A decoy oligonucleotide to NF-κB delivered through inhalable particles inhibits the lung inflammation induced by LPS in rat

[1]D. De Stefano, [2]C. Coletta, [2]R. d'Emmanuele di Villa Bianca, [2]L. Falcone, [2]I. d'Angelo, [2]F. Ungaro, [2]F. Quaglia, [2]R. Carnuccio, [2]R. Sorrentino

[1]European Institute for Research in Cystic Fibrosis (IERFC), San Raffaele Scientific Institute, Milan, Italy; [2]Dept. of Pharmacy, University of Naples Federico II, Naples, Italy

NF-kB plays a prominent role in orchestrating the airway inflammatory response in several diseases, including cystic fibrosis [1]. The specific inhibition of NF-kB by decoy oligonucleotides delivered in the lung may limit the progression of inflammation [2], although rationally designed systems are needed to control drug release and optimize pharmacological response. In this regard, here we have developed and tested *in vivo* an inhalable dry powder for prolonged delivery of a decoy oligodeoxynucleotide to NF-κB (dec-ODN), consisting of large porous particles (LPP) based on poly(lactic-co-glycolic) acid (PLGA). First, LPP containing dec-ODN (dec-ODN LPP) have been engineered to meet aerodynamic criteria crucial for pulmonary delivery, to gain an effective loading of dec-ODN, to sustain its release and to preserve its structural integrity in lung lining fluids. Then, we have investigated the effects of dec-ODN LPP in a rat model of lung inflammation induced by intra-tracheal aerosolization of LSP from *P. aeruginosa*. The results show that a single intra-tracheal insufflation of dec-ODN LPP significantly prevented the neutrophil infiltration induced by LPS up to 72 hours, whereas naked dec-ODN was able to inhibit it only at 6 hours. The persistent inhibition of neutrophil infiltrate by dec-ODN LPP was associated with a significant reduction of NF-κB/DNA binding activity as well as interleukin-6, interleukin-8 and mucin-2 mRNA expression in lung homogenates.
Taken together, our findings show that dec-ODN LPP may provide a new strategy for local treatment of inflammation associated with lung diseases.

1.Park GY and Christman JW. Nuclear factor kappa B is a promising therapeutic target in inflammatory lung disease. Curr Drug Targets. 2006 Jun;7(6):661-8.
2.Cabrini G et al., Targeting transcription factor activity as a strategy to inhibit pro-inflammatory genes involved in cystic fibrosis: decoy oligonucleotides and low-molecular weight compounds. Curr Med Chem. 2010;17(35):4392-404.