Novel biodegradable siRNA carriers for delivery to activated T cells as anti-inflammatory asthma therapy

Yuran Xie[1], Na Hyung Kim[1], Venkatareddy Nadithe[1], Archana Thakur[1,2], Lawrence G. Lum[1,2], David JP Bassett[1], Olivia M Merkel[1,2]

[1]Wayne State University, DETROIT, MI, United States of America

[2]Karmanos Cancer Institute, DETROIT, MI, United States of America

Local, targeted, cell-specific RNA interference (RNAi)-based therapies could improve patients' ability to control asthma. Allergen-induced airway dysfunction was shown to be prevented by downregulating the secretion of Th2 cytokines. However, T cells are hard to transfect cells and not easily accessible for RNAi-based therapies. We recently reported that activated T cells (ATCs) overexpress the transferrin receptor (TfR) which is an internalizing transmembrane receptor that mediates endocytosis of transferrin-bound iron and which is broadly exploited for targeted nucleic acid delivery.[1, 2]

Here we aim to therapeutically downregulate the Th2 transcription factor GATA-3 which is known to drive IL-4, IL-5, and IL-13 secretion in asthma to silence all downstream inflammatory cascades.

Proof of concept results show the optimization of the coupling chemistry of Tf and low molecular weight (LMW) polyethylenimine (PEI) for efficient siRNA delivery to primary activated T cell *ex vivo*, as well as efficient gene knockdown quantified by qRT-PCR. In a murine asthma model induced by ovalbumin (OVA), activated T cells of the lung only showed siRNA uptake in inflamed animals but not in healthy animals, and T cells were preferentially targeted with the Tf-conjugated delivery system *in vivo*. The animals tolerated the treatment with LWM-PEI-Tf well, as reflected in their lung cytokine levels and lung function.

In an approach to optimize the biocompatibility and biodegradability of these nanocarriers, currently novel oligospermine-based[3] conjugates are being synthesized and tested *ex vivo* and *in vivo*.

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