A helper-dependent adenoviral vector rescues CFTR to wild-type functional levels in cystic fibrosis epithelial cells harbouring class I mutations

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ABSTRACT Cystic fibrosis (CF) is a genetic disorder affecting multiple organs, including the pancreas, hepatobiliary system and reproductive organs; however, lung disease is responsible for the majority of morbidity and mortality. Management of CF involves CF transmembrane conductance regulator (CFTR) modulator agents including corrector drugs to augment cellular trafficking of mutant CFTR as well as potentiators that open defective CFTR channels. These therapies are poised to help most individuals with CF, with the notable exception of individuals with class I mutations where full-length CFTR protein is not produced. For these mutations, gene replacement has been suggested as a potential solution.

In this work, we used a helper-dependent adenoviral vector (HD-CFTR) to express CFTR in nasal epithelial cell cultures derived from CF subjects with class I CFTR mutations.

CFTR function was significantly restored in CF cells by HD-CFTR and reached healthy control functional levels as detected by Ussing chamber and membrane potential (FLIPR) assay. A dose–response relationship was observed between the amount of vector used and subsequent functional outcomes; small amounts of HD-CFTR were sufficient to correct CFTR function. At higher doses, HD-CFTR did not increase CFTR function in healthy control cells above baseline values. This latter observation allowed us to use this vector to benchmark *in vitro* efficacy testing of CFTR-modulator drugs.

In summary, we demonstrate the potential for HD-CFTR to inform *in vitro* testing and to restore CFTR function to healthy control levels in airway cells with class I or CFTR nonsense mutations.