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Gene silencing following siRNA delivery to skin via coated steel microneedles: *in vitro* and *in vivo* proof-of-concept

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Abstract

The development of siRNA-based gene silencing therapies has significant potential for effectively treating debilitating genetic, hyper-proliferative or malignant skin conditions caused by aberrant gene expression. To be efficacious and widely accepted by physicians and patients, therapeutic siRNAs must access the viable skin layers in a stable and functional form, preferably without painful administration. In this study we explore the use of minimally-invasive steel microneedle devices to effectively deliver siRNA into skin. A simple, yet precise microneedle coating method permitted reproducible loading of siRNA onto individual microneedles. Following recovery from the microneedle surface, lamin A/C siRNA retained full activity, as demonstrated by significant reduction in lamin A/C mRNA levels and reduced lamin A/C protein in HaCaT keratinocyte cells. However, lamin A/C siRNA pre-complexed with a commercial lipid-based transfection reagent (siRNA lipoplex) was less functional following microneedle coating. As Accell-modified “self-delivery” siRNA targeted against CD44 also retained functionality after microneedle coating, this form of siRNA was used in subsequent *in vivo* studies, where gene silencing was determined in a transgenic reporter mouse skin model. Self-delivery siRNA targeting the reporter (luciferase/GFP) gene was coated onto microneedles and delivered to mouse footpad. Quantification of reporter mRNA and intravital imaging of reporter expression in the outer skin layers confirmed functional *in vivo* gene silencing following microneedle delivery of siRNA. The use of coated metal microneedles represents a new, simple, minimally-invasive, patient-friendly and potentially self-administrable method for the delivery of therapeutic nucleic acids to the skin.

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