Potentiating trouble with combination therapy for ΔF508 patients

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Cystic fibrosis

Deficiencies of CFTR

- ATP
- Nucleotide binding domain
- Chloride
- Phosphate
- Cytoplasm
- Site of common phenylalanine deletion
- Nucleotide binding domain
- Regulatory domain
- Carbohydrate

Health issues

- Sinus Problems
- Nose Polyps (growths)
- Frequent lung Infections
- Salty sweat
- Enlarged heart
- Trouble breathing
- Gallstones
- Abnormal pancreas function
- Trouble digesting food
- Fatty BM's
Origins of cystic fibrosis

CFTR: >1900 MUTATIONS, 6 MUTATION CLASSES (I-VI)

Severe CF

Class III: Channel gating defect
- F508del, G551D, S1251N, R117H

Class II: Protein folding & ER export defect
- F508del, G480C

Class I: Non-functional mini-protein (premature stop codon)
- G542X

Mild CF

Class IV: Chloride conductance ↓
- R117H

Class VI: Endocytosis ↑
- Recycling ↓
- F508del

Class V: Splicing defect →
CFTR mRNA ↓
(~5% normal)
- 3272-26A>G
Current treatment for cystic fibrosis

Potentiators

- Activate apical CFTR by increasing open time of the channel
- FDA approved (January 2012) to treat CF patients with \( G551D \) mutation (Class III)

Correctors

- Partially revert the folding and processing defects (Class II) to increase CFTR in membrane
- Phase II results were reported (June 2014) using Lumacaftor in combination with Ivacaftor

Suppressors

- Prevent premature termination of protein synthesis (Class I)
- Phase III results were reported (June 2012) using Ataluren
Current treatment for cystic fibrosis

VX-770 treatment restores G551D function

Treated for 48 hrs prior to Ussing recordings

- Amiloride blocks epithelial sodium channel (ENaC)
- Stimulates chloride secretion by CFTR
- Directly inhibits CFTR conductance

Chronic VX-770 treatment inhibits functional rescue of ΔF508

Treated for 48 hrs prior to Ussing recordings

- Amiloride: Blocks epithelial sodium channel (ENaC)
- Forskolin: Stimulates chloride secretion by CFTR
- CFTR$_{inh}$-172: Directly inhibits CFTR conductance

VX-770 diminishes biochemical correction by increasing turnover of corrected ΔF508 CFTR

VX-770-induced hindrance of ΔF508 correction is dose-dependent

VX-770 distribution
Chronic VX-770 treatment decreases function of wild-type CFTR
Key physiologically properties not altered in chronically treated VX-700 tissues

VX-770 reduces stability of CFTR

ΔΔG = -8.1 kcal/mol

Proposed energy landscape for interaction of therapeutics with CFTR mutations

Conclusions

Thanks