LUNG SURFACTANT INSPIRED PROTEOLIPID NANOCOMPOSITES FOR SIRNA INHALATION THERAPY

Introduction

Pathologies of the respiratory tract are subject to a growing prevalence and for many of these illnesses an unmet therapeutic need exists. Local inhalation therapy of siRNA holds many advantages for the treatment of lung diseases that are ill-controlled by conventional small molecular drugs. However, to exploit these advantages, safe and effective nanocarriers are needed that are able to guide the siRNA across extra-and intracellular biological barriers towards the cytoplasm of the target cells. As synthetic lipid-and polymer-based nanocarriers often fail to merge safety and efficacy, there is an increasing interest in the use of endogenous bio-inspired materials. For inhalation therapy, one interesting approach is the exploitation of pulmonary surfactant to promote cellular delivery of membrane-impermeable macromolecular drugs, including siRNA.

Technology

Researchers at Ghent University have identified the cationic amphiphilic surfactant protein B (SP-B), an essential component of natural pulmonary surfactant, as a strong promotor of intracellular siRNA delivery, via its specific interactions with cellular membranes. SP-B can be combined with one or more lipids to construct SP-B inspired lipid-based nanocarriers for RNA delivery.

Applications

SP-B inspired nanocarriers show clinical and market value to boost cellular delivery of small RNA therapeutics (including siRNA, antisense oligonucleotides, miRNA) following local administration (e.g. inhalation therapy). Therapeutic applications can be envisioned in many pulmonary pathologies with an unmet medical need, e.g. obstructive pulmonary disease, pulmonary infections and pulmonary fibrosis.

Advantages

SP-B inspired delivery tackles the most important cellular delivery challenges for RNA therapeutics for inhalation therapy.

- ✓ SP-B is an endogenous protein in the lung, improving biocompatibility
- ✓ Only low amounts of SP-B in a lipid-based nanocarrier are needed to improve cellular delivery
- ✓ SP-B strongly promotes intracellular delivery efficiency, enabling dose reduction
- ✓ The activity of SP-B can be tailored by choice of lipids

This technology can be extended to improve delivery of other membrane-impermeable therapeutics as well.

State of development

The impact of SP-B on siRNA delivery has been validated *in vitro* and *in vivo* using SP-B proteolipid nanocomposites. The delivery promoting effect of SP-B has been demonstrated in various cell types, including non-small cell lung cancer cells. The beneficial effect of lung surfactant in general and SP-B in particular has been shown in healthy mice and an acute lung injury model, respectively. Here, improved siRNA delivery was obtained in primary alveolar macrophages. Lung biodistribution and toxicity data of formulations with diverging SP-B proteolipid mixtures are available. Extensive data sets on the intracellular mode-of-action of SP-B have been obtained. Finally, optimization of macroformulation strategies for inhalation therapy are ongoing.

Partnership

Ghent University is seeking a licensing partner or a collaboration to explore the SP-B technology for RNA delivery in the disease of interest and to validate the technology for local pulmonary applications.

Intellectual property

PARTICLES COMPRISING SURFACTANT PROTEIN B AND ONE OR MORE LIPIDS
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The Scientists

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References

Merckx P. *et al.*, Surfactant protein B (SP-B) enhances the cellular siRNA delivery of proteolipid coated nanogels for inhalation therapy. *Acta Biomaterialia* 2018, 78: 236-246. Impact factor: 6.383, category: ENGINEERING, BIOMEDICAL, rank: 4/78 (Q1).

Keywords

Nanomedicines, lung surfactant, inhalation therapy, RNA therapeutics, surfactant protein B

Figure

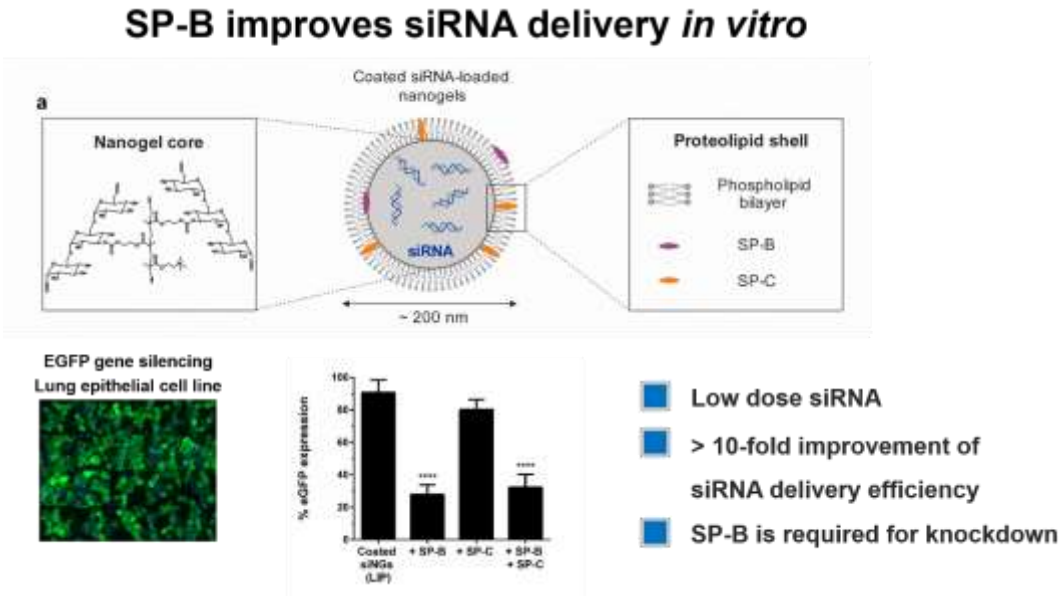

Figure. Evaluation of gene silencing potential of proteolipid coated siRNA-loaded nanogels (siNGs) in H1299_eGFP lung epithelial cells. The siNGs were layered with DOPC:eggPG (85:15 wt%; coated siNGs (LIP)). In this LIP outer layer, SP-B (0.4 wt%) and/or SP-C (0.7 wt%) were incorporated. The eGFP expression was normalized to the expression of cells treated with control siRNA (n=3).

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