



Improved Precision of Nucleic Acid Based Therapy of Cystic Fibrosis



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Project:

The epithelial sodium channel (ENaC) is assumed to play a major role in the pathogenesis of chronic lung disease in cystic fibrosis patients. Its natural regulation by the cystic fibrosis transmembrane conductance regulator (CFTR) appears to be compromised based on the impaired function of CFTR. The missing downregulation of the channel results in increased absorption of sodium ions and fluid across airway epithelia leading to the depletion of the periciliary liquid layer and to the depression of mucus clearance.

This project presents a new approach to the gene therapy of cystic fibrosis by downregulating ENaC using RNA interference. The LMU Munich as coordinator and 10 Partners from 6 european countries are working as a consortium on this project, which is funded by the European Commission for 3 years.

Workpackages:

- 1 Selection and synthesis of siRNA sequences and siRNA expressing minichromosomes
- 2 *In vitro* siRNA application using synthetic carrier systems in cell culture models
- 3 Lentivirus-mediated siRNA knock down of ENaC in various cell lines and CF human respiratory epithelial cells
- 4 Analysis of electrophysiologic effects of ENaC downregulation *in vitro*
- 5 Aerosol application of siRNA constructs
- 6 Suppression of ENaC during fetal and postnatal life as a novel strategy for gene therapy
- 7 *In vivo* application of siRNA constructs using therapeutic mouse models

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