Current trends in mammalian cell culture technology

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IN THE LAST TWO DECADES A NEW GLOBAL HEALTHCARE INDUSTRY WORTH >£63 BILLION PA HAS EMERGED BASED ON THE PRODUCTION OF HUMAN PROTEINS IN GENETICALLY ENGINEERED CELLS, SUCH AS CHO CELLS. IMPORTANT TO THE SUCCESS OF THE INDUSTRY IS INCREASING THE THROUGHPUT AND EFFICIENCY OF CELL CULTURE PROCESS DEVELOPMENT, INCLUDING SCREENING OF CLONES, MEDIUM AND FEED OPTIMISATION AND DEVELOPMENT OF FEEDING STRATEGIES. ALONGSIDE THIS, WE ARE NOW EXPERIENCING THE GROWTH OF AN ADDITIONAL HEALTHCARE INDUSTRY BASED ON CELLULAR THERAPIES AND TISSUE ENGINEERING FOR REGENERATIVE MEDICINE, WHERE THE CELLS THEMSELVES ARE THE PRODUCT. HERE THREE KEY TRENDS IN CELL CULTURE ARE OUTLINED, WITH PARTICULAR FOCUS ON THE WORK BEING CARRIED OUT HERE IN THE UK.

Stem cell bioprocessing

Regenerative medicine “replaces or regenerates human cells, tissues or organs, to restore or establish normal function” (Mason and Dunnill, 2008) and thus includes cellular therapies. Although such therapies, in the form of bone marrow transplants, have existed for several decades it is only in recent years, as our understanding of stem cells and how to isolate, culture and exploit them has grown, that the field has expanded significantly.

As therapies based on adult stem cells (e.g. mesenchymal stem cells) or human pluripotent stem cell-derived cells begin to enter the clinic it is critical that we consider what a stem cell bioprocess will look like and develop the required technologies.

Notably, numerous groups are starting to address the challenge of generating scalable and defined stem cell culture systems (e.g. the Centre for Biological Engineering, Loughborough University; global efforts have recently been reviewed in Want et al, 2012), whilst others are focusing on the derivation of clinical grade human embryonic stem cell lines (e.g. Roslin Cells Ltd). These efforts have been greatly supported by the ever increasing array of defined culture media, culture substrates and dissociation agents that are commercially available. The separation technologies typically used in CHO cell bioprocessing, such as packed bed chromatography, are not suitable because of the difference in scale between whole cells and biopharmaceuticals. Similarly, the industrial applicability of current cell separation technologies such as magnetic activated and fluorescence activated cell sorting is limited by the inability to scale-up effectively. Alongside the development of the stem cell bioprocess there is also a need to identify what QC testing for these products will look like (Rayment and Williams, 2010) and this is a key area of research for organisations such as the UK Stem Cell Bank. It is envisaged that stem cell and stem cell-derived product characterisation will continue to be a theme for the coming years.

Small-scale Bioreactor Systems and Automation

In recent years several miniature bioreactor systems have been developed which aim to mimic larger scale processes and a number are now available in the commercial arena (for a recent review see Bareither and Pollard, 2011). Such systems, which have working volumes ranging from ≤1ml to 5-15ml or ~100ml, enable parallel small-scale fermentations to be carried out, allowing QbD principles to be used earlier in process development, reducing cost and time. Microbioreactors such as these could be used in CHO cell clone selection as well as medium development and process optimisation for CHO or stem cell cultures. Furthermore, they are disposable, ensuring minimum turn-around time, as well as congruence with larger-scale disposable systems which are widely used in industrial environments. The emergence of non-invasive sensor technologies has also allowed accurate monitoring of DO and pH at these micro scales and work is ongoing to develop additional process characterisation technologies. For instance, Ioan Nottingher (University of Nottingham) and Roy Goodacre (University of Manchester) are both developing Raman-based methods for examining the quality of stem cells and in-line medium analysis respectively.

Use of “-omics” technology for process improvement

Last year saw the first CHO genome sequence being reported (Xu et al, 2011) and it is anticipated that this sequence information will enable targeted genetic modifications to be made to cells in order to improve biopharmaceutical production. For example, bottlenecks in folding and secretion of protein products could be overcome or inefficiencies in metabolism addressed. Furthermore, it may be possible to improve one of the most critical and variable steps in the biopharmaceutical development: cell line creation.

Conclusions

Many of the recent advances in cell culture technology have been driven by a variety of disciplines, including biologists, chemical engineers, automation experts and software developers, working together and this will be the key to driving future developments. In particular, those in the field of stem cell bioprocessing will have to learn from the CHO cell community and ideally take a holistic approach to process development such that neither upstream nor downstream processing present a bottleneck to getting these therapies to market.

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