Interview

Immunogenicity: the elephant in the room for regenerative medicine?

Paul Fairchild speaks to Alexandra Hemsley, Assistant Commissioning Editor

Paul Fairchild began his research career in Oxford, UK, where he studied for a doctorate within the Nuffield Department of Surgical Sciences, focusing on the immune response to organ allografts. After spending 5 years as a postdoctoral fellow investigating the etiology of autoimmune disease in the Department of Pathology, University of Cambridge, UK, he returned to Oxford, where he is currently a University Lecturer in Preclinical Medicine within the Sir William Dunn School of Pathology and a Fellow of Trinity College. In 2008, Fairchild founded the Oxford Stem Cell Institute (OSCI), for which he currently serves as Co-Director. As a highly interdisciplinary organization, the OSCI focuses on exploiting the properties of stem cells for the treatment of some of the most intractable chronic and degenerative diseases. It is within this context that he continues to apply his background in transplantation immunology, in order to investigate the nature of the immune response to tissues differentiated from pluripotent stem cells and to develop approaches to the induction and maintenance of immunological tolerance. In a recently published book, *The Immunological Barriers to Regenerative Medicine*, Fairchild explores the immunological challenges that face cell therapies and confronts some common misconceptions about the immunogenicity of pluripotent cells. Here, Fairchild speaks to *Regenerative Medicine* about why immunological issues cannot be ignored as stem cell science moves into the clinic.

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■ **What first sparked your interest in regenerative medicine?**

For the past 17 years, I have had the immense privilege of working at the Sir William Dunn School of Pathology in Oxford, which is renowned for the early work on penicillin that has since fuelled the antibiotic era. Based in such auspicious surroundings, it would be difficult to forget the significant impact that antibiotics have had on life expectancy over the past 70 years. Nevertheless, the magnitude of this medical success story has had important repercussions, bringing with it an unprecedented increase in the incidence of chronic and degenerative diseases, which are likely to dominate healthcare in developed countries throughout the 21st century. In some ways, I therefore like to view regenerative medicine as a natural extension of the story of antibiotics, since the use of stem cells for the rejuvenation or replacement of diseased or worn out tissues is likely to be fundamental to ensuring that increased longevity is not merely responsible for prolonging suffering, but is associated with continued good health and productivity well into old age.

■ **Have immunological issues been underestimated in regenerative medicine to date?**

Although the field of stem cell biology has progressed significantly over the past 15 years, there is little doubt that related areas of the biomedical sciences have failed to keep pace. Undoubtedly, the immunology of regenerative medicine is one such field that has lagged behind our understanding of the basic cell biology of pluripotency. This may have unwittingly led the stem cell community to underestimate the magnitude of the immunological issues involved in cell replacement therapies that have since become apparent.

■ **What has led to the assumption that embryonic stem cells may circumvent the immune system? What is the problem with these assumptions?**

In the months following James Thomson's seminal paper reporting the derivation of embryonic stem (ES) cells from human blastocysts, there was much speculation that cell types and tissues differentiated from them might prove 'invisible' to

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the immune system, should they be transplanted into allogeneic recipients. Although we now know that this is not the case, there was nevertheless a credible scientific rationale for this assumption.

We know from several decades of research into whole-organ transplantation that acute rejection of allografts is driven by resident dendritic cells carried over as stowaways in the transplanted tissues that are responsible for initiating primary immune responses among alloreactive T cells. Needless to say, by controlling the directed differentiation of ES cells along desired lineage pathways, the resulting tissues would be anticipated to be devoid of donor dendritic cells, removing an important stimulus for this pathway of sensitization. Furthermore, it is the unique complement of MHC molecules expressed by each individual that defines their immunological identity, marking any tissues they donate as foreign to the recipient. Given that ES cells appear to be naturally deficient in expression of MHC molecules, however, it was widely assumed that they could not be distinguished as foreign by the immune system of the host and would, therefore, escape rejection. Although these arguments gained significant support at the time, we now know that they are not sufficient to prevent chronic rejection of the tissue for a number of reasons. Firstly, although ES cells are indeed deficient in expression of MHC molecules, the products of MHC genes are readily expressed by their differentiated progeny, with their upregulation being further stimulated by the inflammation that is caused following implantation. Furthermore, this source of MHC and so-called ‘minor’ histocompatibility antigens may be actively acquired by the host’s own population of dendritic cells, which can process and present them to naive alloreactive T cells; the absence of dendritic cells within the implanted tissue itself is, therefore, no impediment to the initiation of an immune response.

■ **Does the recent advent of induced pluripotent stem cells overcome the problems of immunogenicity?**

The advent of induced pluripotency in 2006 was widely acclaimed since it

promised to circumvent many of the issues of immunogenicity that threaten the clinical use of ES cells. Since lines could theoretically be derived from patients in an autologous manner, tissues differentiated from them would share all MHC and minor histocompatibility antigens with the recipient, depriving the immune system of anything it could perceive as ‘foreign’. Unfortunately, we have since discovered that even autologous induced pluripotent stem (iPS) cells are likewise rejected, a finding that was wholly unexpected at the time. It appears that the process of reprogramming to pluripotency reawakens the expression of developmental genes required very early in ontogeny. Since these are normally silenced long before the emergence of the immune system, the T-cell repertoire is not, therefore, rendered tolerant. Curiously, these genes do not appear to be properly silenced during the redifferentiation of iPS cells *in vitro*, which sets their progeny apart from other somatic cells, targeting them for destruction by the immune system in a process that is more closely allied to an autoimmune response than it is to allograft rejection.

■ **What are the unique challenges for allogeneic cell-based therapies compared with organ transplantation?**

Undoubtedly, one of the greatest challenges to face regenerative medicine, and one which sets it apart from whole-organ transplantation, is that a reliance on immune suppression cannot be ethically justified in the same way as it is for the treatment of end-stage organ failure. The simple reason for this dichotomy is that the risks associated with long-term immune suppression are frequently greater than those of the very disease states that may one day be treated by cell-based therapies. Age-related macular degeneration is a case in point, given that clinical trials are currently underway using retinal pigmented epithelial cells differentiated from human ES cells. While it is, of course, undoubtedly distressing to be left with only peripheral vision, the condition is thankfully not life-threatening. By contrast, lifelong dependence on immune

suppression is known to be associated with significant side effects of toxicity and renders recipients readily susceptible to opportunistic infection and malignancy, which remains a significant cause of morbidity and mortality among organ allograft patients. The risks of immune suppression are still further magnified in the context of cell-replacement therapies that use cells differentiated from pluripotent stem cells, as a result of their known propensity for transformation: to actively impede the immune system that eradicates transformed cells under steady-state conditions, while at the same time implanting cells with a tendency for tumorigenesis, would inevitably expose patients to an unacceptable level of risk. Unlike end-stage organ failure, for which the risks of lifelong dependence are clearly warranted, stem cell therapies are likely to be restricted to only short-term applications, which renders them vulnerable to subsequent rejection upon withdrawal of immunosuppression.

■ **In your view, what are the most promising new approaches in development to address immunogenicity for regenerative therapies?**

Until recently, the potential of cellular reprogramming to personalize pluripotency, making it accessible on an individual basis, seemed to offer the greatest hope for circumventing immunogenicity. Nevertheless, the discovery that reawakening pluripotency is associated with the upregulation of developmental antigens, as well as their persistent expression upon differentiation, has rather undermined this vision for personalized therapies. The recent demonstration by various groups of direct reprogramming as a way of generating cell types as distinct as neurons or cardiomyocytes from a starting population of fibroblasts may, however, offer a solution to this issue: by avoiding a pluripotent stage altogether, there may be little need to re-express the developmental antigens that might otherwise serve as targets for deleterious immune responses.

Given the aging nature of the population and the rising incidence of chronic and degenerative diseases, strategies for personalized therapies may ultimately prove

economically unviable, instead favoring reliance on a bank of fully characterized iPS cells, rather than their derivation on demand. While clearly appealing from a pragmatic perspective, such allogeneic therapies will require protocols for the induction of immunological tolerance in order to avoid the need for immune suppression. While protocols using coreceptor and costimulatory molecule blockade have been successful in rodents, their clinical implementation has proven rather more complex.

■ **Do you think the induction of transplantation tolerance will ever be a possibility in the future? Could there be a time when we will no longer be reliant on immunosuppression?**

Although whole-organ transplantation has been practiced successfully for several decades, the induction of immunological tolerance has yet to impact the clinic, raising important questions as to whether it is likely to prove any easier to achieve in the context of cellular therapies than has proven feasible for conventional transplantation. Although admittedly the obstacles remain significant, there are encouraging indications that tissues differentiated from either ES cells or iPS cells may display a weak capacity for immune privilege, which helps such tissues actively repel an immune response targeted against them. Although these properties do not appear sufficient to prevent rejection across anything greater than a minor histocompatibility barrier, they appear to create a microenvironment that is conducive to tolerance induction, making it possible to tap into this capacity to gain indefinite survival of tissues with minimal conditioning of the recipient. Indeed, the acceptance of tissues derived from pluripotent stem cells appears significantly easier using established protocols for the induction of tolerance than it is for tissues derived from any conventional source. Although there is clearly a long way to go before such techniques can be applied within a clinical setting, these observations raise hope for the future success of cell therapies that are not reliant on immunosuppression with its many attendant risks.

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■ What contribution do you hope your new book will make to the field?

I think there is little doubt that the immunology of transplant rejection has begun to take center stage in the field of regenerative medicine and is now recognized to be one of the most intransigent obstacles to the success of stem cell therapies in the future. It is my hope, therefore, that by documenting the issues involved and discussing potential ways of overcoming them, this book [1] will help to galvanize and innovate this long-overlooked aspect of regenerative medicine. It is, after all, only by reaching a consensus in the field and fostering much-needed collaboration between disciplines that enduring solutions to such intractable problems might ultimately emerge.

Financial & competing interests disclosure

As editor of The Immunological Barriers to Regenerative Medicine, discussed in the manuscript, P Fairchild is liable to receive royalties from Humana Press. P Fairchild has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Reference

- 1 *The Immunological Barriers to Regenerative Medicine*. Fairchild PJ (Ed.). Humana Press, NY, USA (2012).