EuroSciCon

EuroSciCon Conference on
Nanotech & Nanobiotechnology

July 12-13, 2018
Paris, France

Nano Res Appl 2018, Volume 4
DOI: 10.21767/2471-9838-C2-012

A MODULAR PLATFORM FOR TARGETED RNAI THERAPEUTICS USING BIOLOGICALLY-LIPIDATED ANTIBODIES

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Small interfering (si) RNAs can be used to silence disease-causing genes. However, their development as drugs has been limited mainly in knocking down liver gene expression, since delivery to other tissues requires development of a targeted delivery carrier. Modulating immune cells function using siRNAs holds great promise in advancing targeted therapies to many immune-related disorders including cancer, inflammation, autoimmunity, and viral infections. However, the ability to effectively knockdown gene expression in leukocytes is still challenging. Here, we present a modular platform to target specific cell types, exemplified here with immune cells, using siRNA loaded lipid nanoparticles (LNP) coated with oriented, targeting antibodies noncovalently bound to a membrane-anchored lipoprotein that recognizes their Fc domain. Unlike chemically conjugated antibodies, these oriented antibodies maintain their high affinity and the LNPs avoid scavenging by Fc receptors on macrophages. A simple switch in 5 different targeting antibodies (against Ly6C, CD3, CD4, CD25 and Itgb7) redirected the LNP for exquisitely specific uptake in diverse leukocyte subsets *in vivo* and enabled specific knockdown in difficult-to-transfect $CD4^+$ cells. Intravenously injected anti-Ly6C-coated LNP encapsulating TNF siRNAs were taken up selectively by $Ly6C^+$ monocytes and activated tissue macrophages, suppressed TNF-α expression in the colon and ameliorated inflammatory bowel disease symptoms in a DSS-induced colitis mouse model, demonstrating the platform's potential therapeutic utility. This approach opens new avenues for studying cell biology *in vivo* and potentially for a wide range of therapeutic applications in a cell-specific manner.

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