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Research Paper

Identifying viable regulatory and innovation pathways for regenerative medicine: a case study of cultured red blood cells

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The creation of red blood cells for the blood transfusion markets represents a highly innovative application of regenerative medicine with a medium term (5–10 year) prospect for first clinical studies. This article describes a case study analysis of a project to derive red blood cells from human embryonic stem cells, including the systemic challenges arising from (i) the selection of appropriate and viable regulatory protocols and (ii) technological constraints related to stem cell manufacture and scale up to clinical Good Manufacturing Practice (GMP) standard.

The method used for case study analysis (Analysis of Life Science Innovation Systems (ALSIS)) is also innovative, demonstrating a new approach to social and natural science collaboration to foresight product development pathways. Issues arising along the development pathway include cell manufacture and scale-up challenges, affected by regulatory demands emerging from the innovation ecosystem (preclinical testing and clinical trials). Our discussion reflects on the efforts being made by regulators to adapt the current pharmaceuticals-based regulatory model to an allogeneic regenerative medicine product and the broader lessons from this case study for successful innovation and translation of regenerative medicine therapies, including the role of methodological and regulatory innovation in future development in the field.

Introduction: background to the case study

Regenerative medicine (RM) is a highly promising area for the development of novel therapies with the capacity to solve intractable human health problems. Applications range from one-off autologous therapies where a patient's own cells are extracted and cultured before being transplanted back into the same patient, to allogeneic therapies requiring large scale culturing of cells from a single donor that are then provided to many patients. Autologous therapies, akin to the 'surgical procedure' model (low volume/high cost), are currently delivering successful treatments in several areas. Allogeneic therapies, the subject of this paper, are much more challenging [1]. They are being developed for widespread distribution to large numbers of patients and will be cultured in large scale production facilities, requiring levels of scale-up that are currently very difficult to achieve. However, successful development of allogeneic therapies will be needed if regenerative medicine is to fulfil its promise to meet future healthcare needs on a significant scale. Such products are analogous to a pharmaceutical production model (high volume/widely distributed product for large patient populations) with its expected economies of scale.

The Bloodpharma case study described in this paper is an important test case for the future development of allogeneic therapies. It involves the industrial scale production of cultured red blood cells (RBCs) from pluripotent stem cell lines and aims

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eventually to meet the need for new sources of blood products arising from problems in the current supply chain, risks of transfusion transmitted infection and risks associated with immune responses for patients requiring repeat transfusions. It illustrates many of the uncertainties faced by allogeneic RM therapies: identifying and developing viable product development pathways and funding models [2–4]; related scientific, technological and regulatory challenges [5] and bio-processing/scale up options [6,7]; difficulties in implementing the regulatory system based on the pharmaceutical model adopted for RM products [8–11]; and reimbursement and clinical uptake [12].

Socio-economic research on RM-related issues has so far been done from a range of mono-disciplinary or narrowly focused perspectives. These include the development, standardisation and regulation of early stage stem cell research [13,14]; the storage and handling of new types of biological material [15]; ethical traditions and international differences in the approval of stem cell research [16,17]; the politics of stem cell research and public engagement [18,19]; socio-economic expectations of stem cell treatment [20,21]; the known and potential risks of cell therapies and the implications of proposed regulations for late stage innovation [22–25]; and the manufacturing, scale up, and supply challenges in delivering RM as a commercially viable technology [6,7,26,27].

This paper describes the first major application of a novel interdisciplinary approach to life science innovation (Analysis of Life Science Innovation Systems (ALSIS)) [2], adopting a strategic mapping approach to the projection of development pathways for cultured red blood cells, and demonstrating how social and natural science collaboration can deliver important new insights on life science innovation processes. This interdisciplinary and systemic approach allows consideration of interactions across the science/innovation/policy/regulatory nexus to deliver insights that would not otherwise emerge from a conventional socio-economic analysis and to support better decision making by both innovators and policy makers. By linking the regulatory pathway with the manufacturing/scale-up pathway for this product, and illustrating where the two must successfully align, this article is the first systemic foresight analysis of a novel product in early stage development and provides data that are relevant to, and can inform, broader debates about the development of regenerative medicine products.

Our analysis focuses on challenges to the development of the Bloodpharma product arising from: scientific and technical uncertainties; the regulatory system; manufacturing/scale up challenges; and the impact of all these factors on potential markets and the overall commercial viability of the product.

Research method and data sources

The Blood Pharma Case Study – target market for the product

The Bloodpharma project is a strategic partnership funded by the Wellcome Trust and the Scottish Funding Council to deliver a stem cell-derived blood product (http://www.wellcome.ac.uk/news/media-office/Press-releases/2009/WTX054309.htm). This was one of three case studies considered for the REALISE project [2], funded by the UK Economic and Social Research Council (ESRC) through the Technology Strategy Board. The authors of this paper (Innogen and Bloodpharma Project researchers) worked together to map the future product development pathway envisaged for the Bloodpharma therapy. This project, and our analysis, were completed in 2012 and do not cover subsequent developments that are resolving some of the important uncertainties described here.

Global demand for blood for routine transfusion is approximately 100 million units/year, each requiring 2.5 × 10e12 RBCs. Previous attempts to develop 'artificial' blood have failed due to problems with toxicity and manufacture [28,29] but stem cell science offers the potential successfully to differentiate RBCs for clinical use. However, achieving this scale of production to clinical grade GMP standard at a price that is competitive with that of a standard unit of blood is currently a challenging aim. The Bloodpharma project has focused initially on the beta-Thalassemia market where patients suffer problems with iron loading, for which drugs with unpleasant side effects must be administered [30,31]. The cultured RBCs could reduce reliance on donor recruitment, and the risks of transfusion transmitted infection and of immune incompatibility, through provision of a 'universal donor' blood group (such as O Rhesus D negative and Kell negative). Since the product will consist of a homogeneous population of young red cells (reticulocytes), the cells should have a longer life span once transfused. This would be of benefit to beta-thalassemia patients, who may require fewer transfusions and therefore experience less iron loading. These benefits would justify a price premium for the initial product, perhaps enabling it to cover the cost of meeting the technical and regulatory constraints described here.

The ALSIS approach

The method we developed for this project, Analysis of Life Science Innovation Systems (ALSIS) [2] uses a strategic mapping approach to project future business models and product development pathways (defined as the full range of activities required to bring a product from conception to end use, including design, production, marketing, distribution and support to the final consumer). These factors, broadly speaking under the control of the innovator, are embedded within an innovation ecosystem that includes the economic, regulatory, societal and political contexts that are beyond the control of the innovator, with either positive or negative impacts on the product business plan. For the Bloodpharma project, critical decision points within the product development pathway arose from the scientific and technological challenges of differentiating sufficient quantities of RBCs from stem cells meeting clinical grade GMP standards for different stages of pre-clinical and clinical testing; and the implications for product development and regulatory science of targeting the niche Thalassaemia market. The main innovation ecosystem components discussed in this paper are the regulatory system and the challenge of meeting requirements related to the use of conventional preclinical animal models and to the conduct of human clinical trials.

The strategic maps in Figs 1–4 were developed using Banxia Decision Explorer software (http://www.banxia.com/dexplore/) and are based on discussions with case study participants during interviews and workshops. They consist of a series of 'concepts', short statements, each representing an action that leads, as shown by the arrows on the map, either causally or temporally to the next

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