
Preface

There has been increasing awareness and interest in the field of stem cell research from researchers, industry, and the general public. This is because of the remarkable potential of stem cells to develop into the many different cell types that are present in the body, providing a cell source for replacement functional tissues. Stem cells have become an essential tool for many other fields, including for developmental biology, development of cell therapies, drug discovery, disease models, and tissue engineering.

Some types of stem cells are known to reside in organ-specific niches and can become activated, proliferating and differentiating to maintain tissue homeostasis, or following injury to replace damaged cell types. These so-called adult or endogenous stem cells are capable of multipotent differentiation but are generally limited to cell types within their organ of origin. Endogenous stem cells have been widely studied to achieve a greater understanding of tissue turnover and responses to injury. Much research is focusing on how we can harness the power of endogenous stem cells as a source for regenerative medicine. While successful clinical application has been achieved for some organs, such as the hematopoietic system, difficulties in isolating and expanding many of these cell types *ex vivo* have limited their widespread application.

Embryonic stem cells have been an essential cell source for our current understanding of cellular developmental biology. These cells are derived from the inner cell mass of the blastocyst of an embryo. Embryonic stem cells have two important properties that make them attractive to researchers. The first is that they are pluripotent, capable of differentiating into all of the cell types of the three primary germ layers. Second, they are capable of expanding indefinitely in culture without losing their pluripotent differentiation capacity. The potential to generate large numbers of differentiated cell types *in vitro* has driven many groups to investigate the application of these cells to treat disease. Although many challenges remain, the potential of these cells to form tumors *in vivo* is a major concern, and the allogeneic nature of the cell source means that immune rejection of the cells is likely.

One of the major contributions of embryonic stem cell research to the field was the identification of “pluripotency factors,” which are factors that promote properties and behavior common to pluripotent stem cells. This knowledge has been applied to generate what are known as “induced pluripotent stem cells,” which are pluripotent embryonic stem cell-like cells generated by inducing the expression of pluripotency factors in mature somatic cells using virus, protein, or small molecule inducers. This technique has facilitated the generation of pluripotent stem cell lines without destroying human embryos and potentially allowing autologous applications. However, these cells still have a high risk of tumorigenicity, which has limited their current applications to *in vitro* studies such as disease modeling and drug discovery.

Perinatal stem cells are a group of cell types that can be derived from postembryonic, perinatal tissues, which includes tissues sourced at the time of birth, but also encompasses the time period from the 20th week of gestation through the neonatal period. These tissues are usually discarded at the time of birth and include the amniotic fluid, the placenta, placental membranes, umbilical cord, and blood. As a discarded tissue source, harvesting of stem cells from these sources represents a simple, noninvasive, and safe means for attaining therapeutic cell types. In addition to being easily accessible, perinatal stem cells can be isolated and expanded

in vitro, with some cell types capable of over 250 population doublings. Perinatal stem cells appear to have properties of both embryonic and adult stem cell types. Some have a highly multipotent differentiation potential, capable of forming functional cell phenotypes from all three lineages of the primary germ layers, but without the detrimental property of tumorigenicity associated with embryonic and induced pluripotent stem cells. The ability to transplant these cells safely, without any reported in vivo tumorigenicity, is a major advantage of these cell types.

During fetal development, perinatal tissues form a protective barrier between two immunologically distinct individuals. This function may confer perinatal stem cells with unique properties of immune privilege and immune suppression. Many studies have observed that perinatal stem cells can be delivered in allogeneic or xenogeneic setting without resulting in an immune response commonly seen with other cell types. Additionally, researchers have characterized the potent immunosuppressive properties of these cells, which are capable of influencing innate and adaptive immune responses in vitro and in vivo.

As described in this book, perinatal stem cells have found widespread application for the treatment of many diseases, injuries, and disorders. These cells have shown the capability to differentiate into functional organ-specific cell types and engraft in injured tissues to restore function following disease or injury. These cells have also found application in preventing or treating disease through modulation of the immune response. With inflammation playing an important role in disease and injury, regulating this response with cellular therapies could have a major impact on healing and tissue regeneration.

This book has been divided into four major sections, each dealing with commonly applied perinatal stem cell types as well as a final section on efforts supporting the clinical translation of these cells. Written by international experts in the field, the contributed chapters cover a wide range of topics, including efficacy, mechanisms of action, the application of perinatal stem cells for the treatment of disease or injury, and clinical translation. These parts are titled: Part I: Amniotic Fluid Stem Cells, Part II: Placental and Placental Membrane Stem Cells, Part III: Umbilical Cord Cells, and Part IV: Clinical Translation.

Part I: Amniotic Fluid Stem Cells

Part I focuses on applications of stem cells derived from the amniotic fluid, beginning with Sveva Bollini and coworkers describing the potential application of amniotic fluid stem cells for cardiac regeneration and discussing three different approaches, namely stem cell-based therapy, paracrine therapy, and cardiac tissue engineering.

Aleksander Skardal presents research demonstrating that delivery of amniotic fluid stem cells has the potential to be an effective cell therapy for facilitating wound healing. This chapter highlights the portfolio of potent growth factors secreted by amniotic fluid stem cells that are integral to skin regeneration and induction of angiogenesis in healing wounds.

Augusto Zani from Paolo DeCoppi's group has provided an excellent chapter describing the treatment of necrotizing enterocolitis with amniotic fluid stem cells. The chapter highlights the application of amniotic fluid stem cells in animal models of necrotizing enterocolitis, where this therapy significantly reduced gut damage and increased the survival of these animals.

Emily Moorefield provides an in-depth overview of the immunomodulatory properties of amniotic fluid cells and discusses the potential application of amniotic fluid stem cell therapy to selectively inhibit the immune response in graft versus host disease.

Margit Rosner from Markus Hengstschläger's group discusses the theory that amniotic fluid stem cells might be involved in fetal cell microchimerism during pregnancy. The authors discuss properties of amniotic fluid stem cells that support a role in fetal cell microchimerism as well as identify features that need to be tested to further support this theory.

Orquidea Garcia from the Children's Hospital Los Angeles has contributed an interesting chapter investigating the potential of amniotic fluid stem cell therapy for lung disease. In this chapter, the authors examine some of the challenges faced in treating respiratory disease, and how amniotic fluid stem cells have demonstrated the potential to address these challenges.

Koji Shido describes studies that aim to reprogram amniotic fluid stem cells into an endothelial cell phenotype and the application of these cells for injury repair and organ regeneration. This comprehensive review highlights recent advances in reprogramming of amniotic fluid stem cells, endothelial induction, and production of paracrine mediators to directly induce organ regeneration.

Andrea Preitschopf and Mario Mikula summarize developmental stages and factors involved in articular cartilage formation and degeneration. The chapter highlights recent advances in the application of amniotic fluid stem cells for the generation of cartilage tissue and how the endogenous cartilage formation process could be recapitulated during tissue engineering.

The chapter written by Simon Hoerstup and coworkers describes the potential application of amniotic fluid stem cells for cardiovascular tissue engineering. The authors comment on studies demonstrating that amniotic fluid-derived stem cells generate living autologous heart valve leaflets in vitro and the successful in vivo translation of amniotic fluid cell-based engineered heart valves into the ovine fetal model.

Jaehyun Kim from Wake Forest Institute for Regenerative Medicine discusses characteristics of amniotic fluid stem cells that make these cells appealing for osteogenic applications and reviews tissue-engineering approaches utilizing these cells for treating bone defects.

In their chapter, Weerapong Prasongchean and Patrizia Ferretti discuss therapeutic approaches for the treatment of birth defects in utero and perinatally. This review highlights the current experimental and clinical evidence of the potential of amniotic fluid stem cells for the treatment of birth defects either in utero or early postnatally.

Teodelinda Mirabella has provided an excellent chapter describing strategies to stimulate therapeutic angiogenesis using amniotic fluid stem cells. This chapter reviews studies that demonstrate the in vitro manipulation to direct amniotic fluid stem cells toward a vascular phenotype, stimulation of endogenous repair through recruitment of host progenitors, and the potential to use their pro-angiogenic secreted factors as a secretome-based therapy.

Part II: Placental and Placental Membrane Stem Cells

Part II is dedicated to chapters describing applications of stem cells derived from the placenta and placental membranes. These cell types include mesenchymal stromal cells from the placenta, amnion membrane, and chorion membrane as well as amnion epithelial cells and chorionic trophoblastic cells.

Ornella Parolini starts the section with a chapter with a brief description of the structure of the placenta and an in-depth description of the various types of placenta and placental membrane-derived cell types. This overview details the phenotypic and functional and immunological characterization that has been performed on many of these cell types.

The second chapter of this section, authored by Gi Jin Kim, describes the characterization of several kinds of placenta-derived stem cells and discusses recent investigations into the therapeutic potential of these cells for repair of liver injury and disease.

Alicia Bárcena from Susan Fisher's lab in the University of California San Francisco has provided an excellent review of the hematopoietic potential of the human placenta throughout gestation and speculates about the possible use of this tissue at birth for the harvest of hematopoietic stem cells and progenitors.

Shan-hui Hsu and coworkers discuss the potential of human placenta-derived mesenchymal stem cells as a candidate cell source for cartilage tissue engineering, describing studies highlighting the essential role of 3D scaffolds for induction of chondrogenic differentiation of these cells in vitro.

Clara Sanjurjo-Rodriguez described various cell types that can be derived from the amnion membrane, specifically human amniotic mesenchymal stem cells and human amniotic epithelial cells. The isolation and comparative characterization of these cell types is discussed.

In their chapter, Tomonori Minagawa and coworkers describe strategies for the use of the human amnion membrane for the reconstruction of functional bladder tissue. They indicate that biomaterials and cells derived from the human amnion membrane have a potential for the reconstruction of functional urinary bladders.

Euan Wallace from Monash Institute of Medical Research provides a comprehensive overview of the application of human amnion epithelial cells for the treatment of chronic and acute lung disease in both the adult and neonate. This chapter reviews the extensive preclinical and clinical studies that have been performed using these cells to treat lung disease and addresses likely mechanisms of action.

In the chapter titled “Potential Efficacy of Amnion Epithelial Cells to Treat Post-Stroke Inflammation,” Christopher Sobey and coworkers review the current treatments and their limitations for treating ischemic stroke. This chapter describes the potential for amnion epithelial cells to improve stroke outcome given their unique properties, which include modulation of the immune response, differentiation into neural tissue, re-innervation of lost connections, and secretion of important factors to restore cellular function.

Courtney McDonald has written an interesting chapter investigating current evidence that human amnion epithelial cells are attractive candidates for the treatment of multiple sclerosis and other neurodegenerative disorders. Reviewed studies demonstrate that amnion epithelial cells suppress inflammation, migrate to inflamed sites within the central nervous system, engraft and differentiate toward neural lineages.

Sankar Venkatachalam expands on the previous chapter with a review of the current evidence of the beneficial aspects of amniotic epithelial cell transplantation for neurological conditions. Included in this review is the investigation of the application of amniotic epithelial cells for the treatment of contusive spinal cord injury.

The final chapter of this section is a review of the therapeutic potential of amnion epithelial cells for diabetes. This chapter, written by Chika Koike and coworkers, highlights the potential of amnion-derived cells to differentiate into insulin-producing cells in vitro and the transplantation of amnion-derived cells to normalize the blood glucose level in animal models of diabetes.

Part III: Umbilical Cord Cells

Part III focuses on cells derived from the umbilical cord blood and tissue and includes chapters describing applications of hematopoietic and mesenchymal-like stem cells. The first chapter, written by David Harris from the University of Arizona, focuses on the collection, processing, and banking of umbilical cord blood. The chapter provides an overview of umbilical cord blood collection, processing, and banking as well as providing an overview of clinical trials using cord blood.

Samberg, Eve, and Borlongan discuss the translational potential of cord blood-derived cells for treatment of a multitude of CNS disorders including Alzheimer’s disease, amyotrophic lateral sclerosis, cerebral palsy, spinal cord injury, and stroke.

The third chapter of this section focuses on the application of umbilical cord blood for the treatment of cardiovascular disease. In this chapter, Santiago Roura Ferrer and coworkers describe umbilical cord blood as a rich reservoir of both hematopoietic and non-hematopoietic cells with great potential as a source for regenerative cell therapy for cardiovascular disease.

Kyoko Baba discusses the use of umbilical cord blood and Wharton’s jelly mesenchymal stem cells, and provides an overview of the osteogenic potential of Wharton’s jelly-derived cells for application in bone tissue regeneration.

Rita Anzalone from Giampiero La Rocca’s group has presented an excellent overview on the application of umbilical cord blood and Wharton’s jelly mesenchymal stem cells for the

treatment of Type I Diabetes. The authors analyze current literature regarding the features and potential of Wharton's jelly mesenchymal stem cells and propose that transplantation of these cells may be useful both to regenerate β -cells and also prevent the autoimmune destruction of remnant and neogenetic β -cells in patients.

The final chapter of this section, written by Benedikt Weber and coworkers, begins by describing the endothelial progenitor cells isolated from term human umbilical cord blood. The chapter details standardized chemically defined cell culture protocols for these cells and their applications in cardiovascular tissue-engineering purposes.

Part IV: Clinical Translation

The fourth and final section of this book deals with the important aspect of clinical manufacturing, commercialization, and patents for perinatal stem cells. This topic is of increasing importance as perinatal stem cell therapies are translated from the lab bench and animal studies into clinical trials, banking, and commercialization.

The first chapter in the section is written by Celena Heazlewood, Nina Iliac, and Kerry Atkinson and provides an in-depth description of the manufacturing of perinatal stem cells for clinical trials. This chapter covers the basic biology of placental-derived mesenchymal stem cells, the regulation and documentation involved in clinical manufacturing, and the personnel, infrastructure, and monitoring requirements for the manufacture of clinical grade MSCs using current Good Manufacturing Principles (cGMP).

Rouzbeh Taghizadeh and coworkers have contributed an excellent chapter exploring in-depth the potential clinical use and benefit of perinatal stem cell and analogous regenerative medicine therapies sourced from the umbilical cord. This chapter details the development of methods of umbilical cord tissue cell banking that maintain the full therapeutic benefit of each respective stem cell population, and goes on to highlight the clinical potential of these cells for the treatment of hematopoietic diseases and cancers, immune-related diseases, as well as autoimmune-related disorder, musculoskeletal injuries, neurodegenerative disorders, cardiovascular-related injuries, and wound repair.

The final chapter of this section is contributed by Tamara Yawno, Euan Wallace, and Rebecca Lim from Monash University. This chapter is dedicated to patents and commercializing of perinatal stem cells. The authors discuss the evolution of patent development for perinatal stem cells as well as highlighting recent patents on the collection, isolation, characterization, and application of stem cells derived from the placenta, placental membranes (amnion/chorion), amniotic fluid, umbilical cord tissue, and cord blood.

Perinatal stem cell research has been ongoing for decades, and the field has now matured to the stage where many groups are progressing through preclinical studies toward clinical application of these cells. Together with this work, many groups are supporting this endeavor by establishing clinical manufacturing techniques, banking facilities, and developing intellectual property for these cells and techniques. Previous books and journals have discussed the specific origins, phenotypes, and properties of various perinatal stem cell populations. This is the first book of its kind to discuss in-depth the current preclinical and clinical applications of these cells, as well as efforts to support the transition of perinatal stem cell therapies from the laboratory to the clinic.

Winston-Salem, NC, USA

Anthony Atala
Sean V. Murphy

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