Automating stem cell bioscience: from GMP to the clinic

Workshop Report

Introduction

The last few years has seen an increased interest in process automation technologies in the field of stem cell research and commercialisation. One proposition is that automation of manual processes will increase standardisation, reduce uncertainty by reducing variability and ultimately reduce cost. The introduction of standard automated systems would not only stabilise practices across laboratories but also by extension stabilise cell lines. Furthermore, the gradual calibration of cell culture systems could serve to further the understanding of ES cells and other types of cell.

Others argue that the push towards automation of cell culture, while welcome in the long-term is premature and raise the question of what sort of underlying knowledge base is required to successfully standardise something. Other types of automated technologies such as imaging systems and screening systems are broadly welcomed as a valuable addition to the field. Moreover, there is concern that process automation may have a deleterious effect on the functional properties of cells, so affecting their quality and so utility.

The central concerns of the field as a whole relate to securing repeatable cultures and scalable cost effective GMP automation; when and how it may be achieved and what hurdles might be anticipated on the way. Underlying this is the complex interrelationship between our understanding of the cells, the requirements for their use, the measurement methods we use to characterise cells, and the automated process technologies capacity to work with these in the presence of biological variation.

Questions of scale-up and clinical quality assurance are therefore complex and in need of review especially given the diversity of automation systems currently available and the regulatory requirements they must ultimately meet. UK work in this area involves a wide number of discrete groups, from bioscientists, immunologists, clinicians, engineers, equipment manufacturers and regulatory agencies such as the MHRA, FDA and social scientists working within the UK stem cell national network who are investigating the impact of standardisation, regulation and new markets for regenerative medicine.

The Workshop which was supported by the ESRC's Stem Cell Initiative (SCI) and co-organised by the SCI and the EPSRC's Remedi project brought together 25 senior members of the regenerative medicine field to explore these issues.

Key issues raised in the Workshop

Attention was drawn at the start of the Workshop to Masons' recent observation that 'The production of large amounts of living human cellular material for therapy is at least one order of magnitude more difficult than that for biopharmaceutical applications' (Chris Mason – *Medical Device Technology* March/April 2007). Technology and regulatory platforms associated with drug discovery are, according to this view, unlikely to provide appropriate models for translational research and innovation in the stem cells field, particularly in regard to scale up and automation.

Currently automation mostly related to basic tasks such as:

Automated handling of batches/extraction of cells
Filling cells for cryo-storage
Automated flask-shaking to suspend cells
Cell expansion

Some of these elements are easier to automate than others, and where less so, labs have to compromise and deploy some manual techniques as well. A key question is how best to link emerging technologies that allow the isolation, separation, selection and expansion of target cells to techniques that will scale this up via automation? Standardising through automation is designed to reduce the variability associated with manual culture techniques. And from a GMP perspective, ensuring automation is cost effective in producing quality cell cultures that meet standards and can provide the basis for next step – especially clinical trials. In addition there are likely to be problems related to securing a balance between standardisation and customisation of products/therapies? However these are addressed, they need to ensure that in respect to successful translation they meet the demands of both clinical *relevance* and clinical *utility*.

The main points and areas for action identified during the Workshop are outlined below, each section introduced with a relevant comment made during the meeting.

Discovery science, variability and automation:

'The key question is how is basic science going to constrain what we do'

- Need optimisation of discovery science before moving towards automation: this implies the need for a uniform monoculture, a media that allows scalable culture across different formats, the avoidance of feeder cells and the reduction of inter-lab variation – one lab producing one protocol is wasted effort
- Automated cell cultures could generate large population of (hESC) cells that look the same yet be genetically (and epigenetically) different: a key issue is how to secure genetic stability while at the same time determining the significance of any variation that remains as passages increase?
- It is important to distinguish between variability as a *biological* process and as a problem related to the *automation* process: is it, for example, possible to determine the 'natural variation' within cells and work with this for automation?
- Variation within hESCs (in the sense of the presence of abnormal cells) appears to be related to size of the population of cells after c.20 passages. This may have implications for the way in which cell expansion/scale-up is designed – it may,

for example, be better to base this on a large number of smaller batches than a single large lot

- How far down the discovery road does one need to go before an indication of efficacy is secured? This can only be answered if have clear criteria for the meaning of clinical efficacy itself
- Variability can in some contexts be useful: if strip out inherent biological variability this might be needed for successful implantation of somatic cells
- While autologous cells need fewer passages to generate clinically useful products if we want to scale up (eg bone marrow stem cell culture) there is a need to optimise platforms across *both* embryonic and somatic cells

The relationship between labs, the supply chain and manufacture

'It's important to develop synthetic surfaces but if we can't manufacture flasks that have a consistent coating at reasonable cost, to scale, then it's a complete waste of time'

- There needs to be better articulation between the experimental protocols of labs and suppliers
- There is a need to define what the production criteria are likely to be *before* the move towards securing clinical grade lines
- *In vivo* functionality should be the over-riding objective of any business model
- Both campaign and continuous manufacturing processes will be required for different types of cell product

Regulation of risks and uncertainty

'When we ask how much variation we can accept it's far more important to ask what can regulatory authorities accept: how do we define the biological consequences of variation we say is, or isn't, acceptable and how are we going to prove it? These are big and difficult questions to answer'

- Regulation has to be seen as a developing set of provisions over time and respond to developments in the science base
- The approach to risk management needs to reduce some of the regulatory burden and allow some flexibility in the regulatory process as well as clarification over the ways in which product vs. process regulation will be handled in the future (and how far being intertwined)?
- A key issue is to ensure that the regulatory guidelines in regard to reproducibility are made clear so firms can feel secure in their techniques for scale-up.
- There is now greater regulatory acceptance for multiple-patient processing but still regulatory caution over patient to patient variation

Need for public sector intermediary agency

'Venture capital is not interested in optimisation and the development of a technology platform'

- Safety issues in regard to scale up (with respect to procedures dealing with quality control of stem cells) and the validation of parameters which can be trialled in automated systems are tasks that are unlikely to be undertaken by discovery

science labs or industry (especially SMEs and large Pharma) because these are seen as mundane by some, and long-term and resource demanding

- Standardising and optimising cell cultures is repetitive work but this will add value to the regulatory (GMP) process inasmuch as would be producing feed-stocks for both public and private R&D.
- Need a non-commercial intermediary agency to provide this service which is located in the public-sector but works in liaison with industry. This might be the UKSCB which already has strong links to both discovery science labs, regulators (MHRA especially) and SMEs.

Conclusion

The Workshop concluded (as in the final bullet point) that there is a need for funding for work to develop the technology platform that can validate both cell quality, robust in vitro (and subsequently in vivo) assays, and scale up.

This might best be delivered through a consortium involving the UK Research Councils, industry (such as through the BioIndustry Association) and the DH. There are other complementary models that could be more widely taken up, such as the ITI Life Sciences initiative in Scotland which has provided £9.5m to develop an automated process to produce high-quality human stem cells.

The business case for the development of a UK-wide technology platform relates primarily to bridging the development gap (and so current market-failure) in translating discovery-led research into therapeutic applications at a scale that makes commercial investment effective.

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