

Preface

Few could doubt the need for regenerative medicine. While the increase in life expectancy we have witnessed throughout the developed world over the past 80 years is undoubtedly a medical success story of unprecedented magnitude, the accompanying increase in incidence of non-communicable diseases (NCDs), with a chronic or degenerative aetiology, represents a significant challenge of the twenty-first century. It is estimated, for instance, that the worldwide incidence of mortality due to NCDs will rise to 52 million per year by 2030, while deaths through infectious disease will continue to decline throughout the same period. Such changes in modern healthcare needs, have created an almost insatiable demand for new treatments capable of harnessing the properties of stem cells to replace diseased or effete cell types, or that rejuvenate tissues from within, through the activity of endogenous stem cells. And there have been numerous recent advances that represent significant steps towards the realisation of this vision. While the routine derivation of human embryonic stem cells (hESC) has made pluripotency accessible in man for the first time, the advent of induced pluripotency has paved the way for its clinical application to be tailored to the needs of the individual. Furthermore, preliminary successes in the treatment of diseases such as macular degeneration of the eye through cell replacement therapy suggest that we may at last be on the cusp of reaping the benefits of the past 15 years of research into the nascent field of regenerative medicine.

Nevertheless, fundamental challenges remain to be addressed before such developments may have any significant impact on global health. The British Government's *Forward look in regenerative medicine*, convened in September 2011, identified the immune response directed at stem cell-derived tissues to be a fundamental roadblock to progress. Although the early days of regenerative medicine were accompanied by unfounded optimism that tissues differentiated from hESC or, more recently, induced pluripotent stem cells (iPSC), might prove to be poorly immunogenic, it is now widely accepted that cell therapies pose no fewer immunological challenges than whole organ transplantation: indeed, unlike conventional transplants, the propensity for tumorigenesis of pluripotent stem

cells, suggests that long-term immune suppression is unlikely to offer a solution to rejection in this particular setting.

It is against such a backdrop that this volume offers an analysis of the scale and nature of the immunological issues facing regenerative medicine, drawing on the expertise of laboratories around the world who have taken up the challenge of applying their expertise in immunology to the vagaries of stem cell biology. In Part I, we explore the extent to which the principles of allograft rejection, learned over several decades from our experiences of whole organ transplantation, apply within the unique context of cell replacement therapy. Part II discusses various innovative ways of addressing the issues of immunogenicity, while, in Part III, we focus exclusively on the induction of immunological tolerance through a variety of novel approaches. It is our hope that this systematic analysis of the current state of the field will galvanise efforts to solve an issue which has so far remained intractable.

I am, of course, deeply indebted to all the authors for their patience and commitment to completing this project. Furthermore, there are many who have played an important part in its completion, often in subtle ways, and invariably without realising how important their contributions have been. I have, for instance, been inspired by many friends and colleagues, of which Bébhinn Ramsay, Steve Cobbold and Kathleen Nolan deserve special mention. The members of my laboratory should likewise be singled out, not only for their encouragement and the many scientific insights they have offered, but for the temporary neglect they have endured with such good humour. To this end, I would like to thank Tim Davies, Kate Silk, Alison Leishman, Naoki Ichiryu, Simon Hackett and Patty Sachamitr for their loyalty and for creating such a dynamic and enjoyable environment in which to work. It would be remiss of me not to acknowledge the enormous debt of gratitude I owe my mentors, past and present, for instilling in me their enthusiasm for science and its application to medicine. Jonathan Austyn, David Wraith, Richard Gardner and Herman Waldmann have all invested huge amounts of time and resources in me over the years, often with precious little reward, but their efforts have certainly not been overlooked! Finally, as is so often the case, it is my wife, Jackie, and my son, Richard, who deserve the greatest recognition for their ongoing support and unfaltering love and encouragement: without their sacrifice of holidays and our usual family Christmas, this volume would never have been completed!

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