

# Preface

## **The Afterbirth: Once Discarded, Now Useful**

Life is an ongoing symphony of building up, taking down, replacing, and remodeling tissues. The skin sheds and regenerates from within, the muscles build in response to exercise, the intestinal lining refreshes continuously. The cells needed for these processes are supplied by endogenous stem cells. Regenerative approaches that may repair sustainable biological tissues can capitalize on that strength of biology by using the cells from the umbilical cord, a tissue critical to gestation and seemingly useless after birth.

The 1950s saw experiments in which transplantation of one cell regenerated a frog, thereby exploring the malleability of cellular differentiation. Also in the 1950s, the first therapeutic bone marrow transplant was used to treat a patient with leukemia. Since then, many thousands of patients have been treated with transplants of blood-forming hematopoietic stem cells derived from bone marrow. Turning these pioneering efforts into successful medical treatments required advances in understanding the immunology of tissue rejection and the developmental biology of the blood-forming tissues, and even more advances in the technologies necessary to handle the cells and support the patients. About 30 years later, the first efforts to use hematopoietic cells from umbilical cord blood began with the treatment of a boy with Fanconi anemia.

This book, written for the research scientist, the medical specialist, and the interested student, gives an overview of current research about stem cells derived from umbilical cord blood and tissue. The book discusses the science surrounding a range of topics, including the various tissues in the umbilical cord, the current state of the research, the medical applications in place at the moment, and the potential for more advanced medical applications. The book also reflects on the complicated ethics concerning umbilical cord tissue collection, banking of tissue samples, and use of cord blood cells and tissues for medical treatments. The book is ultimately a story about cells, donors, patients, technologies, research insights, medical applications, and an emerging specialty.

In the context of regenerative medicine or tissue engineering, cells are the starting point. Cells could be used to replace damaged or degenerating tissues. Cells could be used to provide a helping environment to better sustain remaining endogenous cells. Cells could be used to learn more about development and cellular signaling, lessons that can be translated for application to normal tissues or to disease states. Cells could be used to deliver missing gene products or hormones. Stem cells are of particular utility because of their ability to proliferate and their undifferentiated status, characteristics that may be intricately intertwined.

Stem cells generally have a deceptively simple plan: maintain, proliferate, differentiate, signal, and die. Diversity in the details translates the general plan into the specific developmental pathways that form the various specialized tissues of the body from lineage-dedicated progenitor cells. Chapters on the basic biology of stem cells show that what is learned from the fruitfly *Drosophila* or the tiny worm *Caenorhabditis elegans* can help with understanding how stem cells function and how tissues are built.

The umbilical cord and placenta provide one source of stem cells. Cord blood can be collected from the umbilical cord and placenta after birth. Currently about one in five hematopoietic stem cell transplants use cord blood as a source. Some of the advantages of cord blood over bone marrow have to do with how cord blood is comparatively easy to collect after birth from tissues no longer needed and can be stored frozen in tissue banks. Other sources of stem cells that researchers are currently grappling with are complicated by limited availability, by extra interventions needed to make

the cells useful, and by ethical constraints unique to each type of cell source.

Umbilical cord blood differs from bone marrow or peripheral blood as a source of hematopoietic stem cells. Umbilical cord blood is available in smaller quantities, but from a greater diversity of donors, than bone marrow. The complications attendant to transplantation may be fewer for umbilical cord blood, but bring a different suite of tag-along disease complications than bone marrow. Despite the advances already brought by hematopoietic stem cell transplantation from either source, considerable problems remain. Not all patients may find a match. Not all matches may result in success. The intervention is complicated and brings its own risks. This book considers the merits and problems of each approach.

Although the parallels with bone marrow transplant suggest that cord blood cells may have great utility for hematopoietic disorders, cells derived from umbilical cord may have other uses as well. The blood that the umbilical cord carries, some of which it still holds after birth, has been the main aspect of interest. However, the conduit itself, the umbilical cord, also offers some interesting cells that may turn out to be useful for therapeutic applications. Endothelial cells lining the umbilical vein and also mesenchymal-like cells that form the bulk of the tissue are already showing promise. The book explores some of the possible applications, such as support for vascularization or bone reconstruction. Even the cord blood cells are most likely not a homogeneous population. Subpopulations of cells identifiable by suites of proteins expressed on the cell surfaces seem to differ in their abilities to generate diverse sorts of new tissues. The book discusses outcomes of clinical trials, status of current research, and technologies most productively applied.

Other chapters look at the sorts of clinical settings in which cord blood transplantation might be a suitable option. How have various cancers and disorders of the blood responded to transplantation therapy based on cord blood, bone marrow, or peripheral (adult) blood? What sorts of complications have arisen? How are new technological refinements expanding the value of cord blood as a source of hematopoietic cell transplantation? What limits the number of stem cells in one sample? How does sample size per cord blood unit affect utility for some patients? What laboratory interventions are being developed to address these problems?

Treatments that depend on autologous transplantation, in which cells are derived from the same patient they will be used to treat, are currently quite limited. More often, interventions depend on donors. When the disease is rooted in a genetic anomaly, it may do little good to give the patient more of those same anomalous cells; donated cells with different genetics might do the job better. Both banking for autologous use and anonymous donation each carry their own ethical complications, as the book discusses. A particular advantage of cord blood over bone marrow as a tissue source is that cord blood is comparatively easy to collect and can be stored long-term. These factors cooperate to develop cord-blood collections with better representation of tissues suitable for patients with unusual tissue matching needs and for patients of ethnic minorities not well represented in the bone marrow registries.

Banking of cord blood samples also brings unique ethical challenges. Donors' rights need to be respected, and attempts to play on the heart-strings of parents either facing or anticipating a medical crisis need to be thwarted. Some of the ethical issues revolve around the angst and excitement of parents in the delivery room. With a newborn baby on their hands, and full of hopes and fears for the baby's future, parents may be susceptible to pressures that they should bank the cord blood for their own child's advantage, at a not inconsiderable cost. What costs are reasonable and whether better economic solutions exist, what cooperation between private and public interests is optimal, what situations are best treated by autologous transplant, are all challenging questions discussed here.

A heart-wrenching litany of diseases, disorders, and accidental damages plagues lives. Stem cells seem to offer promise of new medical therapies applied to treat a variety of diseases and disorders. However, we must be cautious in our expectations. Our understanding of stem cells and how they might best be used is still limited. Some of the current views will necessarily be revised as further research clarifies what stem cells can and cannot do. In the research labs, as reflected in this book, scientists are working hard to test the utility of umbilical cord cells as tools to address a variety of medical problems.

Moore's law describes the biannual doubling in capacity of integrated circuits, a pattern of technology growth that has driven similar growth in the memory space of desktop computers and the revolution by which

everyday digital photography has overturned film photography. Similarly, we may expect to see considerable progress in the scientific understanding derived from cord blood tissues over the next few decades. What shape that advance takes remains to be seen. Although the unknown is less a barrier than a challenge to scientists, the translation of insights in regenerative medicine from basic science results to clinical applications must be guided by ethical and thoughtful respect for patients' circumstances.

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