CFTR modulators for treating ARDS and associated lung edema & other endothelial / epithelial barrier dysfunction

Ref. No.: CH935

Background
Epithelial and/or endothelial barrier dysfunction occurs in a variety of diseases, e.g. during stimulation by inflammatory agents, pathogens, or activated immune cells. It results in uncontrolled exchange of fluids, small solutes, larger proteins, or even entire cells across compartments. The acute respiratory distress syndrome (ARDS), is a severe, life-threatening inflammatory disease of the lung triggered by various pathologies such as pneumonia, sepsis and/or trauma, and is characterized by a loss of epithelial and endothelial barrier function (alveolo-capillary injury and increased lung permeability). In spite of intensive care with respiratory support (oxygen, mechanical ventilation, extracorporeal membrane oxygenation), ARDS mortality remains high and pharmacological therapies are lacking. There is hence a strong medical need for specific barrier-stabilizing pharmacologic interventions to prevent from and/or treat ARDS and other diseases involving endothelial and/or epithelial barrier dysfunctions.

Technology
The invention offers modulators of the cystic fibrosis transmembrane conductance regulator (CFTR) for use in prevention and treatment of diseases involving endothelial and/or epithelial barrier dysfunction such as ARDS and associated lung edema and other inflammatory pulmonary diseases. Surprisingly it has been found that the non-mutant CFTR is a suitable target for these diseases. Human pulmonary microvascular endothelial cells (HPMECs) show reduced resistance when stimulated with pneumolysin (PLY), a toxin from S. pneumoniae. Pre-treatment with the CFTR-potentiator Ivacaftor or the CFTR-corrector Lumacaftor has a protective effect on the resistance and permeability of the cells. In ex vivo mouse lungs, the increased lung permeability and lung edema formation induced by PLY can be reduced by pre-treatment with Ivacaftor. Furthermore, in in vivo experiments with S. pneumoniae infected mice, the pre-treatment with Ivacaftor reduces the protein leakage (i.e. barrier dysfunction) in the mouse lung and increases survival rate of the mice. Furthermore, Ivacaftor post-treatment reduces lung edema formation.

Benefits
✓ Novel drug candidate for ARDS with new mode-of-action
✓ Novel use for known CFTR modulators and correctors

Application
Treatment of diseases with endothelial and epithelial barrier dysfunction such as ARDS

Commercial Opportunity
Searching for a licensing or developing partner