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# Cell-based strategies to reconstitute vital functions in preterm infants with organ failure

Kajsa Bohlin, MD, PhD *

*Division of Neonatology and Department of Clinical Science, Intervention and Technology, Karolinska Institutet and University Hospital, Stockholm, Sweden*

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Infants born preterm face a number of challenges. Depending on the degree of prematurity, they are at a risk of developing several specific conditions and diseases related to organ immaturity and complications of long-term neonatal intensive care. Various organ systems are affected, such as the lung, resulting in bronchopulmonary dysplasia (BPD); the vascular system, resulting in pulmonary hypertension; the brain, with the risk of intracranial hemorrhage; the eye with retinopathy of prematurity; and the gut, manifesting in the severe complication of necrotizing enterocolitis. A common hallmark for all these prematurity-related conditions is that inflammation seems to be a major driving force in the pathogenesis, and that injury repair is essential for recovery and long-term health. In addition, the available treatment options are often only supportive, not curative. This chapter reviews the recent advances of stem cell therapy that have opened up new possibilities to restore organ function following prematurity.



## Introduction

Advances in perinatal medicine over the last decades have dramatically improved survival after preterm birth in developed countries [1]. However, in a global perspective, prematurity is by far the leading cause of neonatal deaths, and it remains the second leading cause of death after pneumonia in children under the age of 5 years [2]. Preterm birth rates are rising, and, although it does not appear to

* Department of Neonatology, K78, Karolinska University Hospital Huddinge, S-141 86 Stockholm, Sweden. Tel.: +46 8 585 81356; Fax: +46 8 585 87545.
*E-mail address:* kajsa.bohlin@ki.se.

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be at the cost of higher rates of severe disability, there is increasing concern that survivors of preterm birth are at a risk of learning difficulties, as well as visual and hearing impairments. Emerging evidence regarding long-term health also suggests that prematurity is a risk factor for later development of chronic lung disease [3,4], cardiovascular disease [5,6], and type 2 diabetes [7,8]. The public health consequences of the increasing numbers of survivors after preterm birth are not yet fully understood, but it is clear that there is much to be gained by improving treatments in the neonatal period, for the individual infant with severe complications and for general future health.

Cellular therapies show great potential in a diversity of clinical conditions and diseases, including neurodegenerative disorders, cardiovascular disease, lung injury, diabetes, graft-versus-host reactions, sepsis, and hepatic and renal failure [9]. In various experimental models, stem cells are demonstrated to attenuate organ injury [10–13], and they induce tissue repair processes, the multipotency of these cells leading to them being described as the cellular "Doctors Without Borders." [14] However, the questions of the role, function, and mechanisms of action still hold intriguing gaps of knowledge. In the therapeutic situation, the engraftment of cells seems to be limited, leading to the assumption that the cells may rather serve as bioactive mediators that interact with inflammatory cells and modulate their response [15,16]. The identification of these paracrine effects has opened new options for treatment that may be of great importance in the neonatal period, as the potential side effects associated with cell-based therapies can be mitigated [17].

Infants born preterm, and particularly those with extreme prematurity defined as a gestational age below 28 weeks, face significant morbidity in the neonatal period [18] and lengthy hospitalizations. Intensive care for the smallest and most immature infants has improved dramatically, and a number of life-saving interventions are often effective in the battle against severe complications. Nevertheless, treatments are most of the time nonspecific, and therefore cellular therapies directed at different organ systems at risk of injury following preterm birth are new and promising forms of regenerative medicine in the neonatal period. Most of the work so far has been focused toward the lung and the brain, but novel findings have ignited interest in other areas, such as the gut and the eye, as outlined subsequently.

## Lung

Bronchopulmonary dysplasia (BPD) is the most common severe complication of preterm birth, affecting approximately 45% of infants with a birth weight below 1500 g [19]. The pathophysiology of BPD is characterized by inflammation, fibrosis, simplification of lung structure, and alveolar arrest [20], and the development of BPD is associated with other inflammatory diseases of pregnancy, such as preeclampsia [21]. Lung injury related to mechanical ventilation and oxidative stress still contributes to an increased risk of BPD, but presently the use of noninvasive ventilation, targeted surfactant treatment, and antenatal steroid treatment has shifted the etiology toward greater developmental immaturity of the alveolar and vascular systems of the lung, including developmentally impaired defense and repair mechanisms. Arrested lung growth, the histological hallmark of BPD today, may have an impact on lung function in childhood, which persists into adulthood and increases the risk of chronic lung disease and emphysema later in life [22]. Preventive measures and treatment options for BPD in very preterm infants are limited to supportive therapies; hence, new treatments that facilitate and promote normal lung development are strongly warranted.

The demonstration that bone marrow-derived stem cells could differentiate into alveolar epithelial cells led to stem cell research in neonatal lung disease [23]. A link between low levels of endothelial colony-forming cells (ECFCs) in cord blood and the risk of developing BPD further enhanced the rationale for adopting stem cell therapy in BPD. In nearly 100 preterm infants, with a gestational age <32 weeks, a decrease in ECFCs in cord blood was linked with more pulmonary vascular immaturity and an increased risk of BPD, whereas high levels of ECFCs in cord blood seemed to be protective for BPD development, even in extremely preterm infants [24]. In tracheal aspirates from preterm infants, the isolation of mesenchymal stromal cells is reported to be strongly predictive of the development of BPD [25]. Cells from infants who develop BPD are also reported to hold stable gene alterations favoring hypoalveolarization, suggesting involvement in the pathophysiology of the disease [26].