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Novel Membrane Nanospacers for Targeting Membrane Disorders in Lipointoxication-Related Diseases

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Abstract

Phospholipids (PLs) are the main constituents of biological membranes. They contain two fatty acyl chains, saturated (Saturated Fatty Acids: SFA) or unsaturated (Unsaturated Fatty Acids: UFA). Maintaining the equilibrium between SFA and UFA within membrane PLs is crucial to sustain optimal membrane biophysical properties. Lipointoxication is a pathological Membrane condition under which saturated PLs tend to accumulate within cell at the expense of unsaturated species, with major impacts on organelle function. Accumulation of saturated PLs results in an increase in membrane stiffness and width, with alterations of central cellular processes such as membrane-protein folding and trafficking. Lipointoxication occurs under various physiopathological conditions such as SFA oversupply, originating from diet as encountered in obese individuals, and affects the correct function of pancreatic and muscle cells leading to development of Type 2 diabetes. In hepatocytes, SFA accumulation is associated to Non-Hepatic Steatohepatitis (NASH). Another condition which favors cellular SFA accumulation is hypoxia. Indeed, desaturases catalyzing SFA desaturation to UFA are strictly oxygen-dependent. Respiratory diseases such as Cystic Fibrosis (CF), are characterized by chronic hypoxia in the lungs. SFA/UFA imbalance in patients suffering CF has been consistently reported in numerous studies, and correlations between this imbalance and phenotype severity during the course of the disease have been clearly established (1,2). Independently of the origins of lipointoxication or the targeted cell-type, cellular consequences remain similar: membrane stiffening in the Endoplasmic-Reticulum affects protein folding and vesicular budding, which results in the induction of ER-stress and its associated pathways such as Unfolded Protein Response (UPR) and MAPKinase pathways. In the secretory pathway, lipointoxication alters vesicular budding in the Golgi apparatus, affecting delivery of plasma-membrane proteins. Our research group has demonstrated that CF patients display an accumulation of saturated-PL within their bronchial epithelial cells, in a process that likely originates from chronic hypoxia. Reconstitution of this lipid signature in cultured bronchial epithelial cells results in membrane stiffening in the ER and overall disorganization of this organelle with induction of ER-stress (3). This ER-stress is associated with production of pro-inflammatory cytokines (IL8), induction of the UPR and, if sustained, with apoptosis of epithelial cells. These processes are all trademarks of Cystic Fibrosis disease. In a search for a therapeutic solution, ConicMeds, has designed a new family of candidate drugs, so-called Nanospacers, with an original mode of action. These small molecules display the property of inserting themselves within the membranes of lipointoxicated cells, with tight structure activity relationships, and reverse lipointoxication. Accordingly, our candidate CM22i can abrogate membrane stiffening and alleviate ER-stress, cytokine secretion and apoptosis induction in lipointoxicated epithelial cells. Moreover, likely by down-regulating the MAPkinase pathway, our Nanospacer also proved to be efficient in relieving bronchoconstriction ex-vivo, with bronchial rings obtained from CF patients (3). We could also demonstrate that lipointoxication conditions clearly affect the action of Trikafta. Pre-treatment of lipointoxicated F508del-CFTR cells from CF patients with CM22i, restored Trikafta efficacy. CM22i is developed as an inhaled spray dry powder formulation and provides new potential benefits for the treatment of patients with Chronic Pulmonary Diseases (CF, COPD, IPF or asthma).

Biography

Patrick Page (PhD. MBA, CEO Conicmeds) has led multiple R&D projects in big-pharma companies (Astrazeneca and Merck-Serono). He was co-founder of several biotech companies (Genkyotex, Epiremed and Conicmeds). Patrick was a key inventor/contributor to the discovery and development of drug candidates such as Nolasiban, Setanaxib and OBE022. With 22 years of experience in the pharmaceutical industry, he had major roles as executive/non-executive member or as an independent consultant for several biotechs, playing key roles in the development of business and R&D strategy plans and fundraising. He also performed, on a regular basis, numerous due diligences for venture capital companies, business angels, TTOs and research institutes. He is the scientific director for the Biopark of Brussels South Charleroi (BE). He is in charge of drug development, regulatory affairs and business development activities of Conicmeds.