Taming the lion: the challenge of immunity in regenerative medicine

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When invited to serve as guest editor for this Special Focus Issue of Regenerative Medicine, I felt deeply honored yet somehow daunted by the task. Having begun my scientific career as a card-carrying immunologist, with a particular interest in whole organ transplantation, I frequently receive invitations to speak at stem cell conferences where I am invariably given the remit of discussing the risks of rejection and prospects for its mitigation in the context of cell replacement therapy. But the news is neither good nor welcome: indeed my lasting impression of such occasions is that I have single handedly spoilt an otherwise vibrant party! Because, whether we like it or not, there seems little doubt that the immune system represents a formidable opponent for regenerative medicine that we ignore at our peril. Indeed, many decades of research into whole organ transplantation have done little to wean us off a long-term dependence on immune suppression. And yet such a solution to the problem may be contraindicated for many stem cell therapies, especially those based on the use of pluripotent stem cells for which the risks of tumorigenesis are uncompromisingly high: to suppress the immune system while administering cells with a proven propensity for transformation would doubtless expose recipients to unacceptable levels of risk. But while the challenges posed by the immune system should never be underestimated, there are also reasons for hope. There is little doubt, for instance, that tapping into the properties of pluripotency offers unparal-

leled opportunities in the field of immunotherapy. Indeed, accessing rare cell types of immunological significance through the directed differentiation of pluripotent stem cells, may provide a welcome new paradigm for addressing various unmet medical needs with an underlying immunological basis: it is these emerging opportunities, as well as the inevitable challenges that face the sector, that we have sought to reflect in the articles we have invited from authors, renowned in their respective fields.

The potential for immunological rejection to derail the likely future benefits of regenerative medicine has been appreciated for many years. The need to deal comprehensively with such a threat was amply reflected in the UK Government's 2012 Strategy for UK Regenerative Medicine, in response to which the UK Regenerative Medicine Platform (UKRMP) was founded. The recent establishment of an Immunomodulation Hub as part of this initiative is, therefore, to be welcomed. The nascent hub is outlined in our Organizational Profile, which features an interview with Co-Director, Francesco Dazzi [1] and details of contributions from the various partners in the consortium [2]. The importance of addressing the immunological constraints of stem cell therapies from a pharmaceutical perspective is discussed by Richard Haworth and Michaela Sharpe, who outline how the immune response poses a significant risk factor to the development of novel cell therapies, greatly complicating their progress to market [3]. They advocate the need for assays to

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predict the likely complications that might be encountered, but touch on the difficulties experienced at the preclinical level when using animal models of human disease. Although the differentiation of human pluripotent stem cells into cell types of therapeutic value is now routine in many cases, their behavior *in vivo* and capacity to integrate functionally into target tissues is frequently difficult to assess in animal recipients, requiring either profoundly immune-compromised strains of mouse or the use of high levels of immune suppression in those species for which such genetically modified strains are not available. Nevertheless, long-term use of immune suppression may prejudice the outcome of such experiments, especially in instances where behavioral measures form the best readouts of success, since these may be significantly affected by declining health status caused by side effects of the immune suppressive regime. It is against this backdrop that the Special Report by Robertson and colleagues discusses the simple method of neonatal desensitization in which the administration of human cells to rats during the neonatal period comprehensively intervenes in the rejection of human tissues implanted later in life, permitting their functional integration to be assessed without the confounding impact of an aggressive xenogeneic response [4].

The advent of induced pluripotency in 2006 offered the opportunity to derive pluripotent stem cells from patients in an autologous manner, thereby promising to bypass the immunological consequences of using allogeneic embryonic stem cells as a source of replacement cell types and tissues. Nevertheless, the complex economics and logistics of personalized medicines are likely to preclude the derivation of patient-specific cell lines for all but a minority of indications. Given the need for a more pragmatic solution, Ian Wilmut and colleagues discuss proposals for the generation of a global haplobank of GMP-compliant induced pluripotent stem cell lines to facilitate rudimentary matching between donor and recipient [5]. Although there is little doubt that tissue matching would help reduce the immunogenicity of replacement tissues differentiated from human induced pluripotent stem cells, it is likely that such an approach will require additional strategies for immune intervention to address any remaining histoincompatibility. It is in this context that Eleanor Bolton and Andrew Bradley discuss the magnitude of the immunological challenges that lie ahead and evaluate the various strategies currently being pursued for ameliorating their impact [6].

Although evidence of immunogenicity in a clinical context is currently limited to information gleaned from just a few clinical trials using human embryonic stem cells, for cell therapies based on the use of adult stem cells, much is now known of the downstream immunological consequences. Hematopoietic stem cell transplantation has, for instance, been practiced in some form or other since the 1950s and is, therefore, a well-established approach for the treatment of a variety of disease states, including hematological malignancy. While the success of the approach is greatly limited by the pathological consequences of graft-versus-host-disease (GVHD), attempts to minimize its impact frequently eliminate the beneficial graft-versus-tumor effect, known to help prevent the subsequent relapse of malignancy. Alain Vertès provides a comprehensive review of the causes and consequences of GVHD and prospects for intervening in its pathogenesis [7,8]. One such approach, which has consistently shown promise, involves exploiting the immunosuppressive properties of mesenchymal stem cells which, when coadministered with the hematopoietic stem cell inoculum, have been shown to nonspecifically suppress GVHD. It has long been assumed that their unique properties may render these cells refractory to rejection, even across histocompatibility barriers, making them ideal candidates for the development of an 'off-the-shelf' product with broad applicability. Christine Consentius and colleagues review the evidence for these claims and suggest that it may yet prove premature to draw such

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conclusions, questioning the universal utility of mesenchymal stem cells as an immunosuppressive regime [9]. In contrast, Noga Or-Geva and Yair Reisner outline a novel approach to reducing GVHD based on exploiting the so-called veto activity of CD8⁺ central memory T cells activated to third party alloantigens, a strategy that may facilitate early engraftment with minimal GVHD while potentially preserving the beneficial graft-versus-tumor effect [10].

Although regenerative medicine continues to pose many immunological challenges, it has also provided numerous opportunities to intervene in a variety of disease states with an underlying immunological basis. In our Perspective article, members of my own laboratory review recent advances in the generation of dendritic cell subsets from human pluripotent stem cells [11]. Such a novel source may address many of the current limitations to the use of dendritic cells derived from peripheral blood monocytes and provide a platform for vaccination to tumor-associated antigens and chronic infectious microorganisms, as well as the induction of tolerance to defined protein antigens. Furthermore, Nicholas Bredenkamp and colleagues describe exciting advances in the regeneration of a functioning thymus in old age through exploitation of pluripotent stem cells or the direct reprogramming of fibroblasts to thymic epithelial cells [12]. Such advances may one day permit the reversal of age-related thymic involution, which currently impedes reconstitution of the T-cell repertoire following depletion of T cells in the

periphery due to chemotherapy or chronic infectious agents, such as HIV-1.

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There is little doubt that the immunology of regenerative medicine remains an immature discipline that lags significantly behind the basic science underlying the generation and differentiation of stem cells. Nevertheless, it is our hope that this Special Focus Issue may play a small part in highlighting a topic of strategic importance to the future success of regenerative medicine. Needless to say, I am indebted to all authors for their willingness to contribute to this project in such a timely manner and am enormously grateful to Theo Bond and Elena Conroy from the editorial office for their patience and dedication which has helped make such a daunting task so enjoyable.

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