

# Stem Cells and Regenerative Medicine in Lung Biology and Diseases

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A number of novel approaches for repair and regeneration of injured lung have developed over the past several years. These include a better understanding of endogenous stem and progenitor cells in the lung that can function in reparative capacity as well as extensive exploration of the potential efficacy of administering exogenous stem or progenitor cells to function in lung repair. Recent advances in *ex vivo* lung engineering have also been increasingly applied to the lung. The current status of these approaches as well as initial clinical trials of cell therapies for lung diseases are reviewed below.

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## INTRODUCTION

Lung diseases remain a devastating cause of morbidity and mortality worldwide. Unlike many other major diseases, a number of lung diseases, particularly chronic obstructive pulmonary diseases (COPDs) including both asthma and emphysema, are increasing in prevalence and COPD is expected to become the third leading cause of disease mortality worldwide by 2020.<sup>1</sup> Although important advances in symptomatic treatments have occurred, many lung diseases including asthma, emphysema, pulmonary fibrosis, cystic fibrosis, and others have no cure. Lung transplantation is an option; however, there is a critical shortage of donor lungs and transplantation is complicated by acute and chronic rejection requiring lifelong immunosuppression. Further, lung transplantation is not a panacea as 5-year mortality following lung transplantation is ~50%.<sup>2</sup> New approaches for lung diseases are thus desperately needed.

Recent advances in lung biology have begun to elucidate the identity and function of resident endogenous progenitor cells in the lung, cells that may provide better understanding of lung disease processes and also which may be potentially manipulated for lung repair and regeneration. In parallel, intense investigation of possible reparative roles of exogenously administered adult and embryonic stem cells has demonstrated potential for structural repair for damaged lungs, notably repair of damaged lung vasculature through paracrine effects of circulating endothelial progenitor cells (EPCs). These studies have also demonstrated potent immunomodulatory effects of adult bone marrow-derived mesenchymal stromal cells (MSCs) in a variety of inflammatory and immune lung diseases. These initial observations have led to a cautious initial but growing exploration of EPCs and MSCs in clinical trials of pulmonary hypertension and COPD, respectively, with other clinical investigations planned.

*Ex vivo* lung bioengineering has also accelerated at a rapid pace. Tissue engineering has in particular progressed for components of

the respiratory system including trachea and diaphragm including recent pioneering clinical use of a bronchus bioengineered from a cadaveric scaffold in which autologous MSCs seeded into the scaffold were utilized to generate cartilage-producing chondrocytes.<sup>3</sup> Given the complex anatomical structure and structure-function relationships of the lung itself, *ex vivo* bioengineering of the lung is a more formidable task. Nonetheless, a variety of three-dimensional (3D) scaffolds, including both biosynthetic constructs as well as decellularized whole lungs have been utilized to explore engineering both airway and vascular systems of the lung. This excitingly has included surgical implantation in rat models of decellularized lungs recellularized with a mix of fetal lung homogenates and other cells with short-term survival and some degree of restitution of gas exchange and vascular perfusion achieved.

Lung is thus a ripe organ for regenerative medicine using a variety of approaches. In the following sections, current state-of-the-art findings for each of the above areas of study will be presented, followed by an assessment of future directions.

## ENDOGENOUS LUNG PROGENITOR CELLS

Endogenous lung stem and progenitor cells are thought to contribute to epithelial maintenance and injury repair. There is a large literature in mouse models and a growing literature describing putative endogenous stem and progenitor cells in human lungs. However, one persistent issue in the literature is the terminology and nomenclature utilized. The terms "stem" and "progenitor" are often used interchangeably and inconsistently. This also applies to the wider range of cells including embryonic and adult-origin stem and progenitor cells obtained from other tissues. For the purposes of this review, endogenous adult tissue-specific stem cells can be best appreciated as cells that have capacity for long-term self-renewal and that can differentiate into progenitors or other more differentiated cells in a particular organ. In general, stem cells have a wide differentiation capacity. In contrast adult

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