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Idiopathic pulmonary fibrosis (IPF) is an intractable interstitial lung disease characterized by fibroblastic foci, remodeling and obliteration of alveoli, and a median survival of 3 to 4 years. The only definitive treatment is lung transplantation, an intervention hampered by low availability of donor organs, and severe surgical and immunological complications. Innovative approaches are therefore urgently needed. We identified three major challenges towards improving the prognosis of IPF, and propose to address these challenges in the three research hubs of our consortium: (1) Cell sources should be established to study pathogenesis of IPF and to eventually prevent or reverse fibrosis. In Hub 1, we propose directed differentiation of human pluripotent stem cells (hPSCs) into lung tissue to investigate pathogenesis and establish platforms for drug discovery. (2) Cell removal/delivery methods are needed to either replace irreversibly damaged lung tissue, or the cells that carry pathogenesis of IPF. In Hub 2, we will develop the necessary bioengineering modalities that will take advantage of directed differentiation of hPSCs into lung tissue. (3) The field requires a large animal model for the validation of pathogenetic mechanisms and preclinical validation of novel therapeutic modalities for IPF developed by the first two research hubs. We therefore propose to establish a miniature swine model for IPF to validate pathogenetic mechanisms discovered in Hub1, and cellular replacement approaches developed in Hub 2. The overarching goal of this proposal is to gain desperately needed insight into the pathogenesis of IPF (Hub 1) and to use these insights to inform the development of novel therapeutic approaches for IPF (Hub 2). As IPF is currently an untreatable disease, it is not possible to predict which approaches will be beneficial, and the therapy may be dictated by disease stage. Pharmacological approaches may target the fibrotic process itself, or pathways emanating from epithelial cells that initiate this process and would likely be useful in early stage disease or in patients that are genetically predisposed. Regenerative approaches could consist of cellular therapies, in particular targeting ATII cells, most likely early in disease or in patients predisposed to IPF, but may extend to transplantation of recellularized lung scaffolds in end-stage disease. Both types of regenerative approaches will require bioengineering technologies that will be developed Hub 2 and informed by a deeper understanding of IPF pathogenesis achieved in Hub 1. Ultimately, verification of disease mechanism and preclinical testing of therapeutic approaches requires a large animal model, which is the focus of Hub 3.