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INTRINSIC ACTIVITY

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MEETING ABSTRACT

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Synthetic HDL nanodiscs as a drug candidate in pulmonary inflammation

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Background: High-density lipoproteins (HDLs) are anti-inflammatory lipoprotein particles whose function and composition are critically altered in disease. Therefore, it is reasonable to replace or even increase the loss of HDL function in inflammation. Apolipoprotein A-I (ApoA-I) is the most abundant protein of HDL and is primarily responsible for its well-documented immunomodulatory effects. Artificially synthesized 18–37-amino-acid-long peptides that mimic the activity of full-length ApoA-I are being evaluated in clinical trials for atherosclerosis (*e.g.* NCT04216342). Due to the ease of production and highly specific nature, peptidomimetics are naturally preferred as drug candidates. We aim to re-purpose novel HDL-mimetic nanoparticles, targeting inflammation in the lung.
Methods: We prepared differentially lipidated ApoA-I-mimetic nanoparticles using the NanoAssemblr™ platform and confirmed the size and morphology of the nanodiscs using transmission electron microscopy and native gel electrophoresis. Cholesterol efflux capacity of nanoparticles was measured using macrophages labelled with [^{3}H]cholesterol. Anti-inflammatory effects on human granulocytes were evaluated with chemotaxis assay and flow cytometry. *In vivo* experiments were performed with IL-5 transgenic and C57BL/6 mice.
Results: Upon testing the functionality, we found that the nanodiscs potently mobilised cholesterol *in vitro* and *in vivo*. Moreover, the nanodiscs significantly suppressed monocyte activation and neutrophil integrin activation, and down-modulated the human eosinophil migration response to eotaxin and prostaglandin D_2. Synthetic HDL nanodiscs also reduced eosinophil transmigration in response to eotaxin in IL-5 transgenic mice. All these effects were dependent on the lipidation status of the nanoparticles.
Discussion: ApoA-I-mimetic peptide-based nanodiscs have therapeutic potential in hyper-inflammatory and hyper-eosinophilic diseases such as sepsis and asthma, where immune cell migration and activation is a critical factor for disease exacerbation.
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Keywords: high-density lipoproteins (HDL) – ApoA-I-mimetic nanodisks – pulmonary inflammation

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