ADVANCES IN ANIMAL CELL BIOLOGY AND TECHNOLOGY FOR BIOPROCESSES

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Preface

With the three recently licensed animal cell products (alpha lymphoblastoid interferons, OKT3 monoclonal antibody and tissue plasminogen activator) accounting for over half of the revenues attributable to the new biotechnologies, animal cell culture has emerged from the relative obscurity of the virus vaccine production systems to a prominence which holds both threats and opportunities. The proceedings of the ESACT meeting which are contained within this volume faithfully reflect this situation and can provide workers in this field with insights and inspirations which will help to maintain and catalyse progress in this area.

The upsurge of new knowledge and capabilities in the 'bio-area' which has characterized the last 15 years has presented a welter of opportunities for novel molecules to be used as prophylactics, therapeutics or diagnostics. The production systems which can be adapted to deliver these molecules can be listed as those which are based on chemical synthesis, animal cells in culture, other microbes and, most recently, transgenic animals. In brief, the chemical synthesis of polypeptides for use as 'chemically defined' vaccines has not yet achieved any notable success. Either the molecules are insufficiently immunogenic or they have to be constructed with both B-cell and T-cell stimulating epitopes so that their size could render their synthesis uneconomic. Other microbes have, however, had some success in generating acceptable and effective vaccinal materials such as the Hepatitis B surface antigen made from genetically engineered yeast cells and the *E. Coli*-derived Interleukin-2. Yet many recognize that for the more complex enzymes and antibodies animal cell systems remain the preferred substrate. Antigen combining materials made in non-animal cell microorganisms and consisting of little more than the antigen binding site may achieve a degree of eminence, although this area is one which has yet to emerge with a realised commercial potential. Again, transgenic animals offer exciting prospects of limitless production based on sunlight, grass and offal as the primary feed materials. Nevertheless, many problems remain with the use of whole animals for the production of biologicals – not the least of which are the requirements that the production systems should be safe, efficacious and consistent. The need to closely define, monitor and control all aspects of the production system, coupled with the known hazards of the use of whole animal based biological materials (over half of the haemophiliacs in the UK have been infected with HIV as a result of the injection of whole human blood-derived factor VIII) renders this method of production problematic. There was an interesting twist to the transgenic animal story in that one speaker (Lecocq) described the use of such transgenic animals in making the cell lines which could be used in bioreactor based cultivation systems.

The 280 delegates attending the meeting were less concerned with these issues than those which would enable them to proceed to more effective production

systems based on animal cells in culture. Thus there was much interest in, and indeed some pressure for, the delineation of a number of aliquoted cell preparations to be held by one or more of the cell depositories. These could be used with a particular medium as a consistent control system with which relative bioreactor performance could be more realistically evaluated. To some extent this thinking is a corollary to the thrust of the regulatory agency approach to using defined continuous cell line substrates for the production of biologicals.

It is possible to pick out one or two of the themes which permeated the more than 60 presentations and a similar number of posters. New techniques which were described included the use of Fluorescent Activated Cell Sorters, which seemed to be more for the characterization of the state of a culture than the isolation from a culture of those cells whose properties could be forecasted from the signals they engendered. Other techniques were presented based on acoustic densitometry and spectrocolorimetry. A similar range of new ideas came out of the descriptions of bioreactors where new three-dimensional microcarriers were much in evidence, as well as further developments of the materials which can be used as packing materials for static bed bioreactors. Other systems which involved the use of membranes or hollow fibres to segregate different sections of the bioreactor were also presented, and the point was well made that the volume of the bioreactor did not define the scale or scope of the system – rather the number of cells contained within the system could be a more appropriate way of indicating the system's potential productive performance. For the high cell density bioreactors some 10^{12} cells may be contained in a 10–100 litre volume, equivalent to a 1000 litre reactor operating with 10^6 cells/ml. It is curious to note that the human body may be considered to possess about 10^{13}–10^{14} cells in total! The further development of this apparatus, by the use of a number of separate concentrates of medium components which are diluted to the use level as they are pumped into the bioreactor, was reported.

Media specifically designed for the serum-free growth of hybridoma cells and genetically engineered cells continue to command attention. Many papers dealt with the magic ingredient(s) which turned dross into nectar for the cells, although for the present some such papers only referred in general terms to the way in which the 'factor' was made rather than the precise recipe for its production. It could be that general medium formulations coupled with improved cell handling and weaning techniques could render such proprietary properties surperfluous. Indeed, some basic research into the nature of the weaning process and the study of the basic metabolism of the way in which the cell uses the medium components would achieve marked progress in this area.

On the product side many advances seem to have been made in the area of virus vaccines, and papers dealing with polio, rabies, foot-and-mouth disease, Epstein–Barr virus, equine influenza and HIV were presented. There was much detailed work on the products of genetically engineered animal cells as well as a variety of enzymes (antithrombin and tissue plasminogen activator) and factors from the immune system. Most of the areas in which work on animal cells is progressing were brought up in some form in one or other of the sections of the proceedings.

The remarkable achievement of the last three years has been the licensing of three products made from cell substrates which are either oncogenic in one or other system or which have been derived from an oncogenic cell. That such a change could have occurred was due to the persistence of N. Finter at Wellcome and

colleagues in the USA, who have put together such convincing dossiers affirming the safety, efficacy and consistency of the products that the regulatory authorities were convinced that the balance between cost and benefit was well onto the side of benefit before they issued the licence.

There remain issues to be resolved. How much DNA should remain in a product, and how can we test for pathogenic agents whose effects and natures are completely unknown? How pure is pure and what does it mean to impute that a product is better than 98% or 99% pure? If impurities cannot be detected is the material pure ? Probably not, but is that impurity of significant importance ? Again, we have to consider the cost–benefit account and make decisions based on the probability that although there is a chance of cost, the benefit will be considerably in excess of that cost. These cold reasons do not help when there is the possibility of a death resulting from the administration of a biological. Were that to happen then some moralists would argue that all the benefit imaginable is not sufficient: however other minds may prevail and allow society to make progress even though the cost could be significant. In any event, the papers and discussions related in this volume take us to the forefront of the practicalities involved in this complex area, wherein progress is to be made by the judicious combination of experimental data and convincing guesses at the nature of what we are doing, linked with a philosophical approach which seeks to progress the well-being of our societies.

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