Cell raiser: developing living products for novel therapies

Biomanufacturing expert Dr Robert Thomas gives a telling insight into his career in the field, and describes his work towards more efficiently producing red blood cells for use in cell therapies.

You initially trained as a pharmacist before returning to academia to study liver tissue engineering. What inspired you to change careers and what are your key passions in your current field?

I don’t think I saw this as a complete career change. Cell-based and tissue-engineered products will be part of a new generation of therapeutics, increasingly taking their place alongside the conventional array of small molecules and molecular biologics. As a pharmacist, it was natural to look at research in the production methods and technologies for new-generation therapies. Liver tissue engineering was a natural choice as it offered the potential for enhanced toxilogical screening of standard pharmaceuticals as well as, further in the future, therapeutic tissue-engineered liver-assist devices in liver failure.

My current focus arose out of this early work. It was increasingly evident that, when working with complex biological cultures, one of the major challenges was controlling the experimentation sufficiently to ask interesting scientific questions.

Could you talk us through the innovations your team is developing that are not only economically beneficial but also advance optimisation and process control strategies?

We apply a range of automated technologies to achieve well-controlled processes. Our objectives are generally to establish sufficiently controlled processes to determine the limits of a system and take an informed approach to engineering around those limits. This gives us a data-driven route to either improve production within the limits of current technology, or precisely specify the engineering challenge for a candidate new technology. In other words, we don’t want to develop new technology without understanding the limitations of existing solutions. For example, our work to produce red blood cells has recently demonstrated that these cells can be produced effectively in standard stirred tanks, including advantages of the system mechanical stress. It has also determined how productive this process could potentially be, in terms of both footprint and culture liquids used, and identified engineering targets to improve this.

What role does collaboration between researchers and commercial partners play in the development of these novel technologies?

We are fortunate to work with a number of commercial partners – either as collaborators or contractors. This enables us to trial ideas within industrial settings and ensures our understanding of the challenges in industrial translation and the manufacture of cell therapies remains current. We can work with commercial partners to develop intellectual property created in-house towards market, or to generate new intellectual property targeting specific processes or manufacturing problems.

How do you hope your research will help advance haematopoietic and other cell therapies in the future?

The innovation in biological products needs to be matched by engineering expertise to deliver them to market. Failure to deliver clinically effective products to meet market demand – often due to under-investment in the engineering that controls production cost and quality – will have negative consequences on both investment in the field and future potential benefits. Of more concern is that an inadequate understanding of process and manufacture control and risks increases the probability of ineffective or unsafe products reaching patients; regulators are doing their best to promote the application of risk-based, scientifically designed processes to overcome this – but research exemplifying good process design and control is essential.

It is my hope that the innovations we are developing will ensure that clinical cell therapy products reach the widest market as quickly as possible – and with optimum and reproducible quality. Furthermore, I hope that such processes will be built on an understanding that facilitates rapid development of related products and continual development and improvement of existing products. Finally, I hope that an improved understanding of control will support higher efficiency and more reliable experimentation at the science base, through providing opportunities for enhanced experimental control.
The next-generation manufacture of haematopoietic cell-based therapies

A multidisciplinary team of engineers and biologists based at Loughborough University, UK, is working to bolster cellular therapies by improving the manufacturing techniques used to develop cells in bioreactors.

The challenges of growing cells in bioreactors go beyond the environmental; the cells themselves are maturing and changing throughout the manufacturing process as they differentiate from stem cells to reach their final form.

CHARLES-ÉDOUARD BROWN-SÉQUARD was a Mauritian physiologist and neurologist, and a very interesting man. Active during the mid-1800s, he is perhaps most famous for describing the syndrome that now bears his name – a form of hemiplegia resulting from spinal injury. He was also instrumental, however, in advancing human knowledge of blood, animal heat and even endocrinology. A keen experimentalist, Brown-Séquard is not so well remembered for his more eccentric assays; on several occasions, he attempted to change the biology of a subject by injecting it with animal cells of one sort or another.

But it was not until around half a century after Brown-Séquard’s death that scientists recognised the benefits of injecting patients with human rather than animal cells, hence paving the way for what are known today as ‘cell therapies’. Cell therapies rely on the injection of living cells into the body to improve health, whether those are cells that have been developed in vitro, cells from another donor or simply cells collected from, and subsequently reintroduced, into the host system. The cells introduced in this way can serve a variety of purposes under different disease states, from replenishing cell populations, to bolstering the immune system, to acting as vectors for drugs.

A PRAGMATIC APPROACH

Today, the limitations of cell therapies are still partly based on the scientific understanding of how cells might be used to combat disease – yet, increasingly, the limitations are practical considerations of translation to market. To effectively use cells in cell therapies, they have to be produced in sufficient quantities and with great enough efficiency that the materials for the treatment be readily available, affordable and of a good quality. This necessitates a process that is not unlike manufacturing, as cells suspended in fluid or other media are stirred, heated and cooled, and their environments regulated to ensure development. But what tolerance do cells have to extra-bodily conditions? And what manufacturing methods are most suitable for developing a product that is alive?

Dr Robert Thomas is an Engineering and Physical Sciences Research Council (EPSRC) Fellow and Reader in Manufacturing for Cell-based Therapies at Loughborough University, UK. His research – conducted in close collaboration with industry – focuses on answering just these questions. The investigations being pursued by Thomas and his group centre on complex biological culture systems, and the fine control of such systems required for reliable experimentation. “My current core focus is to understand what causes variation in such culture processes, and to develop novel, efficient methods for assessing risk, determining appropriate process controls and identifying opportunities for optimisation,” Thomas enthuses.

BLOOD IS THICKER THAN WATER

The engineering tools and models being developed by Thomas and his colleagues will enable the more efficient manufacture of cells for therapies of all kinds, but the Loughborough
scientists work, in particular, with blood cells. A haematopoietic cell is a kind of progenitor cell with high plasticity that can differentiate into a variety of cell lineages and, ultimately, turn into any kind of blood or immune cell. It has a range of health applications if handled properly, from immunotherapies supporting donor cells to cellular therapies, whereby native blood cells can be replaced.

In the Centre for Biological Engineering at Loughborough University, Thomas and his collaborators are creating advanced optimisation and process control strategies for cultivating haematopoietic cells. They look for improvements that can be made to both the process models and the bioreactors used in the production of cells, as well as taking a more targeted approach to specific challenges surrounding the production of red blood cells, megakaryocytes and haematopoietic progenitors in conventional bioreactors. “Factorial experimental design and statistical models are used as an efficient approach to identify challenging steps, and development undertaken to overcome specific process sensitivities,” Thomas explains.

THE BLACK AND THE RED
A good example of this is their work on production methods for red blood cells. Currently, there is some hope that low numbers of blood donors might be counterbalanced by the use of red blood cells differentiated from haematopoietic cells in bioreactors – but because the comparative value of blood is so low, these cells would need to be produced in very high volumes and with great efficiency to be economically viable. “We have targeted the economic improvement of haematopoietic cell manufacture through development of process models of media utilisation linked to experimental designs for media optimisation,” Thomas reveals – and indeed, the group’s innovations include growth factor reduction and control in suspension culture. Previously, tools such as bioreactors designed for use in these processes have been proposed without a thorough understanding of cell control and the limits and shortcomings of current technology. But Thomas’ work is seeking to turn that around. By gaining an appropriate understanding of what conditions cells will tolerate, he has been able to give more accurate specifications for future equipment – as well as developing a toolkit for industrialists to reduce costs and increase control of cell culture. Because the haematopoietic cell lineage system is one of the most extensively studied, it provides the ideal backdrop for this work; parameters that can influence the development of the cells such as oxygen levels, pH, cytokine levels and cell-cell interactions are relatively well understood compared with other lineages.

A MOVING TARGET
But the challenges of growing cells in bioreactors go beyond the environmental; the cells themselves are maturing and changing throughout the manufacturing process as they differentiate from stem cells to reach their final form. This transformation often incorporates substantial changes in the metabolic properties of the cell and its sensitivity to its environment, leading to complex dynamic control requirements – in essence, Thomas and his team are trying to hit a moving target. There is also an issue with measuring the quality of cells, since each cell has many measureable attributes; the degree to which a variety of proteins are expressed on the cell surface, for example. This creates a problem of dimensionality, as it becomes complex to accurately define the measurements required for safety and efficacy.

Despite all of the intricacies of their task, however, the researchers at the Centre for Biological Engineering have already made a number of practical leaps in their work. With regard to haematopoietic cells, they have introduced methods for including surface-adhered signalling proteins in standard manufacturing systems to improve the efficiency of the process – and, in collaboration with external consultants, they have also created a software tool to facilitate the modelling and manipulation of the complex dynamics that are ubiquitous and critical in these systems.