**Effect of treatment with oligosaccharide nanomedicine on the rheology of cystic fibrosis sputum**

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**Objectives:** Modulation of sputum rheology represents an important therapeutic target in chronic inflammatory lung disease such as cystic fibrosis (CF). The novel alginate oligomer (OligoG) modulates pseudomonal biofilms and increases susceptibility of multi-drug resistant bacteria to antibiotics and has previously been shown to modify rheology of mucin/alginate gels, mucin/DNA gels and sputum from a CF patient. This study tested the ability of OligoG to modify the rheological properties of CF sputum.

**Methods:** The effect of OligoG on the viscoelastic properties of sputum samples from cystic fibrosis patients (n=23) and in a longitudinal study (10 weeks) was studied using shear and extensional rheology. Samples were subjected to 7 treatment modalities:

1. distilled water control;
2. 7% saline;
3. 100 nM dornase alpha (Pulmozyme®; Pz);
4. 0.2% OligoG;
5. 2% OligoG;
6. 100 nM Pz and 0.2% OligoG;
7. 100 nM Pz and 2% OligoG.

An oscillatory frequency sweep was conducted and the values of storage and loss modulus (G’, G”) analysed to detect changes in viscoelasticity. Extensional rheology was employed to detect changes in 2% OligoG treated sputum, in comparison to the control.

**Conclusion:** OligoG significantly decreased the storage and loss modulus of sputum (P < 0.0001), as well as the extensional viscosity. OligoG also significantly potentiated the effect of Pz (P < 0.01). These studies show that use of inhaled oligosaccharide nanomedicines such as OligoG may provide a novel, well-tolerated therapeutic approach in the treatment of impaired lung clearance and chronic bacterial colonization in chronic inflammatory lung diseases.

**Development of nanomedicines for the treatment of pulmonary biofilm infections: Insights from advanced fluorescence microscopy studies**

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**Objectives:** Despite recent advances, clinicians are still confronted with low success rates when treating biofilm based infections. In CF patients, pulmonary biofilm infections are an important cause of morbidity and mortality. Recently, increased sensitivity of biofilms towards nanoparticle encapsulated antibiotics was shown in vitro. When applying this concept to pulmonary biofilms, two aspects need to be evaluated for the development of a suitable nanocarrier. Firstly, the particles need to be mobile in the highly visco-elastic mucus in order to reach the biofilms. Secondly, the nanoparticles need to be able to penetrate into the biofilm for a maximal antimicrobial effect.

**Methods:** In earlier work, transport studies based on Single Particle Tracking (SPT) microscopy of differently functionalized polystyrene nanoparticles showed that PEGylation is essential for transport in CF sputum and biofilms. Currently, confocal microscopy and fluorescence recovery after photobleaching are used to gain insight in the nanoparticle size cutoff for efficient transport into clusters of *B. multivorans* biofilms using PEGylated micelles (25 nm), PEGylated silica (25, 45, 75 nm) and PEGylated polystyrene (100, 200 nm) nanoparticles.

**Conclusion:** The micelles, silica and 100 nm polystyrene nanoparticles were observed to diffuse well inside the clusters. Although further investigation is required, first experiments show that 200 nm nanoparticles penetrate less, suggesting a cutoff size of about 100 nm. Combining different fluorescence microscopy techniques can thus aid in the rational design of nanocarriers for drug delivery with optimal transport properties in mucus and biofilms.