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Topical application of siRNA for treatment of hair follicle pathologies

Elena Feinstein[1], Shan Gao[2], Sharon Avkin[1], Hagar Kalinski[1], Igor Spivak[1], Anat Brafman[1], Jinyu Huang[2], Naidan Luo[2], Hongyan Zhang[2] and **Hagit Ashush[1]**
[1]Quark Pharmaceuticals Inc, Israel
[2]Suzhou Ribo Life Sciences Co. Ltd, China

Short inhibitory RNAs are a novel class of therapeutics acting via specific inhibition of target gene expression. The most advanced siRNA drugs are currently in Phase 3 clinical trials for several systemic and local applications. Here, we demonstrate for the first time the possibility of effective topical delivery of synthetic siRNA compounds into hair follicles both in vivo in mice and in human skin explants. In human scalp skin explants, topical treatment with siRNA produced significant dose-dependent up-to 60% suppression of target gene mRNA expression as well as significant reduction of the target protein levels. Topically administered siRNA inhibits its target gene activity only at the site of application since it does not leak into systemic circulation as shown both in vivo in mice and ex vivo in Franz diffusing cells containing human skin. No skin irritation following repeated topical applications of siRNA was observed either. The proof on concept of efficacy of topical siRNA treatment in ameliorating hair loss was demonstrated in the mouse model of chemotherapy-induced alopecia (CIA) using p53 targeted siRNA. P53 gene codes for a protein activated in response to chemotherapy in matrix keratinocytes and leading to their apoptosis. Mice lacking P53 in their germline do not develop CIA. Backs of mice were depilated to synchronize hair growth in this area in anagen VI, when matrix keratinocytes become sensitive to cyclophosphamide treatment that elicits massive hair loss in the previously depilated area. The results indicated that siRNA-treated mice were partially rescued from hair loss while demonstrating significantly accelerated (by 8-9 days) hair re-growth in the affected area compared to control. Altogether, the data support the possibility of development of oligonucleotide-based therapeutics (or cosmeceuticals) for treatment of hair follicle-associated conditions such as different types of alopecia and acne vulgaris.

efeinstein@quarkpharma.com

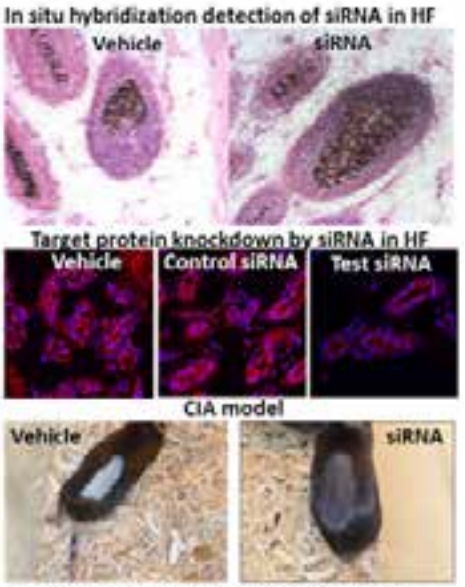

Figure 1. **Upper panel:** Hematoxylin-eosin staining. siRNA –black dots. **Middle panel:** cell nuclei – blue, target protein – red. **Lower panel:** day 21 after depilation/day 11 after cyclophosphamide treatment. **HF** – hair follicles.