrate the possibility to resect large mucosal areas (up to 7x3 cm) by sub-mucosal dissection as proof of principle to treat patients with early gastrointestinal cancer non-surgically. Such techniques will reduce mortality and morbidity significantly compared to surgical resection.

In conclusion, there is an urgent clinical need to develop new large animal models of human disease. Such models will facilitate pre-clinical evaluation of novel diagnostic, prevention and treatment strategies that can be than directly translated into the clinic.

Session 2. Existing and prospective animal disease models

In this session different animal models were presented by the speakers, followed by a general discussion and additional contributions from the various participants, such as information from Lars Bolund that they used Hand Made Cloning for the production of genetically designed pigs as models for degenerative disease processes. Primary pig fibroblasts were genetically modified in culture and their nuclei transferred to enucleated pig oocytes. The procedure activates the oocytes and the reconstructed embryos are developed to the blastocyst stage in vitro before being implanted in the uterus of surrogate sows. Thus, these embryos give rise to live piglets with the genetic design of the fibroblasts used as nuclear donors. Their first pig models for degenerative disease processes are now in use.

Animal models for respiratory disease, David Collie

Respiratory disease is the major cause of mortality in the UK accounting for approximately 1 in 4 deaths, and exceeding mortality associated with non-respiratory cancer and coronary heart disease. It is the third commonest cause of long-term illness in adults (behind musculoskeletal and cardiovascular disease). Annual costs associated with respiratory disease (primary care, in patient, outpatient, day care and drug costs) exceed £2.5bn and production losses exceed £3bn annually. The major causes of mortality are pneumonia, COPD and cancer of the respiratory system whilst asthma is the major contributor to long-term respiratory illness. Whilst transgenic technologies as applied to rodent models have had major impact on understanding fundamental mechanisms underlying disease states it is clear that, particularly for the complex respiratory disorders such as asthma and COPD, differences in anatomy and physiology between such models and humans sometimes limits their usefulness – particularly in the context of predicting clinical efficacy of potential therapeutic strategies. This observation highlights the issue that

no animal model will ever be perfect and that a philosophy open to the contrasts that will exist between different species and model systems will be better placed to identify the key issues that account for variability in disease phenotype in the modelled species. Large animal intermediate model systems can fulfil a leading role in this regard and indeed continue to make telling contributions in the context of all the major respiratory disease categories. In future such model systems should be strategically employed in a coordinated manner such that readouts can be related between laboratories and predictive benefits maximised.

Animal models for immunological disorders, Artur Summerfield

Large animals such as pigs and dogs have a high potential as complementary animal models to study the pathogenesis and treatment of diseases in which a malfunctioning of the immune system plays an important role. These are immunodeficiencies, autoimmunities, allergies and also diseases in which immune responses are critically involved such as infections, cancer, metabolic diseases (e.g. diabetes), and many other diseases associated with severe or chronic inflammation.

The main advantages of these models over murine models are: (i) Pigs in particular but also dogs are anatomically and physiologically similar to man when compared to mice. Examples for this are the skin, the gastrointestinal tract and the lung. (ii) Although the immunological principles are conserved in mammalian immunology, there are significant differences in the details of the regulation of important immunological functions such as expression and functioning of pathogen recognition receptors, or regulation of tolerogenic versus inflammatory activity by macrophages, dendritic cells and T helper lymphocyte subsets. Recent studies performed in pigs demonstrate that these elements are more similar between pigs and man as compared to mice and man. (iii) In large animals the study of rare cell subsets is easier to perform. Not only the peripheral blood compartment also but lymph and internal organs (though endoscopic techniques) are accessible. (iv) Several disease models are already proposed or in use, and immunological studies can be implemented in the future. Since the immune system is strongly influenced by many other organ systems such as the endocrine and neurological system, the interaction with other disciplines will be highly synergistic with respect to the promotion of improved and novel models for biomedicine. (v) The porcine immune system is well characterised and sufficient information and reagents are available to perform most studies. It is evident that not all aspects known for mouse (and human) immunology have been described in pigs and dogs. It will thus be necessary to characterise defined immunological elements peculiar to a particular model. This information will not only be important for the model but also in terms of animal health research and the comparative immunobiology of mammals.

Animal models for diabetes and metabolic disorders, Sietse-Jan Koopmans

Domestic (mini) pigs have been proven to be a valuable animal model in nutritional, pharmacological and toxicological research. The reasons for that are the many anatomical and physiological similarities between pigs and humans. The large resemblance of the gastro-intestinal tract, body size and body composition, and the omnivorous food choice of the pig are additional reasons to select this large animal species for (preclinical) nutritional and pharmacological studies. The large comparability of the structure of the pig genome with that of the human genome and

the availability of many “omics-tools” in the pig offer great opportunities for biomedical studies in pigs.

Both humans and pigs are prone to the development of obesity and related cardiovascular diseases such as hypertension and atherosclerosis. Bad cholesterol (LDL) is high and good cholesterol (HDL) is low in pigs, like in humans. Some stress related mental disorders, such as anxiety disorder and depression, can be mimicked in pigs as well. Unhealthy nutritional conditions (e.g. high fat/sugar feeding) and unhealthy life styles (e.g. lack of physical exercise) of human beings can be perfectly mimicked in pigs. Disease-relevant pig models fill the gap between rodent models (rats and mice) and primate species including humans.

The BioMedical Research (BMR) Division of Wageningen UR in Lelystad has extensive experience in nutritional and pharmaceutical research in both healthy and diseased pigs. (Pre)diabetic pigs have been proven to discriminate very well between meals with a different glycemic index or a different carbohydrate/protein/fat constitution regarding the postprandial responses of blood glucose, insulin, free fatty acids, triglycerides etc. Therefore diabetic pigs are presently used for the selection and preclinical development of prototype diets for hospitalised diabetic patients. Metformin and pioglitazone, drugs used in the treatment of type 2 diabetes mellitus in humans, are equally effective in type 2 diabetic pigs and therefore this pig model is suitable for testing new anti-diabetic drugs. In a recent study it was shown that the administration of the drugs rimonabant and sibutramine (both substances have targets in the brain) to pigs reduces food consumption and increases short term satiety in these animals, thereby showing that this non-rodent species is suitable for the evaluation of nutritional and pharmacological strategies aiming at body weight management.

In summary: There exists a strong rationale for the use of pigs in studies designed to investigate the functional effects of novel foods, food components or drugs. Well designed pig studies may help to obtain proof of principal of functional food components or drugs, select the final candidate compound for clinical studies, and contribute to the safety evaluation of novel foods and drugs.

Animal models: regenerative medicine and stem cells, Cesare Galli

The development of stem cell technologies in large animals may serve both as a tool for engineering the genome and as a model of cell transplantation for regenerative medicine. Bovine, sheep, pig and horse have been used for the derivation and culture of both embryonic and mesenchymal stem cells. The derivation of embryonic stem cells relies on the large supply of fertilised in vitro produced pre-implantation embryos. Most of the cell lines generated from large animals embryos have only some of the features of stemness that are considered essential for mouse or human embryonic stem cells, and usually undergo spontaneous differentiation after a short period in culture. Under culture conditions that favour neural differentiation the Galli group have derived neural precursor cell lines from bovine and ovine embryos.

Mesenchymal stem cells are easily collected from bone marrow and adipose tissue from the four species mentioned. They have a finite life span (from 40 to 70 population doublings) and retain the ability to differentiate into derivatives of the

mesenchyme including cartilage, bone and fat. These cells have been successfully cultured, characterised and marked with eGFP and used in a model of tendon lesion repair in the horse.

Jan Motlik also reported the isolation of porcine neuronal stem cells and hair follicle stem cells. They were interested in models for neurodegenerative diseases and functional skin replacement.

Session 2. Socio-ethical issues

This was a very interesting session resulting in extensive discussion concerning public opinions and ethical consideration.

Public perception of genetically modified organisms, Rafael Pardo Avellaneda

Until about 1960 public perceptions of science was seen as information for the regulator, the scientific community, companies and other stakeholders. Traditionally, public views on scientific advances were not part of the “public opinion” landscape and played no role in the regulatory process. Scientific advances had a profile characterised by low salience or low awareness for the public; only noticed, if at all, after leaving the laboratory. Only a small segment of the public followed scientific events, the so-called “attentive public”, i.e. individuals interested and informed about science (<10% population). Scientific advances were viewed as either not problematic or positively received; the assumption was that virtually any scientific advance was good and an indicator of “progress”.

Since the 1960s, there have been episodes and trends of uneasiness or even resistance to subsets of science and technology: nuclear energy, genetic modification of plants and animals, cloning, human embryo research ... and, perhaps, pharming and nanotechnology. This resistance is associated with a number of factors. Chief among them are: The emergence in the mid-sixties of the environmental conscience and values, affecting worldviews of nature and animals. An explosion of information about risks and an attitude of zero tolerance of risks linked to science and technology, a culture of benefits without side effects. Since then, biotechnology is embedded in a complex space of perceptions, characterised by high expectations for reaching many desirable goals, but combined with significant reservations about the means to be applied.

Results of a recent multi-country study on attitudes to animal biotechnology (12 European countries, the USA, Israel and Japan) showed a differentiated landscape of perceptions of genetic modification of animals rather than a holistic perception (positive or negative). Genetic engineering in animals was generally viewed very negatively, this included genetically modified animals for food production. Somewhat less negatively viewed -but still negative- are applications to improve animal or human health. Therefore, special care should be taken in the case of genetic modification of animals, since, in addition to the general reservations about genetic engineering, it activates prevalent images of closeness to humans, suffering of animals, and animal rights, which in turn could trigger strong resistance. For the public, not all biomedical goals warrant the genetic modification of animals, nor would

hype about GM as the tool for solving the world's medical needs resonate with most individuals.

Still, there is a high level of positive expectations about science, trust in scientific institutions and, although less so, in the regulatory agencies. A transparent, unbiased regulatory framework and an active role of scientific organisations, adopting an objective style in the communication of the significant scientific advances taking place and their plausible practical promise could play a major role in sustaining a fruitful dialogue with the public and gaining its acceptance and support.

Ethical issues, Peter Sandoe

Five issues arise regarding the use of large animals as models for biomedicine.

1. Likely benefits to humans. Benefit is more than just pursuing an important aim or important area of study. It is also essential that the study is carried out in a way that delivers valid, relevant and reliable results. Evidence from animal and clinical studies carried out simultaneously rather than sequentially show that compared to clinical study design, animal studies tend to be poorly designed in terms of sample size, randomisation and blinding. A study published in the Journal "Stroke" Sep 1 2005 showed that of 97 substances that made it from pre-clinical (animal) to clinical (human) trials, only one was found to be effective.

There are 3 potential explanations for unsuccessful translation from preclinical to clinical trials. Preclinical (animal) trials give false positive results. Clinical (human) trials give false negative results. Or, both show correct results but the results are different, that is the animal models used are not good models of the human condition.

One should therefore examine whether animal experimentation is always the right tool. Animal models are only models, and just as models may give new insights they may also lead astray. One possible example is the use of rabbits fed with fat as models of atherosclerosis in humans. Another possible example could be the use of toxicological models as the only means of protecting humans against various hazards. Ideally, the choice to use animals as models of human diseases should be based on an unbiased assessment of the needs from the point of view of human medicine. In reality, there will be a lot of bias stemming from the fact that research institutions have invested in expensive new methods (e.g. cloning of animals). Sometimes a method seeks a problem rather than the other way round.

This has not been to argue that animal experimentation is not beneficial. Rather it is to argue that the benefit cannot be taken for granted. There is room for critical discussion case by case. Complacency and overselling should be avoided.

2. Reasonable costs to animals. To adhere to the ideal of refinement, researchers have to use animal models where they achieve results with a minimum of harm to the involved animals. This is easy to say but to what extent are refinement measures applied? Taking for example, analgesia and anaesthesia to control pain. Richardson and Flecknell (2005 ATLA 33, 119-127) found that post-operative analgesia was only applied in 20 % of potentially painful procedures. There may be other problems than pain, such as in neurodegenerative diseases where there is loss of sensorimotor

function. Researchers should consider housing adaptations and set humane endpoints for experiments.

Journals as the major means of communication between scientists could play an important role in promoting refinement. Is that potential used? Evidence from the literature e.g. chemically induced rodent models of Huntington's disease show that refinements to minimise animal distress are often not described in publications. This may mean that scientists are using them without including the information in publications; however it is sometimes obvious that they don't. Journals could play a more active role by ensuring that referees consider refinement and by providing space (possibly as supplementary material) to describe refinement.

3. Will large animals really give more benefits? Some problems arise when moving from rodents to large animals. Are these animals as well defined and as well described as the rodent models? Will it be possible to get sufficient sample sizes? If no good answers are forthcoming then the potential benefit of using animals that are "anatomically and physiologically closer to humans" may be lost.

4. Is it wise to move up the socio-zoological scale? In one way it is right that an animal is an animal. However, there is a social reality where some animals matter more than others. The obvious example is the human, which we even for ethical reasons resist calling an animal. When researchers start to move up the socio-zoological scale reactions should be expected.

5. Is it wise to mix the agendas of agriculture and biomedicine? There are scales of public acceptability regarding the type of organism and the use to which they are put. From most to least acceptable: human, animal, plant, micro-organisms. And in terms of use from most to least acceptable: medicine, health/ environment, agriculture, food. We know that in Europe there is a huge resistance to the use of biotechnology on animals used for food production. This is part of the explanation of why many researchers who used to work on farm animals now move into biomedicine. But there will be a suspicion that at the end of the day the technologies will be brought back into agriculture. Cf. the recent European debates on cloning.

In conclusion: For the future research on large animal models it must be mandatory to address pertinent ethical issues about benefits to humans and costs to animals. It will be naive and unwise to ignore "perception issues" relating to the socio-zoological scale and the potential mixing of agendas of agriculture and biomedicine.

Session 4. Coordination of research efforts - a European consortium. Round table discussion.

At this stage Eckhard Wolf gave a brief summary of the workshop so far, including:

- The clinical need for large animal models, the need for multiple animal models, as one model may not cover all symptoms of a human disease.
- The pros and cons of companion animals versus livestock animals.
- The gap between public research and industry.
- The need for a convincing example such as a model for CFTR.

- The need for systematic phenotyping, as already exemplified with the European mouse clinic.
- The need for an animal archive

This set the scene for a very productive round table discussion, which profited greatly from the input of the participants from industry, such as Antonio Iglesias from Roche. The industrial view is that simply providing a physiologically relevant animal model will not be sufficient for companies to employ them in pre-clinical trials. Animal disease models will only be accepted as useful if they are fully validated.

3. Assessment of the results, contribution to the future direction of the field

The aim of research into large animal models is to bridge the gap between basic research and the bedside. Ideally an animal model of a human disease should replicate the pertinent human genotype and phenotype. Whether this results from a natural mutation or is produced through genetic modification is in principal irrelevant. Although experience with the mouse has shown that genetically engineered models replicate the human diseases more faithfully. As genetic engineering is only practical in livestock species the workshop participants agreed to concentrate efforts on porcine animal models of human diseases. They further agreed that to progress in the field several essential goals should be reached:

- Production and evaluation of a number of genetically defined large animal models (pig) to provide the proof of principle.
- Establishment of a European Technology Platform capable of evaluating the porcine models.
- Establishment of a European Swine Research and Resource Centre.

The response of all participants was that this was a very successful workshop because of the interdisciplinary backgrounds of the participants and because many participants had had no previous personal contact. The informal atmosphere and ample time for discussion resulted not only in a common agreement to establish a European research group based on the workshop participants, and more immediately has led to new personal contacts already resulting in a couple of collaborative projects between individual participants.

A seven-member task force was put in place to pursue the common goals. They will prepare a presentation for their national EU representatives. The intention will be to seek EU funding in order to establish a European Technology Platform for phenotyping porcine models. Furthermore, collaborative projects should be evaluated with the possibility of applying for further funding from the ESF (Eurocores).

The production of large animal models has the potential to bring great benefits for human medicine and the European research community has much to offer in this area. This is a new field and a new direction for animal science and is certainly not a trivial task. To succeed it will be essential to co-ordinate efforts and resources at a European level.

4. Final programme

Thursday 25 September 2008

Morning	<i>Arrival</i>
12.00-13.00	<i>Registration and Buffet Lunch</i>
13.00-13.05	Official Welcome Dekan Prof. Dr. Wenzel (Technische Universität München, DE)
13.05-13.15	Welcome, outline of the structure and objectives of the meeting Angelika Schnieke (Technische Universität München, DE)
13.15-13.30	Presentation of the European Science Foundation (ESF) Jan Motlik (ESF Standing Committee for Life, Earth and Environmental Sciences)
13.30-14.30	<i>Tour of the Weihenstephan brewery</i>
Session 1:	Clinical needs, technical strategies, commercial issues <i>Chair: Lars Bolund</i> (Aarhus Universitet, DK)
14.30-15.00	Clinical needs Dieter Saur (Technische Universität München, DE)
15.00-15.30	Genetic engineering in livestock - state of art and emerging technologies Bruce Whitelaw (Royal (Dick) School of Veterinary Studies, Roslin, UK)
15.30-16.00	Pigs as models for biomedical research Jan Motlik (Institute of Animal Physiology and Genetics, Libechov, CZ)
16.00-16.20	<i>Coffee break</i>
16.20-16.50	Canine models for biomedical research David Argyle (Royal (Dick) School of Veterinary Studies, Roslin, UK)
16.50-17.20	Commercial aspects John R. Dobrinsky (Executive Director, Minitube International, Wisconsin, USA)
17.20-19.00	General Discussion
19.00	<i>Dinner</i>

Friday 26 September 2008

Session 2:	Existing and prospective animal disease models <i>Chair: Mathias Müller</i> (Veterinary University of Vienna, AT)
09.00-09.30	Animal models for respiratory disease David Collie (University of Edinburgh, Roslin, UK)
09.30-10.00	Animal models for immunological disorders Artur Summerfield (Institute of Virology and Immunoprophylaxis, Mittelhäusern, CH)
10.00-10.30	Animal models for diabetes and metabolic disorders "Insulin resistance in diabetic and obese pigs" Sietse-Jan Koopmans (Animal Sciences group, Wageningen University, NL)
10.30-11.00	Animal models: regenerative medicine and stem cells Cesare Galli (Università di Bologna, IT)
11.00-11.30	<i>Coffee break</i>
Session 3:	Socio-ethical issues <i>Chair: Jacek Jura</i> (National Research Institute of Animal Production, Balice, PL)
11.30-12.00	Public perception of genetically modified organisms Rafael Pardo Avellaneda (Fundacion BBVA, Madrid, ES)
12.00-12.30	Ethical issues Peter Sandoe (University of Copenhagen, DK)
12.30-13.30	<i>Lunch</i>
Session 4:	Coordination of research efforts - a European consortium? <i>Chair: András Dinnyés</i> (Agricultural Biotechnology Center, Gödöll, HU)
13.30-14.00	Concept for a coordinated effort - experience with mouse models Eckhard Wolf (Ludwigs-Maximilians University Munich, DE)
14.30-15.00	Round table discussion <i>Chair: Angelika Schnieke and Eckhard Wolf</i>
	Topics:
	<ul style="list-style-type: none"> • joint effort • funding options • virtual institute • follow up meeting
15.00-15.20	<i>Coffee break</i>
15.20-16.45	Round table discussion continues Brainstorming and plans for action
16.45-17.00	Concluding remarks
17.00	Meeting closes

5. Statistical information on participants' age, gender and country of origin

Age

Age data was available for 15 of 23 participants

Under 40	0
40-50	10
50-60	3
Over 60	2

Gender

Female	1
Male	22

Countries of origin

Austria	1
Czech Republic	1
Denmark	2
Germany	4
Hungary	1
Italy	1
Netherlands	3
Poland	2
Spain	1
Switzerland	3
UK	3
USA	1

6. Final list of participants

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