In Vitro Pharmacology of KB407, an HSV-1-Based Gene Therapy Vector, for the Treatment of Cystic Fibrosis

Cystic fibrosis (CF), the most common inherited genetic disorder in the United States, is caused by mutations in the gene encoding cystic fibrosis transmembrane conductance regulator (CFTR). Lack of functional CFTR in secretory airway epithelia results in defective Cl-, bicarbonate, and thiosulfate secretion, coupled with enhanced Na+ absorption and mucus production, leading to dehydration and acidification of the airway surface liquid1-3. CF is characterized by recurrent chest infections, increased airway secretions, and eventually, respiratory failure4.

While FDA approval of four small molecule modulator therapies has been a boon to CF patients harboring the specific mutations responsive to these drugs, these modulators only treat a subset of the CF population. In particular need for effective drug intervention are the ~10% of CF patients harboring CFTR mutations that result in severely reduced or absent CFTR expression (class I mutations), as these patients suffer from the harshest and deadliest forms of CF5. Regrettably, no suitable therapies are approved for treating this most sensitive patient population. To this end, Krystal has developed KB407, a replication-defective herpes simplex virus type 1 (HSV-1) gene therapy vector encoding human CFTR, for molecular correction of CF.

INTRODUCTION

MATERIALS & METHODS

Test Article
KB407: Krystal Biotech, Inc.’s propriety replication-incompetent, non-integrating HSV-1 vector expressing human CFTR.

Table 1. Critical Reagents

RESULTS

In Vitro KB407 Dose-Ranging in CF Patient-Derived Small Airway Epithelial Cells (SAECs)

CONCLUSIONS

• KB407 infects primary CF SAECs in a dose-dependent manner, resulting in robust expression of human CFTR at the transcript and protein levels.
• The vector efficiently produces functional, full-length CFTR protein that properly traffics to the cell membrane.
• KB407 transduction leads to a striking alteration of organoid morphology from a compact budding CF phenotype to a cystic organoid phenotype exhibiting wild-type characteristics, irrespective of the underlying CFTR mutation, within 24 hours of infection at MOIs ranging from 1 to 40.
• The corrected cystic morphology of multiple CF PDOs exposed to low doses of KB407 suggests that high levels of exogenous CFTR expressed in a minority of cells is sufficient to establish disease correction.
• These data support KB407 as a novel gene therapy for the treatment of cystic fibrosis.

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REFERENCES