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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 to 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 expressing 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-alpha 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.

Biography

Itai Benhar is a full Professor, Vice Dean for Research at the George S Wise Faculty of Life Sciences, Tel-Aviv University, Israel. He received in 1992 a PhD in Molecular Biology from the Hebrew University, Israel and was a Post-doc 1992-1995 at NCI, NIH. He joined Tel-Aviv University as a tenure-track assistant professor in 1995 and is a full professor since 2008. He is an expert in the fields of antibody engineering, drug discovery and drug delivery with over the 20 years of being active in these fields, 92 peer reviewed articles and 11 patents.

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