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# Placental stem cells: The promise of curing diseases before birth

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## ABSTRACT

Regenerative medicine is a rapidly expanding and promising field for many diseases and injuries. Stem cells for regenerative therapies have originally been obtained from bone marrow, but are now readily extracted from a variety of adult tissues. Fetal tissue has recently garnered interest for its ease of differentiation into a variety of phenotypes and its relative abundance of pluripotent-linked transcription factors. However, much ethical concern surrounds the methods of obtaining fetal cells. The placenta has emerged as a potential source of fetal derived cells due to its favorable technical and ethical characteristics, as well as its promising therapeutic properties. This preview focuses on providing an overview on the derivation and characteristics of placental derived stem cells as well as delving into their various clinical applications and potential future directions.

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## 1. Introduction

Regenerative medicine is a rapidly expanding and promising field for many diseases and injuries. Stem cells for regenerative therapies have originally been obtained from bone marrow, but are now readily extracted from a variety of adult tissues. Fetal tissue has recently garnered interest for its ease of differentiation into a variety of phenotypes and its relative abundance of pluripotent-linked transcription factors. However, much ethical concern surrounds the methods of obtaining fetal cells. The placenta has emerged as a potential source of fetal derived cells due to its favorable technical and ethical characteristics, as well as its promising therapeutic properties.

## 2. Derivation and characteristics of placental stem cells

While many sources of fetal stem cells are the center of ethical dilemmas regarding methods of collection, placental stem cells are obtained with little risk to the developing fetus. Chorionic villus sampling (CVS) has been routinely performed for genetic testing, usually during the first trimester. This method avoids damaging the fetus and provides a source of autologous stem cells. Allogeneic applications of placental stem cells are also possible through

donations of otherwise discarded placenta after birth or miscarriage.

Early gestation placenta can generate a wide variety of types of stem cells, including mesenchymal stem cells (MSCs), HSCs, EPCs, trophoblasts, myogenic progenitor cells, and perivascular stem cells [1–3]. MSCs are multipotent stem cells that are widely used for various clinical applications, and our lab has done seven years of preclinical research specifically on placenta derived mesenchymal stem cells (PMSCs). Protocols to derive PMSCs have already been established, including explant culture, enzyme dissociation, and enzyme + explant culture [4]. PMSCs have greater expansion potential and possess greater immunomodulatory capacity than adult bone marrow MSCs [5,6]. Our preclinical studies have shown that PMSCs secrete immunomodulatory and angiogenic cytokines which aid in healing and remodeling of tissue [1]. When expanded in neurotrophic media *in vitro*, PMSCs display neuroprotective growth factors in large amounts, preventing *in vivo* neuron damage [7].

## 3. Clinical applications of placental stem cells

A number of potential regenerative therapies using PMSCs are currently being explored. For adult diseases, placental cells have been investigated in animal models for almost every disease imaginable, from wound healing [8] and diabetes [9] to cartilage repair [10], chronic lung injury [11], ischemic heart disease [12], and liver disease [13]. Phase 1 and 2 clinical trials are underway in various countries for diabetes, ankylosing spondylitis, aplastic

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anemia, myelodysplasia, hematologic disorders, and graft versus host disease as examples.

#### 4. Unique potential fetal applications

The fetus is perhaps the ideal recipient of stem cell therapies. After all, the fetus is not “re”-generating but is in fact “generating” new organs and tissues throughout gestation. The fetal environment is the perfect milieu for stem cell therapies because cells are already in the ideal “media” for generation and remodeling. With the advancement of prenatal diagnostic techniques, many more diseases and structural anomalies can be identified before birth. Indeed, the origins of many common “adult” diseases are being identified in fetal life.

Placental stem cells can be harvested in the first trimester and expanded for potential autologous use in the afflicted fetus [1]. Autologous stem cells remove any concern about long-term tumor risks and may be more acceptable to pregnant mothers. One would be using the baby's own “supercharged” cells to heal problems before birth.

##### 4.1. Augmenting fetal organ development

Underdeveloped organs might benefit from the therapeutic properties of PMSCs. For example, lungs that have not developed properly may be at risk for pulmonary hypertension. PMSCs have demonstrated an ability to aid the maturation of lung cells when planted in an underdeveloped lung, which prevents such problems down the line [14].

##### 4.2. Induction of fetal tolerance for future organ transplant

Not only are PMSCs helping advance treatment of birth defects and development issues, but they can also progress postnatal tolerance for future transplants [15]. If one knew that a fetus would need a future kidney transplant, one can imagine a fetal bone marrow transplant that creates a chimeric immune system and induces tolerance to the baby's future organ donor. Stem cells can be used as a delivery vehicle for genetically mutant proteins [16]. These proteins limit the formation of inhibitors such as FVIII, which cause rejection of a transplanted organ. Limiting these factors early in gestation facilitates the postnatal tolerance of the transplant. This becomes increasingly important as 3D organ printing and further advancement of surgical techniques make transplants even more prevalent.

##### 4.3. Fetal genetic engineering and hematopoietic stem cell transplant

Placental stem cells can be used to deliver other proteins and augment engraftment of hematopoietic stem cells and could be used to treat hemoglobinopathies, such as sickle cell disease and hemophilia. Current trials are underway for the fetal treatment of osteogenesis imperfecta.

##### 4.4. Fetal tissue engineering

Our lab is currently investigating the use of placental stem cells as a possible treatment of a number of structural and genetic birth defects. PMSCs can be used in tissue engineering to replace structures that are missing, such as the diaphragm in congenital diaphragmatic hernia. Our lab is working to develop a muscle patch for repair of the diaphragm using autologous myogenic precursor cells seeded on an extracellular matrix. This novel therapy is currently being tested in a rat model of congenital diaphragmatic hernia.

PMSCs have also shown vast potential in the treatment of neurodegenerative diseases such as spina bifida, which is one of our lab's largest projects. We deliver early gestation PMSCs suspended in a hydrogel onto the spina bifida lesion before closing the dura and skin [17]. The neuroprotective cytokine factors secreted by PMSCs have proven successful in rescuing motor function in the well-established ovine model used in our lab, and we will soon be moving forward to a human clinical trial.

#### 5. Conclusion and future directions

In the future, nearly all diseases could be diagnosed and treated or prevented by manipulation before birth. The fetus could be both the source and recipient of novel and important stem cell therapies with the best chances for success, eliminating many of the barriers associated with allogenic stem cell transplants. Using fetal cells in the fetal environment is the ideal recipe for successful stem cell therapy.

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#### Conflict of interest statement

All authors declare that they have participated in the experimental design, data acquisition, analysis and interpretation and manuscript drafting and critical revision. They have seen and approved the final version. They have no conflicts of interest.

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