63 Resveratrol improves chloride secretion in cystic fibrosis mice homozygous for the F508del mutation

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Introduction: Resveratrol is a polyphenol found in red wine that possesses a wide range of biological effects and has anti-oxidant properties. All these biological effects are related to NF-κB pathway which it is thought to be dysregulated in CF patients secondary to CFTR dysfunction.
Aim: To investigate the potential impact of resveratrol on CFTR function in CF mice.
Methods: Three weeks apart, nasal potential difference measurements (NPD) were performed in 5 CF mice homozygous for the F508del-CFTR mutation in the 129/FVB outbred background (a) without treatment (baseline) and (b) after intraperitoneal injection of resveratrol (20 mg/kg) diluted in physiological serum. Normal distribution of NPD measurements was confirmed by Shapiro test. Between-groups comparisons were evaluated using paired ANOVA coupled to t Test.
Results: Total chloride secretion improved from 4.8±3.5 mV (baseline) to 11.7±3.4 mV (Resveratrol) (P = 0.015). Baseline PD and response to amiloride were not modified.
Conclusion: Total chloride secretion improved with resveratrol. These preliminary data prompt us to further study the potential effect of resveratrol in cystic fibrosis.

64* Correction of ΔF508-CFTR in human airway epithelia and ex vivo rectal biopsies by *s-cis*-locked bithiazole corrector-29

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Defective CFTR chloride transport is a prominent feature in cystic fibrosis (CF). The *s-cis*-locked cycloheptathiazolothiazole 29 (corrector-29) was previously designed and identified as the most potent bithiazole corrector of defective ΔF508-CFTR with EC_{50} in vitro ~450 nM (Yu et al., J. Med. Chem. 51: 6044–6054, 2008). However, its efficacy in human tissues has not been reported.
The purpose of this translational study was to evaluate the efficacy of corrector-29 on ΔF508-CFTR in human CF epithelia. We performed transepithelial short-circuit current (I_{sc}) measurements in primary cultures of human bronchial epithelial (HBE) cells and ex vivo native rectal biopsies from ΔF508-CF and non-CF subjects. CFTR immunoblot analysis was done on the same rectal biopsies.
After 24 h incubation at 37ºC with 10 μM corrector-29, there was a vehicle-independent, forskolin-stimulated increase in ΔF508-CFTR-mediated chloride secretion of 5.4±0.3 μA/cm^2 (S.E.) in HBE cells (n = 8) and of 4.5±0.5 μA/cm^2 in rectal biopsies (n = 16), indicating ~25% of normal CFTR function in non-CF controls. CFTR immunoblot analysis showed an increase in mature CFTR protein (band C) in ΔF508-CF rectal biopsies incubated with corrector-29 but not in untreated biopsies.
These data provide evidence for substantial ΔF508-CFTR correction by corrector-29 in disease-relevant human CF epithelia and support the utility of ex vivo assays in native rectal tissue for CF drug development. Preclinical testing of candidate CF drugs can help to prioritize and optimize compounds for translation into clinical trials. This work was supported by CFF, CFRI and the Christiane Herzog Foundation.

65 Phase 3 study of ataluren (PTC124®) in nonsense mutation cystic fibrosis (nmCF): baseline data

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Background: Ataluren is an investigational drug that induces readthrough of nonsense mutations to produce full-length, functional CFTR in patients with nmCF.
Methods: This Phase 3, randomized, double-blind, placebo-controlled study enrolled 238 patients ⩾6 years of age with nmCF at >40 sites internationally to receive ataluren 10 (morning), 10 (midday), 20 (evening) mg/kg or placebo daily for 48 weeks. Standard outcome measures include spirometry, health-related quality of life as assessed by the Cystic Fibrosis Questionnaire-Revised, and sweat chloride. Novel outcome measures include assessment of pulmonary symptoms and exacerbations using the Exacerbation of Chronic Pulmonary Disease Tool with patient-reported data collected daily by mobile phone, objective cough rate in the community setting as measured by an ambulatory recorder, nasal potential difference using standardized equipment and procedures, and high-resolution chest computed tomography.
Results: 238 patients (M/F = 121/117) were enrolled. Baseline characteristics include median [range] age = 22[6–53] yrs and %-predicted FEV_1 = 61[40–90]. Available baseline data relating to the use of the novel outcome measures will be presented.
Conclusion: Ataluren therapy couples a patient's genetic diagnosis with a mutation-specific therapeutic approach designed to address the underlying genetic defect. Pretreatment data from this study will augment understanding of disease severity in the nmCF subpopulation and the feasibility of several innovative outcome measures. Funded by PTC Therapeutics; Genzyme; and Cystic Fibrosis Foundation Therapeutics, Inc

66 Synthesis of survival evidence in a model of cystic fibrosis disease progression

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Improved knowledge of CFTR protein defects has raised the possibility of treating the cause of CF, which may improve survival. However, survival is an impractical endpoint for CF trials. Intermediate outcomes that predict long-term survival may provide tools for assessing the impact of novel CFTR therapy. We synthesized published evidence to create such a tool and developed a model of mortality in CF as a function of age and prognostic factors.
A systematic literature review of CF disease progression was performed in Medline and Embase. Prospective or retrospective cohort and case-control studies that reported mortality jointly with prognostic factors were accepted. Covariates of interest included gender, lung function, weight-for-age, pancreatic sufficiency, diabetes, lung microflora and number of acute exacerbations. Results were synthesized by Bayesian meta-analysis techniques.
Seven studies, together including >20,000 patients, provided sufficient published data for the model. Survival over time was described with a Gompertz model with its scale parameter affected by birth cohort, gender, lung function, respiratory infection with *Burkholderia cepacia* and *Staphylococcus aureus*, diabetes, number of exacerbations, and pancreatic sufficiency. The shape parameter was assumed to be only affected by birth cohort.
According to our model, lung function is the main determinant of life expectancy but other important factors include acute exacerbations, infections, diabetes and pancreatic insufficiency. Patient characteristics and clinical endpoints from treatment arms can be entered into the model to help predict and compare long-term outcomes.