Preface

The first successful cord blood (CB) transplantation was performed in October 1988, using HLA-matched CB cells from a female sibling to treat a boy with Fanconi anemia.1 More than 23 years later, the recipient of this CB transplant is alive and well and cured of the hemato logic manifestations of Fanconi anemia. This first CB transplantation was initiated based on a laboratory study that suggested the presence of a therapeutic dose of transplantable hematopoietic stem and progenitor cells (HSCs and HPCs) in a single collection of CB; it also suggested that the collected CB could be maintained in viable form for a short time in its own plasma for transportation from a distant obstetrical unit to a site where it could be frozen in cryopreserved form and stored as part of a cellular banking system for future use.2 The two main investigators from my laboratory, Giao Hangoc and Scott H. Cooper, who helped with the biologic studies reported,2 are shown in Fig P-1 with myself. The large dry shipper was used to hand deliver the CB unit for the first transplantation.1 The smaller dry shipper was used to deliver the CB units for the next four transplantations, as well as for two of the second five transplantations performed. The CB units for the first five were hand delivered by Scott Cooper to the transplant sites (three in Paris, one in Cincinnati, and one in Baltimore), and the last two were shipped by overnight mail. It is now known that such frozen CB units can be stored for at least 23.5 years in cryopreserved form with efficient recovery of functional HSCs and HPCs after careful thawing.3 The poster in the background of Fig P-1 described the 15-year experience with recovery of frozen CB, information that was later published.4 There have been over 25,000 CB transplantations performed worldwide to treat the same variety of malignant and nonmalignant diseases treated by bone marrow cells.5

In the years since that first CB transplantation, much has been learned from the innovative clinical and scientific efforts of many investigators. Participants in the three international CB conferences I held in Indianapolis in 1993, 1997, and 2001 are respectively shown in Figs P-2 through P-4. It was at these meetings that the past, present, and future of CB transplantation were discussed. There is clearly still much to be learned to make CB transplantation a more efficacious clinical procedure.

This is the third book on CB to be edited by myself and published by AABB. The first was published in 1998 (Cellular Characteristics of Cord Blood and Cord Blood Transplantation), and the second in 2004 (Cord Blood: Biology, Immunology, Banking, and Clinical Transplantation). With all the new information available since the AABB publication in 2004, it was felt that the time was right to provide a comprehensive overview of the current state of the art of CB cells and CB transplantation. The 2004 volume had 17 chapters. The present one is composed of 39 chapters by experts in their respective fields.
The book is divided into six sections and is meant to provide an up-to-date review of what is currently known in CB and related areas of interest. It is only when we have knowledge of the present status of this field that we can move forward to advance the still emerging efficacy of this area that is of great clinical relevance and significance.

Section 1 covers CB biology: hematopoiesis, stem/progenitor cells, and the microenvironment that nurtures these cells. Chapter 1 provides a brief historical overview of hematology, CB, and the links between the nervous and hematopoietic systems. This chapter is meant to provide the reader with the fascinating history of hematology, in short, and to introduce other chapters in this section. Chapter 2 focuses on developmental hematopoiesis and as such places CB in the context of development. The third chapter covers the area of hematopoietic cytokines and growth factors, information of use for
the reader to more easily grasp the role of these cytokines and growth factors in the regulation of hematopoiesis in general and their uses for modulation of the expansion and engrafting capability of CB HSCs and HPCs. The fourth chapter provides the reader with a comprehensive understanding of how HSCs and HPCs can be recognized, defined, and isolated through phenotypic recognition of cell surface and intracellular markers. More significantly, this chapter defines the links between the phenotype and function of HSCs and HPCs, as phenotype does not always recapitulate function, especially under stress hematopoiesis. It is very important for the readers to understand this distinction between defining a cell by phenotype and defining the function actually manifested by the phenotyped cell. In contrast to the understanding of hematopoiesis in the mouse and mouse HSCs and HPCs, quantitative assays for human hematopoie-
sis, especially for human HSCs, are not necessarily as definitive. Human HSCs can engraft immunodeficient mice, so Chapter 5 describes immunodeficient mouse models in detail for assessing human hematopoiesis. A recent paper\(^6\) published by the laboratory of John Dick in Toronto, Canada, dealing with the phenotypic isolation of human HSCs that would allow a single such cell to engraft an immunodeficient mouse should be read in the context of Chapters 4 and 5 to complement information in these two chapters. Chapter 6 covers the interesting and unusual very small embryonic-like stem cells recently found in CB by this group. The microenvironmental niche has not yet been absolutely defined. The next three chapters in Section 1 cover ever-expanding information on different microenvironmental niches that nurture HSCs and HPCs in vivo. This information is crucial to future advances in the treatment of hematologic and related
disorders and will have increasing relevance for understanding malignancy in the future. Chapter 7 deals with the vascular marrow niche; Chapter 8 deals with cellular components and the regulation of the HSC niche; and Chapter 9 details the dynamic and modifiable nature of HSCs and their niches. Chapter 1 leads into the above material on microenvironmental niches by dealing with the interconnection of components of the nervous and hematopoietic systems, and hematopoiesis and HSC/HPC regulation.

Section 1 serves as an introduction to the chapters in Section 2, which deal with pre-clinical and clinical means to enhance engraftment of limiting numbers of CB HSCs and HPCs. One disadvantage of CB in comparison to marrow or mobilized peripheral...
blood for HSC/HPC transplantation is the number of cells collected in CB, which can be limiting for transplantation of adults and higher-weight children. Although clinical efforts are ongoing to compensate for this limiting number of CB cells present in single CB collections by use of double CB transplantation (an area covered extensively in Section 5), double CB transplantation, while effective, is not without its own problems. Disadvantages of double CB transplantations include cost (double that of a single CB unit) and increased graft-vs-host disease (GVHD) compared to single-unit transplantation. An advantage of single-unit CB transplantation is that it elicits little GVHD. Moreover, little evidence yet exists that double CB transplants significantly accelerate time to engraftment for neutrophils and platelets, a familiar concern in single-unit transplantation of CB compared to marrow and mobilized peripheral blood transplants. Hence, efforts to find means to enhance the speed and overall engraftment of single CB units for transplantation continue. Toward this goal, Chapter 10 describes preclinical information for using prostaglandin E2 and other eicosanoid-based strategies to enhance engraftment. Chapter 11 describes preclinical efforts to use inhibition of the cell surface protein CD26, a dipeptidylpeptidase IV (DPPIV), to enhance engraftment, as well as efforts toward an ongoing pilot clinical study evaluating this inhibition of DPPIV strategy. Chapter 12 describes the preclinical and clinical efforts to expand ex vivo at least short-term repopulating HSCs using Notch ligand interactions and cytokines in culture. Chapter 13 describes how an understanding of the process of fucosylation can be used in a preclinical, and possibly future clinical, setting to improve CB engraftment. Chapter 14 describes preclinical efforts that led to clinical evaluation of the use of intrabone transplantation of CB cells to influence engraftment.

Section 3 describes the generation or presence of nonhematopoietic and hematopoietic cells in CB for potential use in regenerative medicine. There have been numerous reports recently of the generation of induced pluripotent stem cells (iPSCs) from many cell sources, including CB. These iPSCs have been generated from starting populations of both mature and immature cells and have the interesting capacity, after attaining an embryonic-stem-cell-like state, of functioning as either fully or partially reprogrammed cells and of responding to induction of differentiation into cells of the three embryonic germ cell layers (mesoderm, ectoderm, and/or endoderm). Although it is not clear whether such iPSCs will ever be ready for prime-time use in a clinical setting,6 these cells allow for insight into cell biology and the reprogramming process, and perhaps someday they will be of clinical use, at least at a diagnostic level. Chapter 15 and Chapter 16 describe current knowledge about iPSCs generated from CB. A number of nonhematopoietic cells have been identified in CB, including endothelial progenitor cells, and this cell population is covered in Chapter 17. In addition, other nonhematopoietic cells or hematopoietic cells for other possible uses are covered from a preclinical point of view in Chapter 18 and are covered in Chapter 19 in a preclinical and clinical context. Chapters 18 and 19 deal with the potential of the utility of CB cells for regenerative medicine. The authors of Chapter 18 and 19 mention, and I highlight here myself, that it is not yet apparent whether many of the animal model studies at a preclinical level in this area of regenerative medicine have been or can be duplicated by other laboratories, an essential concern before considering clinical trials in this area. Also, it is important to note that preclinical evidence for regenerative medicine approaches may not translate into clinical efficacy. It seems reasonable that a very cautious approach to regenerative medicine is needed at this time.7

One attribute of CB transplantation, at least at the level of transplantation of a single CB unit, is the decreased GVHD elicited compared to that seen in marrow transplantation. This lowered risk has allowed the
opportunity to use partially HLA-disparate CB grafts for transplantation. However, immune reconstitution is slower in CB vs other sources of HSC/HPC transplantation, such as marrow or mobilized peripheral blood. Therefore, Section 4 is devoted to the area of immune cells in CB and immune cell recovery after CB transplantation. Chapter 20 describes the immaturity of CB immune cells, with dysregulation of gene expression and protein production. Chapter 21 focuses on the differentiation and trafficking potential of CB helper T lymphocytes. Chapter 22 describes a role of T regulatory cells in allogeneic HSC transplantation. Chapter 23 discusses CB graft lymphocytes and their unique biology as relevant to neonatal immune tolerance. Chapter 24 describes T-cell-dependent immune competence after CB transplantation, and Chapter 25 focuses on natural killer cells from CB. Chapters 20 through 25 provide a comprehensive view of the state of knowledge regarding CB immune cells and their reconstitution after CB transplantation. Modulation of CB immune cells could enhance the efficacy of CB transplantation.

Section 5 focuses on clinical CB transplantation. This is a very active area of investigation, and it is only in the last few years that more CB than marrow transplantations have been performed per year. CB transplantation for leukemia in children is covered in Chapter 26. Transplantation for treatment of nonmalignant disorders is described in Chapter 27. Chapter 28 provides information on the use of CB cells for adults. Chapters 29 through 31 describe the use of double CB transplants from unique perspectives: CB transplantation for malignant disorders in Chapter 29, determinants of engraftment after double CB transplantation in Chapter 30, and reduced-intensity conditioning and double CB transplantation in Chapter 31. Section 5 is rounded out by Chapter 32 discussing the underutilization of CB for transplantation, including the extent of the problem, causes, and means to improve this situation. It is clear, as the efficacy of CB transplantation is enhanced and other potential uses of CB cells are identified and verified, that CB will be sought after as a possible preferred source of transplantable cells.

Section 6, the last section in the book, focuses on the logistics of managing CB at the transplant site, differences and similarities between public and private CB banking, and regulatory issues in CB banking. The management of CB at the transplant center is covered in Chapter 33, while CB banking is detailed in Chapters 34 and 35. Chapter 36 describes CB banking efforts in developing countries. Chapter 37 and 38 include accreditation and regulation of CB banking, as well as worldwide searching and distribution of CB units. CB banking and transplantation is undergoing increased regulatory scrutiny, and Chapter 39 provides information on the current status of the US Food and Drug Administration regulations that apply to CB. It will be clear from Chapters 33 through 39 that the field of CB banking and transplantation is evolving for the better and that the highest quality control is needed at each stage of each process (collection, banking, transportation, and transplantation). While regulation of these different processes is still in a state of evolution, it is apparent that more, rather than less, regulation is in store for the field. Although I believe that most involved in the field of CB banking and transplantation will agree that regulation of these procedures is important, it is hoped that this regulation will not become so onerous that it has the unintended effect of interfering with the progress of these vital processes associated with CB transplantation.

From a personal perspective, having been involved in the field of CB banking with my laboratory setting up the first proof-of-principle CB bank to deal with the first HLA-matched sibling CB transplants, I sometimes wonder if CB transplantation would have been possible, or how much longer it might have taken to complete the first CB transplantations, had all the regulations now set in motion been so at the time of our initial studies. This should not be taken to suggest
that I feel regulation of this field is not important. It is very important to have regulation, so long as these efforts do not compromise future progression of the field.

It has been very gratifying having been involved in the field of successful CB transplantation since its inception and having helped to initiate the national and international efforts that started this field. Especially, I have enjoyed meeting and interacting with all the scientific and clinical investigators who have brought this area to its current state. CB transplantation has come far. I hope the chapters in this book will help those already involved in different aspects of CB biology, banking, and transplantation to continue this progression. Also, it is my desire that this book serve to stimulate enthusiasm in others not yet involved in the field to help find the means to enhance knowledge in the use of CB cells.

I am grateful to Laurie Munk at AABB Press for continuing, over a number of years, to entice me to take on the editorship of this most recent book. Most of all, I am thankful to the authors of the chapters in this book for taking time from their very busy schedules to produce the quality of reviews that make up this book. Together, we look forward with continued enthusiasm and anticipation to the new basic laboratory, clinical, and CB banking efforts that will take our field to a higher quality level. The beneficiaries of this effort will be the patients who will be treated by CB cells, and we can share in the satisfaction of successful results.

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References