

Preface

The last decade has witnessed the consolidation of “regenerative medicine” as a recognized scientific field, encompassing disciplines as diverse as cell biology, immunology, developmental biology, and surgery. The report on the isolation of human embryonic stem (huES) cells by James Thomson in 1998¹ opened our eyes to a ground-breaking notion: that defective tissues could be replaced by an unlimited source of self-renewing cells with the ability to morph in vitro into any of them. The revolutionary nature of this idea is evidenced by the fact that concepts such as “regenerative medicine” or “stem cell therapies” were not in common use in the scientific literature until the late nineties. Until then, and despite reports of embryonic stem cells obtained from several animal species,²⁻⁴ there was no identifiable organized quest for a “human tissue building block,” as there was one, for example, to decipher the entirety of the human genome. In retrospect, it is as though the majority of the scientific community had not envisioned applications for these unique cells other than to create animal models for human diseases, increase live-stock output, or improve the production of therapeutic proteins from transgenic animals. This seeming “unexpectedness” was further confirmed when, shortly after this breakthrough, all major scientific journals started to publish a plethora of reports on the therapeutic potential of stem cells of adult origin. Since the technology to isolate and expand adult stem cells had already been in use for a long time before Thomson’s discovery, it remains surprising that very few had openly contemplated until then the idea of using adult stem cells for medical purposes. Be it as it may, the field has gone a long way throughout this past decade. Several adult stem cell types are currently in clinical trials for a variety of conditions ranging from myocardial infarction⁵ to graft-versus-host disease,^{6,7} and huES cells will shortly follow suit.

Among the many conditions potentially treatable by stem cells, type I diabetes (a disease where the endocrine pancreatic cells that synthesize and secrete insulin are destroyed by autoimmune processes) holds a position of privilege. Unlike many other commonly cited targets of stem cell approaches (such as Parkinson’s disease or spinal cord injury), there is already an effective cell therapy for type I diabetes. Indeed, islet transplantation has been shown to completely restore normoglycemia in human patients,⁸⁻¹⁰ and even if there is a progressive loss of function of the graft over time,¹¹ patients invariably report a much higher quality of life than before the

procedure.¹² Based on our experience with this therapy, it is not unreasonable to expect that any stem cell type with the ability to give rise to insulin-producing, pancreatic endocrine-like tissues will also work in a transplantation setting.

In this context, this book has been conceived with the goal of presenting the state of the art in regenerative therapies for the pancreas. First, we will briefly describe how the adult organ works (in the chapter “The Pancreas”). Then, we will thoroughly review the two physiological processes that should be recapitulated in different therapeutic settings, namely *pancreatic development* (in the chapter “Pancreatic Development”) and *islet regeneration* (in the chapter “Pancreatic Regeneration”). The chapter “Stem Cell Differentiation: General Approaches” will examine the general experimental strategies used to differentiate stem cells, regardless of their origin, whereas the chapters “Embryonic Stem Cells and Pancreatic Differentiation” and “Adult Stem Cells and Pancreatic Differentiation” will focus, respectively, on the utilization of embryonic and adult stem cell types for the procurement of transplantable insulin-producing cells. The latter will include special sections on bone marrow cells, umbilical cord blood stem cells, ductal and acinar cells, and mesenchymal stem cells. The chapter “Transdifferentiation” will drift away both from the general concept of stem cell differentiation and the two islet neogenesis processes known to happen in vivo (development and regeneration), to touch upon *transdifferentiation*, an intriguing phenomenon by which terminally differentiated cells from other tissues might be induced to alter their phenotype to become islet-like cells. We will conclude with a general overview of the remaining challenges and clinical perspectives of all of the above strategies.

Despite what many may perceive as a slow pace in translating basic findings into clinical therapies for type I diabetes, the last 10 years have been very productive in terms of shaping the overall direction of the field, many times as a consequence of a trial-and-error process. Progress has been steadfast, however, and the current state of the art suggests that stem cell-based trials, perhaps combined with immunological therapies, might be just around the corner. Because type I diabetes is a complex disease, a cure will only come from a multidisciplinary effort, which will almost certainly include a strong stem cell component. It is our hope that this book will help frame the problem for researchers and clinicians alike.

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