Stem Cell Biology and Regenerative Medicine

David S. Allan
Dirk Strunk *Editors*

Regenerative Therapy Using Blood-Derived Stem Cells

Humana Press

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Preface

Blood has long been viewed as a conduit for therapy, stemming from the ancient days of phlebotomy to remove evil humors to the development of successful blood transfusions to replace missing blood components. The identification and characterization of hematopoietic stem cells by Drs. Till and McCulloch revolutionized the field and soon after, non-hematopoietic stem and progenitor cells were characterized from the blood and bone marrow. Some of these cell types and various blood-derived cell lineages are involved in the repair of various types of tissue damage that span the spectrum of medical disorders. The goal of this book is to provide an up-to-date review of the various types of blood-derived cells with regenerative capacity, identify opportunities for intervention by examining specific clinical applications, and recognize the regulatory environment that will encompass future therapies in regenerative medicine.

Through the contributors to this volume, we have succeeded in providing insight on numerous blood-derived cell types, including endothelial progenitors, mesenchymal stromal/stem cells, umbilical cord blood-derived undifferentiated somatic stem cells and others. Further, the concept of using umbilical cord blood is discussed throughout the book and several authors describe the current status of regenerative therapy for cardiac disease and neurological disorders. Technical and conceptual issues such as ex vivo expansion and the generation of induced pluripotent stem cells are covered and regulatory insight from various jurisdictions provides a degree of clinical relevance that may shape the immediate future of regenerative medicine.

We wish to thank the many contributors for their tremendous commitment and their precious time in preparing the insightful chapters that comprise this book. Some are long-time friends and contacts while others are new and welcome collaborators. All the contributors are dedicated to advancing our collective knowledge regarding the field of regenerative therapy. The cooperation and contributions from our colleagues and fellow authors has been inspirational. The guidance and support from the series editor, Dr. Kursad Turksen has been most valuable and the staff at Springer has been especially helpful in making this project a reality. In particular, we are indebted to the administrative assistance and invaluable editing performed by Monica Farrell and Stéphanie Rochette.

We hope this book will stimulate enquiring minds and future investigation in this exciting and evolving field of research. The community of dedicated researchers and health care providers will need to engage at all levels to continue the push towards viable treatments that improve the lives of patients around the globe.

Ottawa, Canada — David S. Allan
Graz, Austria — Dirk Strunk

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Chapter 1
Undertaking Regenerative Medicine Studies with Blood Stem Cells

Sowmya Viswanathan and Armand Keating

Abstract In this chapter, we provide a perspective on the advances achieved to date in regenerative medicine, identify some of the challenges confronting the field, and make specific recommendations aimed at hastening the translation of research to effective clinical practice. Regenerative medicine is well positioned to address many of the urgent unmet medical needs of the global community. The stakes are high, but success will come only from the collaboration and mindfulness of specialists from diverse fields and from the focused attention of funding agencies.

1.1 Cells, Secreted Factors, and Mechanisms of Repair

Stem cells have been used to treat a variety of malignant and nonmalignant hematological disorders since the first bone marrow transplantation in 1959 (Thomas et al. 1959). Interest in regenerative medicine, however, increased considerably after the identification of diverse populations of stem/progenitor cells from different tissues and was propelled further by promising results in animal models of injury and disease. Although numerous preclinical studies and early phase clinical trials have shown encouraging results, underlying mechanisms remain poorly understood. The discrepancy in efficacy among various cell sources, clinical trials, indications, and preclinical studies remains challenging and requires further investigation.

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The popular notion that cell therapy is synonymous with cell *replacement* therapy persists despite the lack of convincing evidence for the transdifferentiation of adult cells and limited evidence for prolonged donor cell engraftment or cell retention at sites of injury. In most cases, there is no correlation between improvements in functionality and cell dose, suggesting that beneficial effects may not arise solely from the local involvement of donor cells but may be due to other factors such as paracrine effects (Gnecchi et al. 2008). For example, conditioned medium from endothelial progenitor cells (EPCs) can ameliorate hind limb ischemia in rat models (Yang et al. 2010). Also, soluble factors from CD133+ bone marrow cells are neuroprotective in a murine model of brain ischemia (Bakondi et al. 2009). Thus, there is growing interest in the field to move from cell therapy to cell-free therapy using secretomes from stem/progenitor cells.

In some instances, cell replacement therapy is still needed. Embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) can generate tissue-specific, differentiated cells to replace absent or injured cells. For example, human iPSCs can generate fully functional human platelets (Takayama et al. 2010) that in the future could provide a much needed alternative to costly volunteer donor platelets that can lead to complications such as sepsis (Kruskall 1997). iPSCs may also be useful in treating monogenic diseases by replacing cells harboring disease-causing mutations by gene targeting and correction technology as demonstrated in a mouse model of sickle cell anemia (Hanna et al. 2007).

In many cases, the therapeutic cell of interest may not be a stem cell at all. This is particularly evident in our evolving understanding of the therapeutic role of mesenchymal stromal cells (MSCs) from cells that engraft and give rise to differentiated cells (i.e., stem cells) to cells that secrete anti-inflammatory, antiapoptotic, angiogenic, antifibrotic, and immunomodulatory factors (Singer and Caplan 2011). The therapeutic effects of MSCs can often be reproduced by MSC-conditioned medium (Oh et al. 2008; Ma et al. 2006; Ye et al. 2006), which contains proteins secreted in response to injury signals such as TNF-α–stimulated gene/protein 6 (TSG-6) (Milner et al. 2006; Milner and Day 2003) able to directly promote corneal (Oh et al. 2010) and myocardial (Milner et al. 2006; Milner and Day 2003) tissue repair.

Another issue to consider is the heterogeneity of cell populations used for preclinical and clinical investigations. Bone marrow cells which contain a mixture of hematopoietic stem/progenitor cells, EPCs, and MSCs are most often used in clinical applications as they are easy to obtain and isolate. However, the variable clinical outcomes obtained with these heterogeneous cells are difficult to interpret. This is underscored by the results of several clinical trials with bone marrow–derived cells for treating cardiac diseases including acute myocardial infarction (AMI) and chronic ischemic heart disease (Martin-Rendon et al. 2008; Kang et al. 2008; Donndorf et al. 2011). Systematic and meta-analyses of several clinical trials show slight to modest improvements in hemodynamic parameters including left ventricular ejection fraction (LVEF) (2.99% in Martin-Rendon et al. 2008; 2.88% in Kang et al. 2008, 5.90% in Donndorf et al. 2011) without concomitant changes in short-term clinical events such as arrhythmias, rehospitalization for heart failure, or performance status.