

ANIMAL CELL TECHNOLOGY FOR NEW HEALTHCARE PRODUCTS

15th European Society for Animal Cell Technology (ESACT) Meeting
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The ability to culture mammalian cells on a large scale has simplified the production of antibodies for diagnostics, and of therapeutic agents such as erythropoietin and tissue plasminogen activator. Cultured cells themselves are becoming increasingly important as products, for use in *in vitro* screens as well as for *in vivo* use after manipulation *ex vivo*. Over 400 delegates descended upon the Loire Valley to hear presentations covering recent developments in the use of cultured mammalian cells for biotechnology. As is customary for ESACT, the topics were varied – ranging from the mechanics of growing cells on a large scale through to the development of novel cell lines and their applications for gene therapy, high-throughput screening and the production of vaccines, antibodies and other pharmaceutical products. In this short report it is impossible to do justice to all of the topics covered at the conference, and the sessions covering issues of integrated bioprocessing, which are crucial for efficient large-scale production systems, have not been included here. However, the flavour of the rest of the meeting should be apparent from the range of subjects covered. The invited speakers gave excellent talks on diverse subjects including DNA methylation and its role in the genetic manipulation of the mammalian genome (Rudolf Jaenisch, Whitehead Institute, Cambridge, MA, USA); the use of human cells as therapeutic agents (Howard Green, Harvard Medical School, Boston, USA), the engineering of glycosylation patterns in mammalian cells (Jay Bailey, ETH, Zurich, Switzerland) and how genomics, target identification and structure-based design could provide a complementary rather than competitive approach to animal cells for human therapy (Tom Blundell, University of Cambridge, Cambridge, UK).

Dolly versus the single cell

In addition to the main symposia there was an evening workshop on the use of animal cells versus transgenic animals for the production of recombinant proteins – an opportunity for fans of Dolly the transgenic sheep to make the case that the whole is greater than the individual cell. As might be expected, the debate was lively. Rolf Werner (Boehringer Ingelheim, Biberach, Germany) discussed the pros and cons of the two systems: the general view seemed to be that, although production in animals is more economical, the system is less defined and this might hamper the registration of products derived from transgenic animals. Furthermore, pharmaceuticals such as insulin could leak into the blood of the animal and consequently impair its health, which is not a problem in cell culture.

New technologies for healthcare products

Kevin Brindle (University of Cambridge, Cambridge, UK) gave an excellent presentation on the use of nuclear magnetic resonance to investigate the behaviour of mammalian cells growing in high-density hollow fibre systems. (Hollow fibres are artificial supports used to grow cells in high density to mimic conditions in the tissues). He described both the distribution of cells within the extracapillary spaces and their metabolic activity, demonstrating that this technique can be used to study the behaviour of cells under tissue-like conditions. Augustinus Bader (Leibniz Laboratories for Biotechnology and Artificial

Organs, Hannover, Germany) reported on a modular bioreactor made up of a stack of flat-sheet membranes, which has potential as an artificial device to bridge organ functions.

Use of animal cells for *in vitro* testing

The existence of this session reflects an increasing investment in this field by most industries and some universities. Iris Pribilla (Schering, Berlin, Germany) highlighted the impact of animal cell technology in the field of cellular screening: not only in the area of finding new pharmaceutical leads but also in toxicological applications, as exemplified by Christiane Guguen-Guillouzo (INSERM, Rennes, France) in an impressive presentation on hepatocyte systems. An even more complex culture technique providing an artificial model of the arterial wall was described by Yves-Jacques Schneider (Universite Catholique de Louvain, Louvain-la-Neuve, Belgium).

Production of viral vectors for gene therapy

This is an area of increasing interest to animal cell technologists and one where the potential for major therapeutic benefit is still to be realized. Presentations in this session ranged from a consideration of the scientific aspects in a discussion on the use of adeno-associated virus vectors by Olivier Danos (Généthon, Evry, France) to manufacturing and safety considerations (Jeffrey Ostrove, Magenta, Rockville, MA, USA). Two presentations focused on the development of new, improved packaging cell lines: one for retroviruses (Sean Forestell, SyStemix Inc., Palo Alto, CA, USA) and one for adenovirus vectors (Jan Boeson, Introgene BV, Leiden, The Netherlands). Another two concentrated on gene transfer into myoblasts using the mouse (Luis Garcia, INSERM, Créteil, France) or dog (F.Perraud, Transgene SA, Strasbourg, France) as a model.

Biosynthesis and post-translational modifications of recombinant proteins

The fact that the quality of the protein produced in recombinant systems is now as big an issue as the quantity was reflected in the presentations in this session. The variation in glycosylation patterns with culture conditions was considered by David James (University of Kent, Canterbury, UK) and Natascha Schill (Biogen, Cambridge, MA, USA); and the degradation of recombinant insulin by intracellular enzymes by Stephen Pak (University of New South Wales, Sydney, Australia).

Developments for immunologicals and vaccines

Presentations in this session covered the use of new vaccine adjuvants (Moncef Slaoui, SmithKline Beecham, Rixensart, Belgium) and their use in pre-clinical studies as well as the clinical development of vaccines against genital herpes and malaria. The development of immunotherapeutic treatment of chronic diseases such as chronic hepatitis B and cancer was also discussed. Peter Liljestrom (Karolinska Institute, Stockholm, Sweden) described the use of recombinant, amplifying Semliki Forest Virus vectors to express high levels of antigen over a short period of time, and Polly Roy (University of Oxford, Oxford, UK) the use of multicomponent baculovirus vaccines to co-express 2-8 genes from a single virus in structures that mimic stages of normal virus assembly.

New cell lines

The development of well-differentiated *in vitro* models continues to be a holy grail for cell culturists. In this session an approach for isolating a new hepatocyte cell line was described by Gary Jennings (HepaVec GmbH, Berlin, Germany) and the possible applications of such cells were outlined. An elegant skeletal muscle model based on isolated viable muscle fibres that can be cultured, manipulated then reintroduced into regenerating muscle *in vivo* was presented by Terry Partridge (Royal Postgraduate Medical School, London, UK). Anna Wobus (Gatersleben, Germany), showed how embryonic stem cells can differentiate *in vitro* into a variety of cell types including cardiovascular, myogenic and neurogenic cells. Such cell systems could be used to study development *in vitro*, but also have applications for pharmacotoxicological screening.

Cell physiology and metabolic engineering

Cell proliferation and apoptosis are two inter-linked fundamental processes that are important for the control of the industrial production of drugs, and that must be fully understood in order that they can be regulated. Peter Muller (Gesellschaft für Biotechnologische Forschung mbH, Braunschweig, Germany) reported that the activation of the interferon-regulated factor 1 (IRF-1) fusion protein with oestradiol reduces cell growth. Yon Kim (Tokyo University, Tokyo, Japan) presented evidence that a *c-jun* anti-sense gene can inhibit both cell proliferation and apoptosis. Bernard Massie (CNRC, Montreal, Canada) showed that overexpression of the E1B-19 kDa gene in cell-cycle-arrested NSO cells can increase their productivity. Rabinder Singh (University of Birmingham, Birmingham, UK) presented evidence of enhanced survival mediated by *bcl-2* overexpression in amino acid-deprived conditions and in high-density perfusion systems. These presentations indicated that key cell cycle and apoptosis genes and the proteins they encode provide obvious targets for a new approach to control in large-scale production.

Concluding remarks

The strength of ESACT meetings lies in their holistic approach to animal cell technology. There are no parallel sessions – delegates have the opportunity to attend sessions that are both directly and indirectly related to the area they are working on. At Tours, as at previous meetings, the whole process was considered, from the initial genetic studies of the cells through the stages of production to the regulatory issues surrounding product release. There was a mix of academic and industrial scientists and plenty of opportunity to interact both formally and informally in splendid surroundings. A most interesting and enjoyable time was had by all.

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