European Respiratory Society
Annual Congress 2013

Abstract Number: 5066

Publication Number: P747

Abstract Group: 5.1. Airway Pharmacology and Treatment

Keyword 1: Chronic disease **Keyword 2:** Genetics **Keyword 3:** Public health

Title: Chemically modified mRNA as a novel treatment for cystic fibrosis

Dr. Azita J. 31442 Mahiny azita.mahiny@med.uni-tuebingen.de [1], Prof. Dr Rupert 31443 Handgretinger rupert.handgretinger@med.uni-tuebingen.de MD [2], Prof. Dr Dominik 31444 Hartl dominik.hartl@med.uni-tuebingen.de MD [1] and Prof. Dr Michael S.D. 31445 Kormann kormann.michael@gmail.com [1]. [1] Paediatric Infectiology and Immunology, University Hospital Tuebingen, Tuebingen, Germany, 72074 and [2] Children's Hospital, University Hospital Tuebingen, Tuebingen, Germany .

Body: Monogenetic disorders such as Cystic Fibrosis (CF) may be treated by supplementation with the functional active protein or by administration of a vector encoding the desired gene product. However, current therapeutic efforts with DNA-based or viral vectors remain largely unsuccessful in treating this fatal disease. As an alternative approach we propose messenger ribonucleic acid (mRNA)- based transcript transfer, which offers several benefits: it excludes the risk of any insertion of nucleic acid, which may come along with mutations and random integration. Immunological side effects can be successfully suppressed by using modified nucleotides, concomitantly increasing the stability of mRNA in vivo. Administration of mRNA into the murine lung is performed by using an intratracheal spray applicator, which nebulizes the mRNA solution. All mRNA used is modified to mimic endogenous mRNA. Nanoparticles may facilitate the resorption of the administered mRNA into the lung epithelium. We could already demonstrate that the substitution of Surfactant Protein B (SP-B) by intratracheal administration of SP-B encoding mRNA lead to a healthy status of transgenic SP-B mice (Kormann et al. Nat Biotech 2011; 29: 154-157). Here we establish the substitution of CF transmembrane conductance regulator (CFTR) in a murine gut-corrected CF model by administration of CFTR-encoding, modified mRNA. Inflammatory responses, lung function, electrophysiological as well as histological parameters will be measured. Our preliminary results demonstrate the potential of using chemically modified CFTR mRNA as a viable treatment for CF. This novel technique is currently optimized in our group.