Development of a PI3Kγ-derived peptide as a novel F508del-CFTR potentiator

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Background and rationale. The underlying cause of cystic fibrosis (CF) is a mutation in the gene encoding the CF transmembrane conductance regulator (CFTR), a cyclic AMP (cAMP)-stimulated chloride channel. A number of CFTR correctors and potentiators, restoring membrane expression and cAMP-mediated activation of the channel, have been developed, but their efficacy is not fully satisfactory (1, 2).

Hypothesis and objectives. The ultimate goal of this project is to validate a novel therapeutic tool for CF. We recently developed a peptide targeting the kinase-independent function of PI3Kγ (3), which we found involved in the regulation of cAMP-mediated gating of the CFTR. Here, we hypothesize that this molecule could be therapeutically exploited to rescue the conductance of the most prevalent CFTR mutant, F508del-CFTR.

Essential methods. The biological function of the PI3Kγ peptide was assessed in clinically-relevant CF models, namely human primary airway epithelial monolayers and primary intestinal organoids (4) from F508del patients. Moreover, with the aim of reducing the costs of peptide synthesis as well as potential side effects of the compound, chemical optimization procedures were initiated.

Results. The peptide potentiated F508del-CFTR and was significantly more efficient than the gold-standard CFTR potentiator VX-770 both in bronchial monolayers and in intestinal organoids. Furthermore, the peptide improved F508del-CFTR conductance even after chronic Orkambi®, a condition wherein the gold-standard potentiator VX-770 is totally ineffective, without interfering with channel stability. On the contrary, the peptide per se ameliorated F508del-CFTR stability at the plasma membrane.

Spin-off for research & clinical purposes. The PI3Kγ-derived peptide is covered by patent number TO2014A00110 - WO/2016/103176 and received the Orphan Drug Designation by the European Medicinal Agency (EU/3/17/1859) in 2017. We therefore intend to develop the PI3Kγ peptide as a novel medicinal product that could be used, either alone or in combination with gold-standard therapies, in F508del patients.

References

1) Cholon, D.M., et al. Potentiator ivacaftor abrogates pharmacological correction of DeltaF508 CFTR in cystic fibrosis. Sci Transl Med 6, 246ra296 (2014). https://doi.org/10.1126/scitranslmed.3008680 PMid:25101886 PMCid:PMC4272825

2) Claire E. Wainwright, C.E., et al. Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. N Engl J Med 373, 220-231 (2015). https://doi.org/10.1056/NEJMoa1409547 PMid:25981758 PMCid:PMC4764353

3) Perino A. et al. Integrating cardiac PIP3 and cAMP signaling through a PKA anchoring function of p110γ. Mol Cell. 42(1):84-95 (2011) https://doi.org/10.1016/j.molcel.2011.01.030 PMid:21474070 PMCid:PMC3265115

4) Dekkers, J.F., et al. A functional CFTR assay using primary cystic fibrosis intestinal organoids. Nat Med 19, 939-945 (2013). https://doi.org/10.1038/nm.3201 PMid:23727931