

Pulmonary surfactant-related peptides as endosomal escape enhancers for local pulmonary delivery of siRNA

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THE FUTURE OF DELIVERY SCIENCE



Respiratory diseases Unmet medical needs



800 million confirmed COVID-19 cases



Asthma affects more than 250 million people



COPD is the third leading cause of death



RNA therapy Unmet drug delivery needs

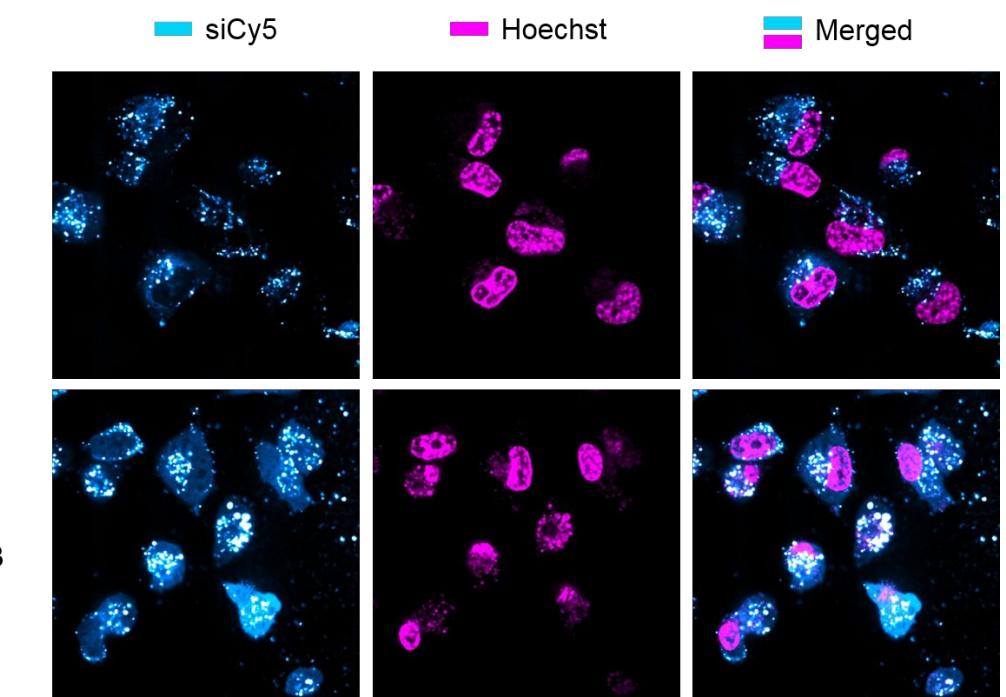
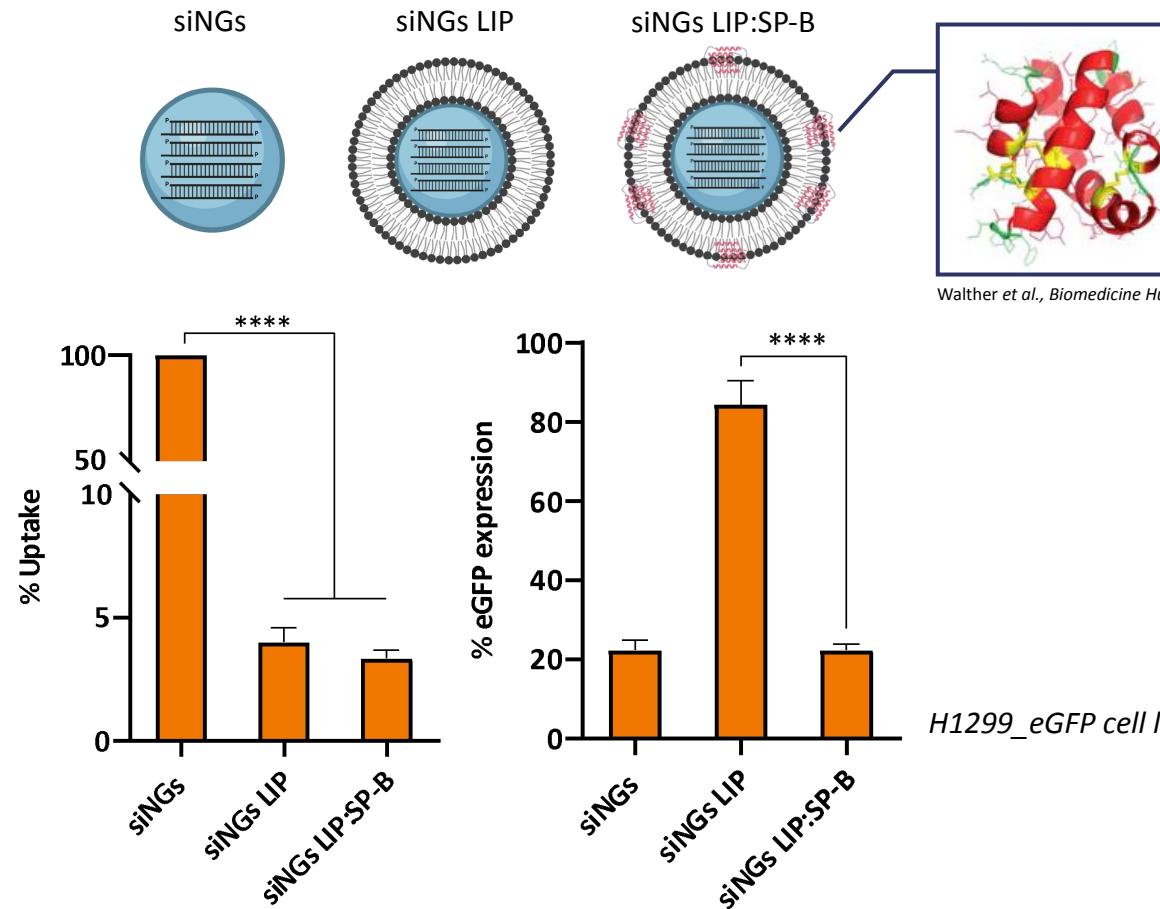
✓ Antiviral siRNA molecules

✓ Anti-inflammatory siRNA molecules

AIM

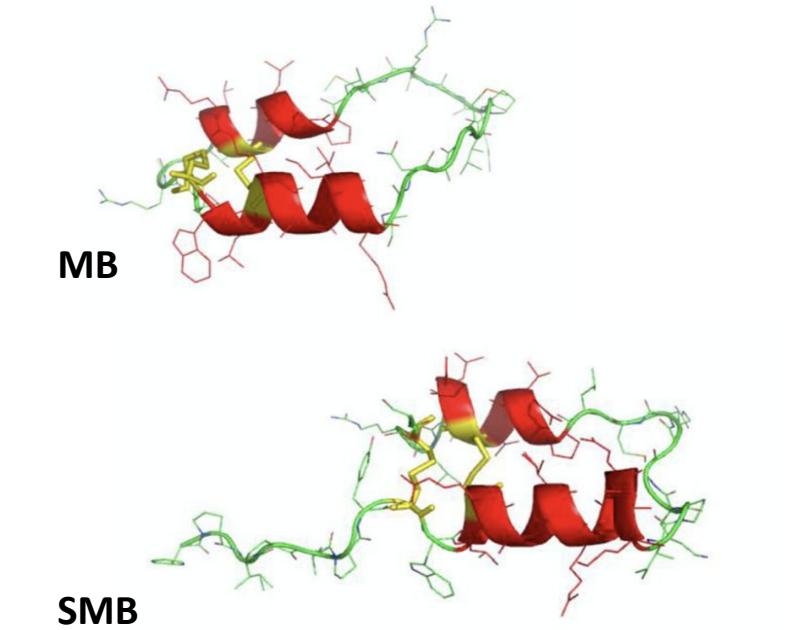
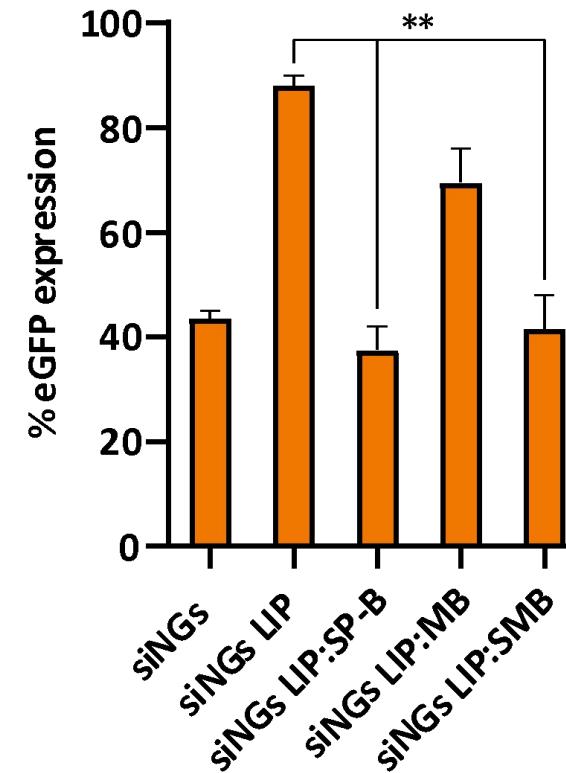
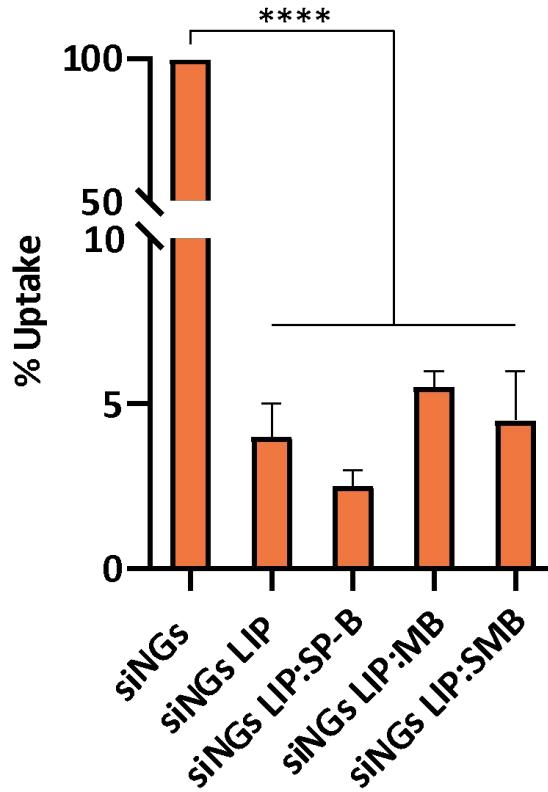
Repurposing lung-related substances to design
biocompatible nanocarriers

Surfactant protein-B (SP-B) enhances delivery of siRNA molecules



Mini-B (MB) and Super Mini-B (SMB)

- MB: C- and N-terminal helix of native SP-B
- SMB: same as MB + first seven AA (FPIPLPY; insertional sequence)

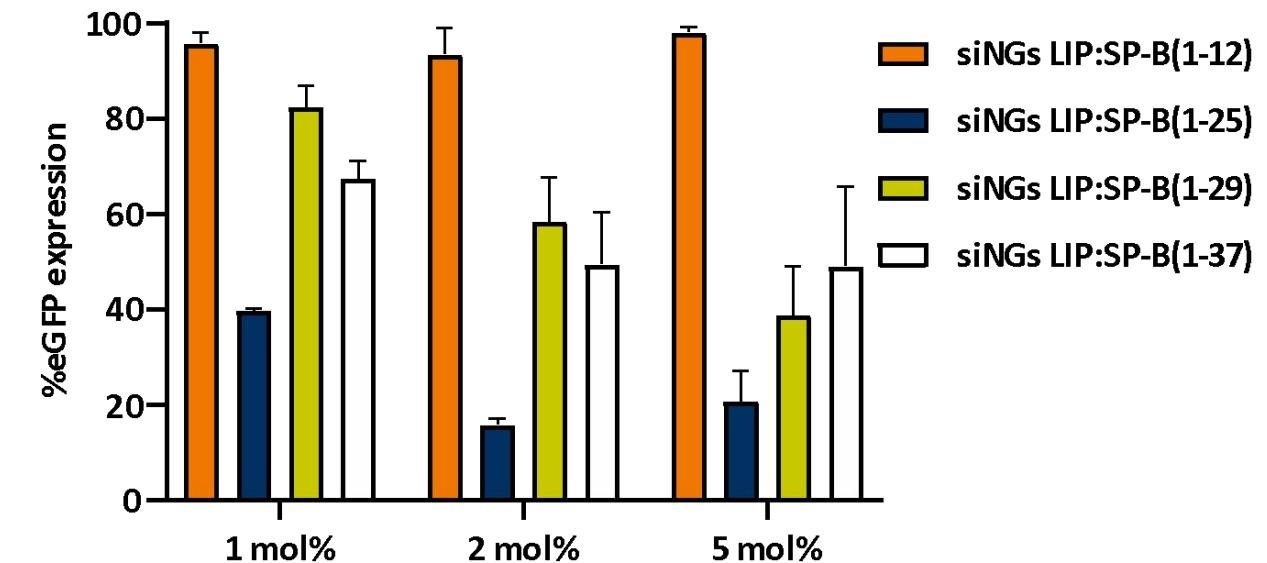
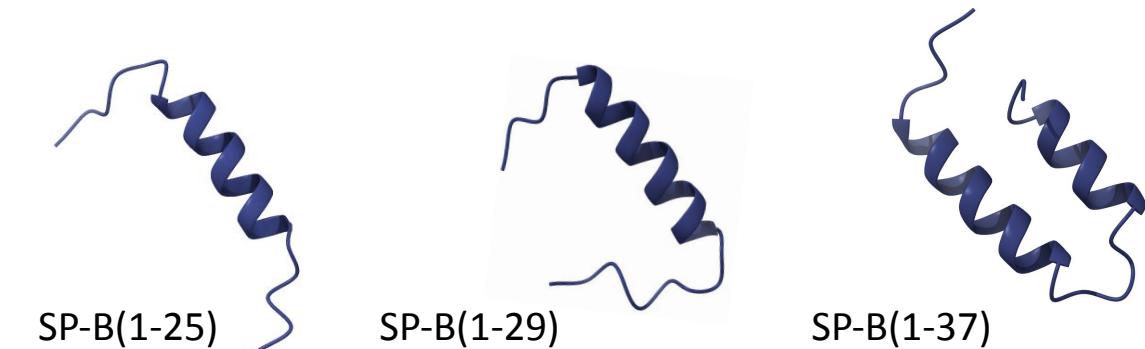
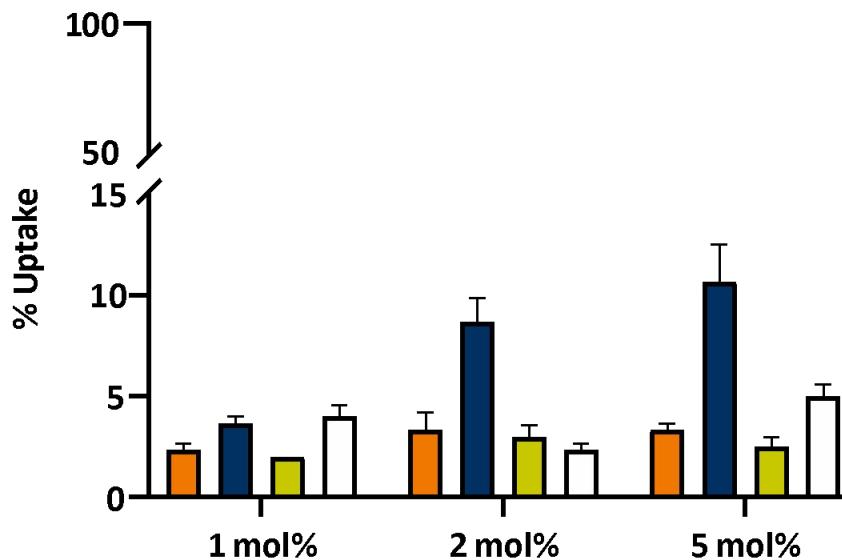


Walther et al., Biomedicine Hub 2016

✓ Importance of insertional sequence

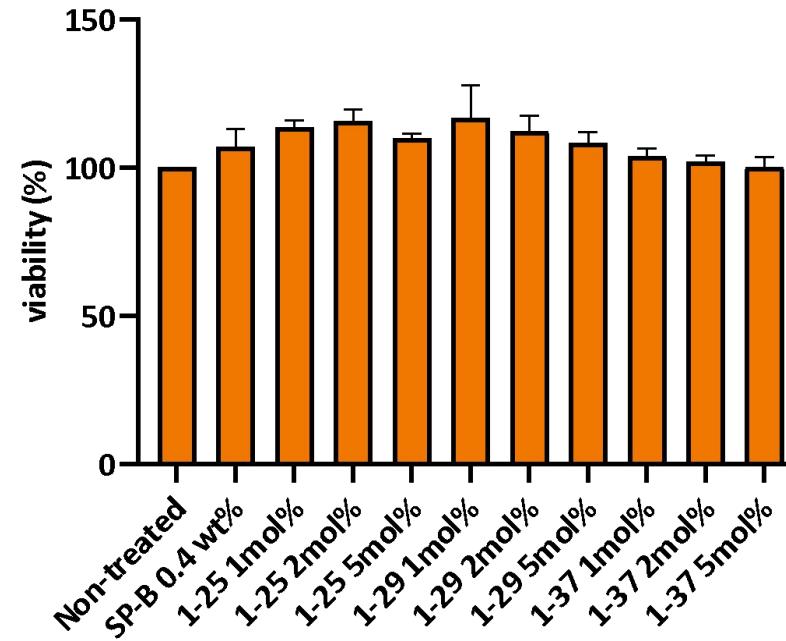
SP-B 1-12, 1-25, 1-29 and 1-37

- 1-12: extended insertional sequence
- 1-25: 1 alpha helix
- 1-29: same as 1-25 + 'ALAV'
- 1-37: whole N-terminal part, 2 alpha helices

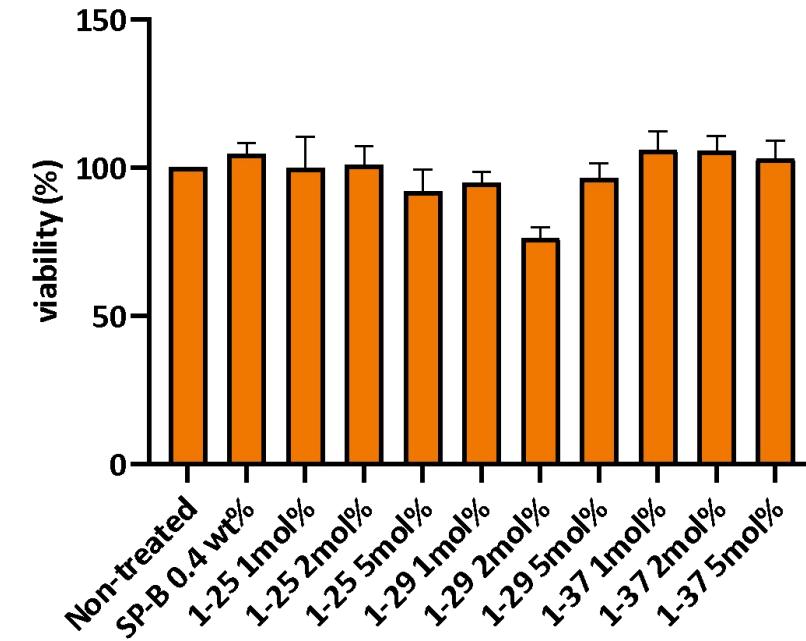


SP-B and related peptides do not lead to cellular toxicity *in vitro*

✓ Acute toxicity



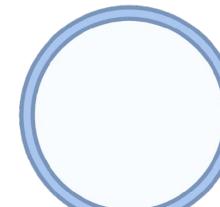
✓ Chronic toxicity



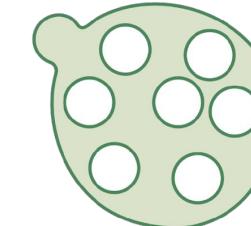
SP-B and related peptides induce fusion with intraluminal vesicles (ILVs)

Anionic lipids

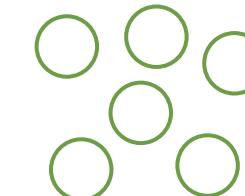
Plasma membrane
Early endosome



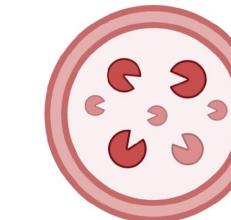
Late endosome



ILVs

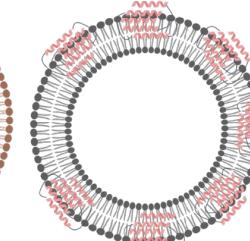
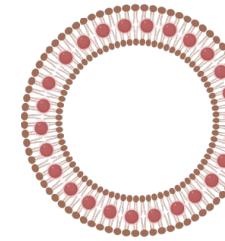


Lysosome

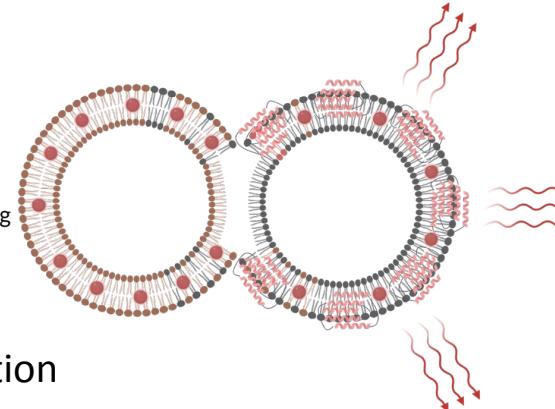


Cholesterol and pH

ILVs

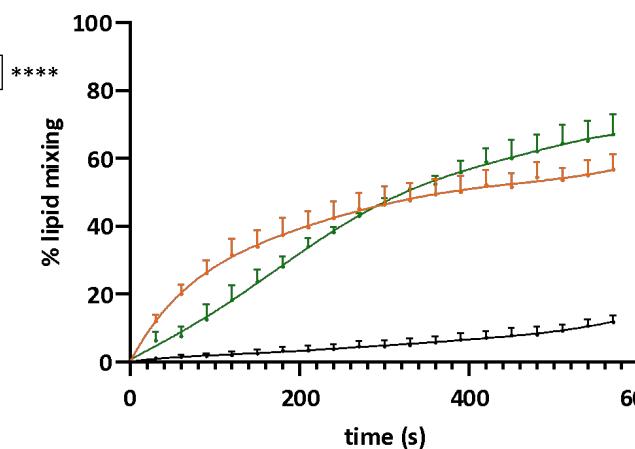
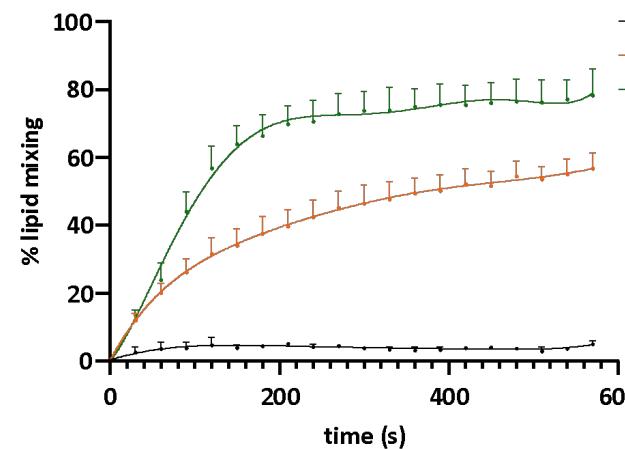
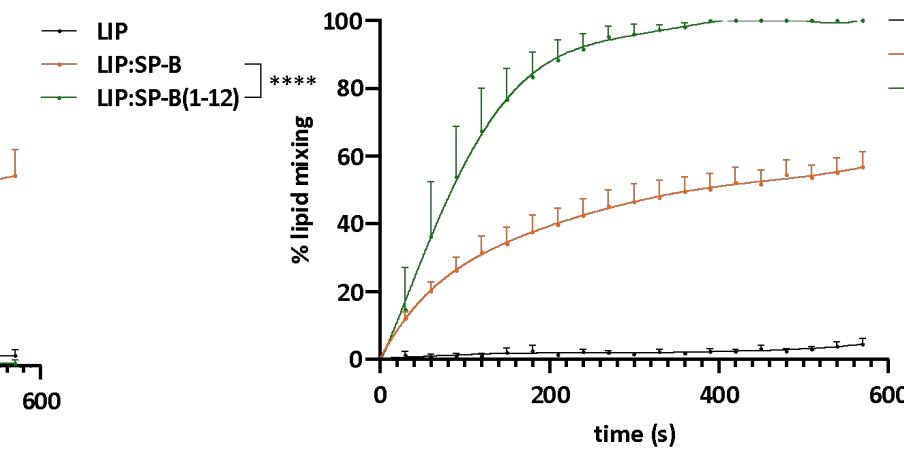
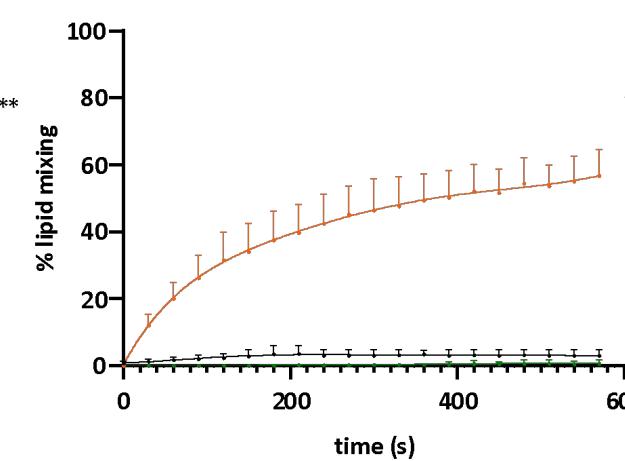
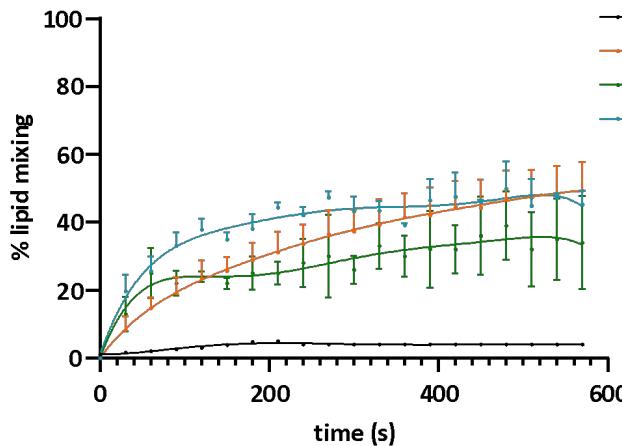


Lipid mixing
R18 dequenching

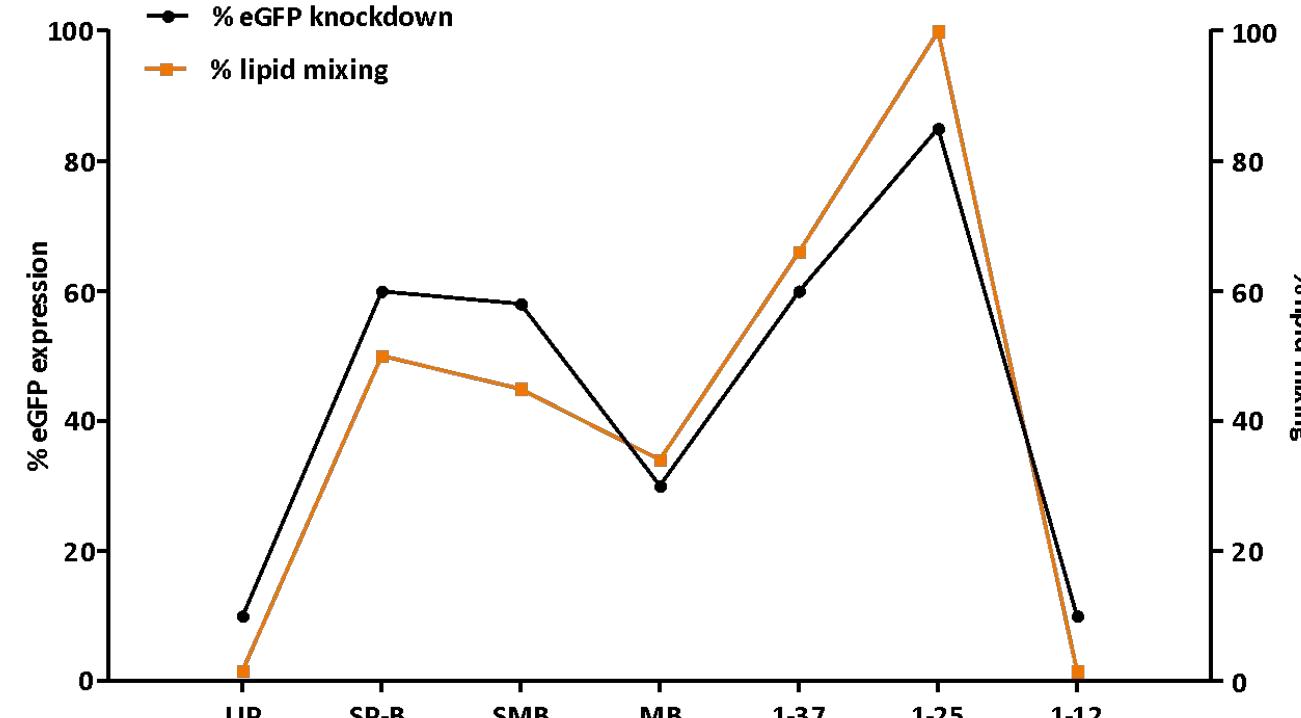


Surfactant formulation

SP-B and related peptides induce fusion with intraluminal vesicles (ILVs)

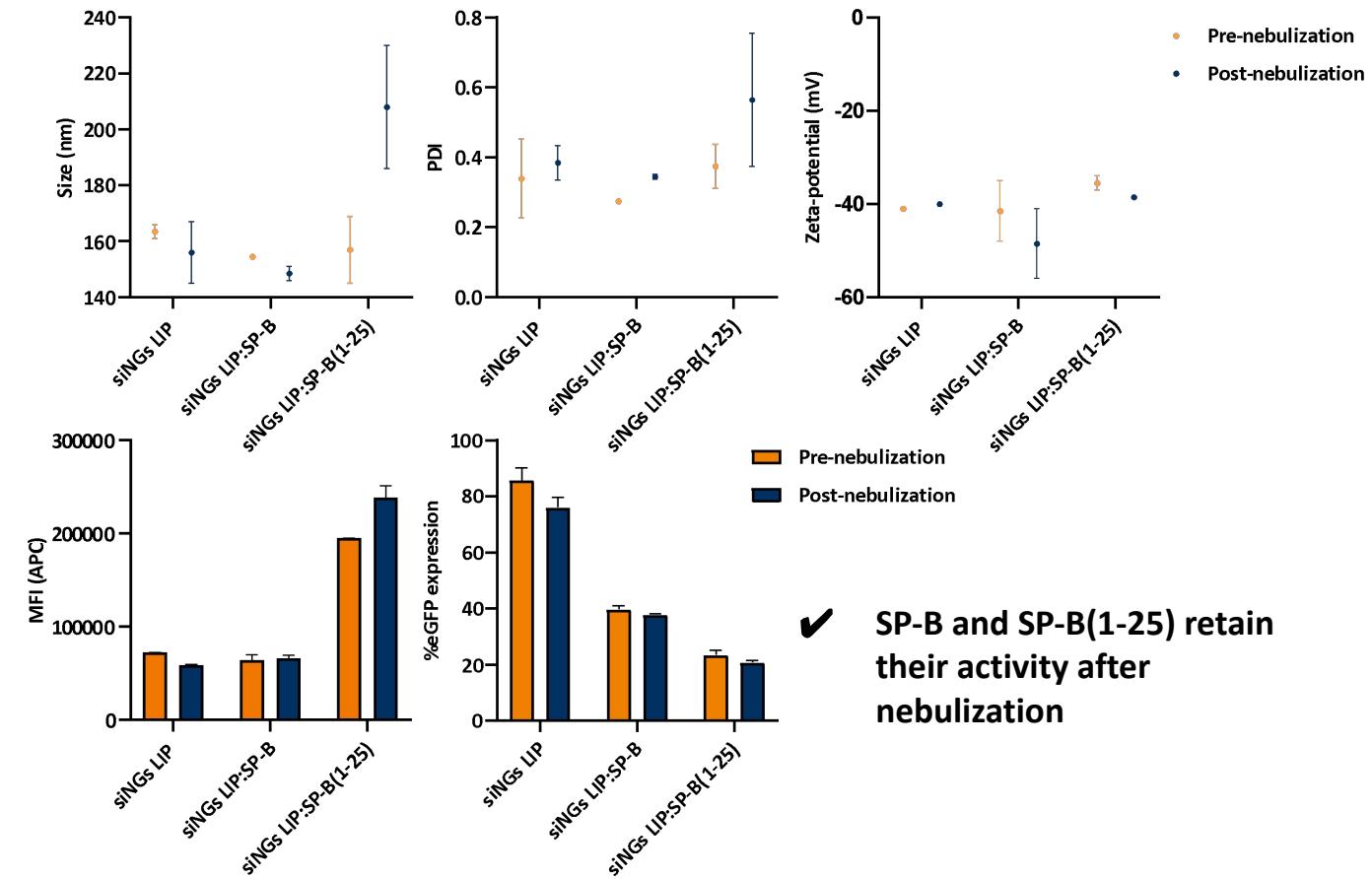
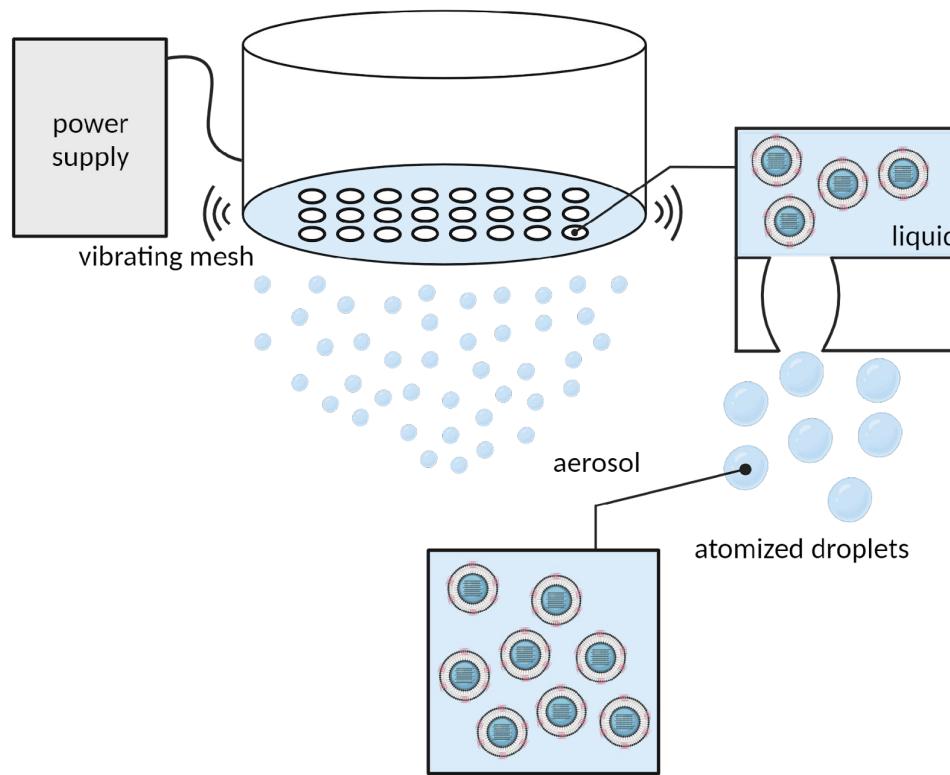


SP-B and related peptides induce fusion with intraluminal vesicles (ILVs)



- ✓ Correlation between eGFP knockdown *in cellulo* and lipid mixing with ILVs *in vitro*

Surfactant formulations can be nebulized without loss of activity



✓ SP-B and SP-B(1-25) retain their activity after nebulization

Surfactant-related peptides
enhance siRNA delivery



Design of a biocompatible
formulation platform

Induction of endosomal escape
via fusion

Suitable for nebulization
processes

Acknowledgements

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Laboratory for
General Biochemistry
and **Physical Pharmacy**

biopharmaceutics
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