A kinase-directed approach to rescue functionality of F508del CFTR

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Background. CFTR F508 deletion (F508del) is the by far commonest mutation causative of Cystic Fibrosis (CF). F508delCFTR undergoes premature degradation subverting proteostasis regulation and generating fragments which have the potential to up-regulate the protein kinase CK2 that, in turn, can favour CFTR fragmentation and reduce CFTR stability.

Hypothesis & Objectives. The project provide the rationale and proof-of-concept for the design of an original and novel therapeutic strategy that restores CFTR channel function by targeting the specific context in which the mutant CFTR channel fails to traffic to the cell surface. It focuses on the derailed CF proteostatic environment that is driven by the mutant channel, instead of on CFTR protein itself. Our strategy induces a self-sustained positive loop that ameliorates the CF phenotype by inhibiting protein cross linking that blocks autophagy and dampening overactive CK2. The workflow is summarized in the following tasks: 1) Identification and functional characterization of endogenous CK2 targets whose phosphorylation is altered by F508delCFTR; 2) In vivo confirmation of the CK2/CFTR functional link; 3) Analysis of known kinase modulators as a new class of molecules useful to rescue/stabilize F508del-CFTR; 4) In vivo validation of CK2/protein kinases modulators as reagents able to rescue CF phenotypes.

Methods. In vitro and in vivo models of CF have been used to test whether treatment of CF cells as well as CF mice with potential CK2 modulators are able to play a role in the process leading to premature degradation of F508delCFTR and have the ability to prolong the rescue of F508delCFTR obtained with the proteostasis regulator cysteamine or the corrector VX809.

Results. This strategy has shown good promise by using two drugs, cysteamine and epigallocatechingallate, to reverse the key features of the disease [1]. The pharmacological inhibition of protein kinase CK2 prolongs the rescue effect of cysteamine after its washout and it has been used in a single-centre, open-label phase-2 clinical trial.

Spin-off for research & clinical purposes. Refining existing leads through a target-driven drug discovery approach will be useful to identify old/new and more efficacious compounds (or combination of compounds) which favour a better and longer rescue of mutant CFTR. The published clinical trial has shown the rightness of our approach that represents a good example of affordable safe drug-repurposing strategy.

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