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CELLULAR THERAPIES: REGULATING A SECTOR IN TURMOIL

*Aidan Courtney**

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* CEO, Roslin Cells (<http://www.roslincells.com/>); Visiting Fellow, SCRIPT, AHRC Centre for Research on Intellectual Property & Technology Law, School of Law, University of Edinburgh. This Editorial has emerged, in part, from the author's participation in a project entitled "21st Century Healthcare: Challenges and Paradigms in Biomedical Research Governance" undertaken at the University of Edinburgh. For more on this, see <http://www.genomicsnetwork.ac.uk/innogen/research/innogenresearchprojectsa-z/projecttitle.24385.en.html>.

1. Introduction

“Business as usual” does not get used much in cell therapy. Fundamental change can be found in the underlying science, the production processes used and the intended clinical applications. Each is very different from where they were ten years ago, and likely to be equally different a decade from now. A pressing question is whether the current regulatory regime is suited to accommodating these innovative therapies. Moreover it is not enough to have knowledge of the regulatory pathway and thresholds today. With new therapies taking five to ten years to develop, those undertaking their development need to have confidence as to what the regulatory requirements will be in 2016 or 2020. If regulatory change is needed, the sooner it is implemented the better.

Of course, some very common types of cell therapy – blood transfusion, spinal fluid transplantation, and solid organ transplantation – are well established. But these are the old guard where the cells provided by the donor are the ones used in the patient. New cell therapies differ in that the originally donated cells are “processed” in one or more ways in a laboratory setting. The cells in the final product arise from cell division which takes place outside the human body,¹ and very often these cells exhibit different properties to those provided by the donor. The capacity to transform the characteristics of cells makes it possible to produce cells which perform a desirable function that would be difficult to source from donors. Moreover, the ability to increase the quantity of cells exponentially through cell division in a “cell bio-processing” facility makes it possible to produce cells in sufficient quantities to treat ailments which afflict very large numbers of people.

As cell therapy develops, the use of human cells increasingly takes on a manufacturing quality and is less like a surgical procedure. With vast numbers of cells produced from a single donated tissue sample, there is no longer a one-to-one relationship between the donor and the patient – as is the case for solid organ donation. Manipulating the cells *ex vivo* unequivocally introduces property concepts to the human cells “generated”. While organ donation falls within the remit of the Human Tissue Authority and is legislated for by the *Human Tissue Act 2004*, cell therapies which involve the donated cells being processed come within the scope of the EU’s Regulation (EC) No 1394/2007 on Advanced Therapy Medicinal Products (“ATMPs”) for which the MHRA is the competent authority in the UK. As such, the new therapies are regulated in the same manner as pharmaceutical drugs, requiring immense cost and many years of pre-clinical and clinical study before a product is marketed.

A critical issue which arises time and again for any rapidly innovating environment is whether the legal and regulatory structures developed beforehand are fit for purpose in the current and future circumstances. Quite what “fit for purpose” might mean can, and should, be debated at length. The recent report of the Academy of Medical

¹ As such they are fall outside s 30 of the *Human Tissue Act* “Prohibition of commercial dealings in human material for transplantation” by virtue of the exceptions in subsection 30(9) and also subsection 54(7) of the Act.

Sciences,² which considered the broader topic of health research in general in the UK, identified four principles which can be paraphrased as: to protect research participants from harm; to facilitate research; to be proportionate; and to maintain public confidence in the purpose and delivery of such research. The report's remit did not extend to promoting commercial investment in therapy development, which must also be a key objective of the legal and regulatory structure.

Given these aims, cell therapies pose particular challenges for the regulatory process due to uncertainties in the underlying science and the production technologies used. Some of these are new, and some familiar to those involved in the early development of recombinant protein based therapies.

2. The Science: Do We Know Enough?

At the heart of cell therapy is our understanding and more to the point our ignorance, of cell biology. Cells are immensely complex artefacts with moving parts, the capacity to create copies of themselves and, in some cases, to transform into something different. They are not the same as an inert small molecule which can be described with a high degree of precision by a chemical formula. This dynamic nature and our incomplete understanding of the fundamental biology does not make for a solid foundation from which to develop a therapy which meets the norms established for the pharmaceutical industry. Continuing fundamental research into the underlying biological processes is essential, but when developing new therapies, pragmatism must be the guiding hand and we should not let the perfect get in the way of the good especially where there are unmet clinical needs.

The lack of knowledge as to how many cell therapies work, and the lack of data as to what might be happening to a patient who has received a cell therapy must give pause for thought. If there are uncertainties, they should be clearly articulated and accepted by the patient, the clinician and the regulator alike. When new therapies go wrong, as inevitably some will, a bad dose of "if I knew then what I know now" will not help the development of the sector. Some examples should illustrate the point:

- **What cells do you have?** A population of cells in culture will not be uniform. This is particularly true for stem cell based therapies or any others where the starting population of cells is transformed (differentiated) into cells of a different type for use the therapy. Some unprocessed or partially processed cells will invariably be in the mix. Techniques exist to sort or select cells to get to a more homogenous population. But proving a negative, in this case that there are no undesirable cells in the therapeutic product, is always open to doubt. Regulators do not require 100% purity but will require evidence that the cells produced are safe and can be produced to the same degree of purity time after time.
- **Where did they go?** The human body is not clockwork and transplanted cells are not new cogs. While a transplanted organ remains where it is placed, the same is not always true of transplanted cells. Cells may migrate, or may not survive very long in the patient. Even if the cells

² *A New Pathway for the Regulation and Governance of Health Research* (2011), available at <http://www.acmedsci.ac.uk/index.php?pid=47&prid=88>.

remain where they are transplanted, demonstrating this is not easy as tracking cells *in vivo* for more than a short period is extremely difficult.

▪ **What do they do?** A frequently used term in cell therapy is “paracrine effect”. This refers to the ability to the cells to influence the cells nearby through the signalling molecules that they secrete. Far from being a replacement cog for a worn out clockwork mechanism, cell therapy can be more akin to transplanting a small pharmaceutical factory into the patient which pumps out chemicals based on the circumstances it finds itself in. Identifying what these factors are remains immensely challenging and so “mode of action” may remain unclear.

For each of these questions the unknowns far exceed the knowns. This situation is nothing new in medical research, but cell therapy pushes the boundaries of how these uncertainties can be addressed. The conventional process to address such unknowns relies on lab based analysis, animal experiments and finally human clinical studies. Given that cells respond to their environment, any *in vitro* analysis will always suffer from not properly replicating the microenvironment in which the cells *in vivo* would find themselves. At the very least one might want to see the cells growing in a three dimensional structure rather than as a monolayer in a culture plate. A similar concern arises with animal experiments. For each therapy being developed, the relevance of animal experiments needs to be assessed. What can be learned from transplanting human cells into an animal regarding how those cells might behave if transplanted into a human needs clear scientific thinking. As well as xenotransplantation issues, long term regeneration of tissue or the number of cells to be transplanted in the proposed human therapy may influence the scope and relevance of animal models. Given the expense and time required for animal experiments, those developing a cell therapy need to engage in an early dialogue with the regulators to clarify what will be required.³

An equally perplexing challenge arises with initial clinical studies. The basis for such Phase I studies can be found in the ICH Guideline for General Considerations for Clinical Trials.⁴ Written in the late 1990s for the regulation of drugs rather than cell therapies, it identifies the purpose of Phase I trials as: estimation of drug safety and tolerability; characterisation of a drug’s pharmacokinetics; pharmacodynamics; and preliminary study of its activity or therapeutic potential. An underlying premise being that drugs will be absorbed, metabolised and then cleared from the patient’s body. Updating this to consider transplanted cells as medicinal products requires careful consideration. Defining a minimum dose in cases where the cells may persist *in vivo* for an indefinite period may not be easy. Similarly the use of healthy volunteers may be inappropriate. These challenges are not limited to cell therapies and lessons can be learned from other novel therapies. The severe systemic adverse reactions which arose in the Phase I trial in Northwick Park Hospital, London, in 2005 of the monoclonal antibody therapy, TGN1412, illustrates how a trial intended to demonstrate safety can

³ See EMA Reflection Paper of stem cell-based medicinal products, 14 Jan 2011, EMA/CAT/571134/2009 at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/02/WC500101692.pdf

⁴ CPMP/ICH/291/95 see www.emea.europa.eu/pdfs/human/ich/029195en.pdf.

go disastrously wrong. The findings of the independent report into this incident are likely to influence how first-in-man trials for cell therapies are designed and risk-assessed.⁵

3. Production: The Process is the Product

It is undoubtedly a major milestone to have data that a cell therapy is safe and effective when treating ten, or even a few hundred, patients. But there is still a long way to go before the therapy will attain marketing authorisation and be sold in the EU. A critical issue arises if the production techniques used to produce the cells needed to treat a small number of patients cannot be simply scaled up to produce much larger numbers.

Changes in the manufacturing process after having conducted a safety trial would require demonstration that the new product was sufficiently similar to the one used previously to allow the safety data from that earlier trial to be used for the new product. Changes made after a later trial, which has demonstrated the efficacy of the product, would need to show that the new product was sufficiently equivalent to rely on both the safety data and the efficacy data. This significantly harder task puts a pressure on those developing the therapy to “lock down” the production process before these pivotal trials are undertaken.

But scaling up production is unlikely to be simply a matter of using more staff and cell culture vessels. Therapeutic proteins can be produced using yeast or mammalian cells cultivated in small and then much larger suspension cell culture systems without changing the basic process. But this is not an option for many cell therapies. Very often cells will only develop normally if they are in contact with other cells, from which they derive developmental cues. Producing functional cells in large quantities may require robotics or other high volume bio-processing technologies, which would represent a fundamental change from the low volume, manual processes used to produce the cells for the initial Phase I trial.

This step change in the production process is a problem for regulatory approval and a dilemma for those developing the new therapy. Do they invest in developing a more scalable production process before they have successfully completed a trial to show efficacy of the product? The answer must be yes. Otherwise incurring the cost of a Phase II or Phase III trial could be money and time wasted, if the regulator subsequently asks for extensive additional testing to show that the cells produced by the new and old processes are equivalent in both safety and function.

In very many respects the industry and regulators have been here before. The increasing use of therapeutic proteins especially monoclonal antibodies in the 1990s is often cited as having raised similar issues. Over time better production and analytic techniques have developed to understand the characteristics of such proteins and we are now seeing the EMA authorise “biosimilars”, i.e. therapeutic proteins which have the same properties as ones already authorised, but which are produced in different

⁵ See “Expert Group on Phase One Clinical Trials: Final Report” (Chairman: Prof Gordon W Duff), available at http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_063117.

manufacturing resources. How the regulators respond to the possibility that this approach may be applied to monoclonal antibodies may shed light on their approach to the equivalence of cell populations produced by differing technologies.⁶

4. Clinical Therapy: Choosing the Right Target

Scientific and processing challenges will make it hard for a cell therapy to navigate the regulatory process, and those developing therapies must be smart as well as clever. Choosing the right therapy may give some much needed flexibility. For instance, a therapy to treat a disease of the eye may only need a few tens of thousands of cells and so it may well be possible to produce cells for a large trial or commercial use using the original process. Whereas a treatment for diabetes may need billions of cells, and for liver disease hundreds of billions of cells, which would require much greater investment and new technologies to meet large scale application. Not surprisingly many current programmes focus on the eye.⁷

Choosing the right first therapy may also mean selecting a rare disease rather than a common one. Several companies developing cell therapies have sought to have their therapy granted orphan status.⁸ In the EU, Orphan Medicinal Product designation is defined by Regulation (EC) 141/2000 and provides incentives, such as fee waivers, and most critically ten years of market exclusivity. It is intended for the diagnosis, prevention or treatment of conditions affecting no more than five in 10,000 people in the EU, or life-threatening, seriously debilitating or serious and chronic conditions for which it is unlikely that the revenue after marketing of the medicinal product would cover the investment in its development.⁹ These incentives and protections fit well with companies trying to develop a first cell therapy. The focus on a small market may not be a diversion away from the main opportunity if the cells and/or the processing know-how can be used to produce therapies for larger markets at a later stage.

5. Conclusion

There can be little doubt that cell therapy will be very different in ten years' time. One key development will be the number of therapies which have navigated the regulatory landscape and secured marketing authorisation. The increasing collective wisdom of the scientists, engineers, clinicians, regulators and investors, involved in these early products will lead to a more mature sector thereafter. The transition of monoclonal antibodies from science to therapy has taken decades and cell therapy, particularly those involving stem cells, will almost certainly take as long.

⁶ See C K Schneider and U Kalinke (2008) 26 *Nature Biotechnology* 985-990

⁷ See for example www.thelondonproject.org/ and <http://www.advancedcell.com/act-stem-cell-related-research-pipeline/retinal-pigment-epithelial-cell-program/>.

⁸ For example Advanced Cell Technology see <http://www.actcblog.com/2011/03/act-receives-positive-opinion-for-orphan-drug-designation-from-european-medicines-agency-for-hesc-derived-rpe-cells-for-treatment-of-stargardt%E2%80%99s-disease.html> and Athersys: see <http://ir.athersys.com/releasedetail.cfm?ReleaseID=509426>.

⁹ See European Medicines Agency guidance on Orphan designation at www.ema.europa.eu.

Cell therapy offers immense benefits but, in the next decade at least, it will not have the same degree of precision as is found in pharmaceutical chemistry. As such it will always be possible for regulators or others to ask questions which those developing the therapies cannot answer. As long as the risks and benefits of the new therapies are evaluated pragmatically then progress will be made. But this also places a responsibility on those at the leading edge of the sector not to overstate the promise of their therapies or cut corners on the work to be done - one bad trial could undermine confidence of the general public, regulators and politicians. If this confidence and pragmatism can be maintained, then the glory years for cell therapy are just ahead.