Targeted deliver therapeutic siRNA into activated T cell by Tf-ss-PEI conjugate for therapy of asthma

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Summary
The new targeted bioreducible delivery system Tf-ss-PEI can deliver therapeutic siRNA for asthma therapy into activated T cells that play an important role in airway inflammation processes.

Introduction
With increasing environmental problems and air pollution, asthma has become a major public health problem which affects 235 million people worldwide. Asthma is characterized by chronic airway inflammation caused by infiltration of Th2 cells and eosinophils in the lung.¹ As we know, CD4⁺ cells play an important role in airway inflammation due to their production of Th2 interleukins, IL-4, IL-5, and IL-13. GATA-3 is a transcription factor that controls Th2 interleukin production². To enhance siRNA delivery efficiency, we designed a targeted delivery system Tf-ss-PEI which is formed by three components: transferrin (Tf) is a glycoprotein to target the Tf receptor which is overexpressed on activated T cells³; the bioreducible linker SPDP (N-Succinimidyl-3-(2-pyridyldithio)-propionate) helps the polymer conjugate to dissociate from Tf inside the cell, and polyethyleneimine (PEI) can condense and protect siRNA during the delivery.

Method
Transferrin glycoprotein was crosslinked with low molecular weight 5 kDa PEI with the bioreducible linker SPDP and the conjugate was purified by FPLC (fast protein liquid chromatography). Flow cytometry was applied to determine transferrin receptor expression in primary human activated T cells (ATCs) as well as to measure Tf-ss-PEI mediated and targeted delivery efficiency of fluorescent siRNA in primary cells ex vivo and in vivo in an ovalbumin (OVA) induced murine asthma model². Real time PCR can quantify the efficiency of targeted delivery and knockdown of the housekeeping gene GAPDH on the mRNA level as proof of principle.

Result
The expression of transferrin receptor on primary human T cell can be increased to 95% after activation with the anti-CD3 OKT3 antibody for 11 days. Based on such high Tf receptor expression, Tf-ss-PEI achieves very high siRNA uptake in vitro and in vivo.

Real time PCR results indicate that Tf-ss-PEI can efficiently deliver siRNA and knockdown the GAPDH gene.
Conclusion
We have demonstrated that Tf-ss-PEI can efficiently and specifically deliver siRNA to activated T cells in vitro and in vivo. Our targeted delivery system could be an innovative and promising asthma therapy in the future.

Reference

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