



# Topical siRNA for management of androgenic alopecia and oily skin

# About Quark

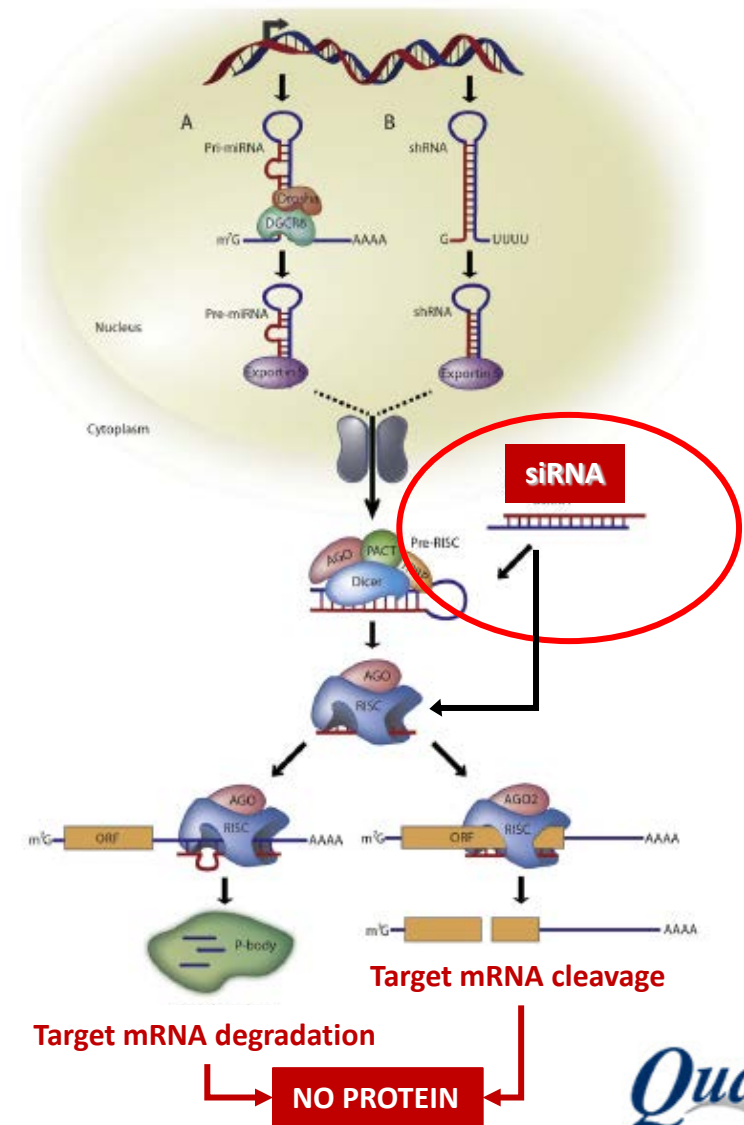
- Founded in 1993; privately held
- Late stage pharmaceutical company with 2 Phase 3 programs, 5 Phase 2 programs and rich pipeline with POC in non-clinical efficacy models
- Headquarters: Fremont, CA – preclinical and clinical development
- Fully owned subsidiary, QBI Enterprises Ltd: Ness Ziona, Israel – platform development, drug discovery
- JV in China - with Suzhou Ribo Life Science – Kunshan RiboQuark Pharmaceutical Technology Co, Ltd

**Focus: discovery and development of siRNA-based therapeutics**



# siRNA-Based Drugs Act Through Specific Inhibiting Gene Expression via RNA Interference

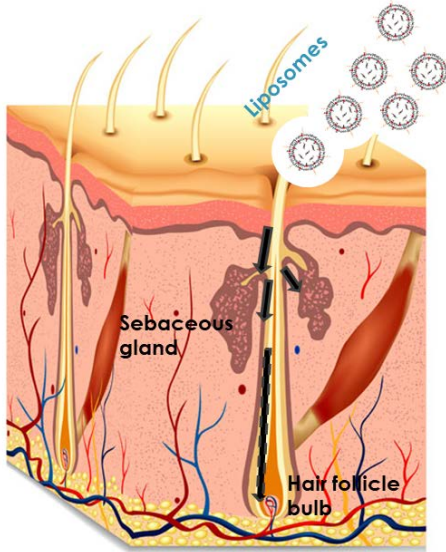
- **RNA interference (RNAi)** is a universal biological mechanism within living cells (mammalian, plants, fungi, bacteria) that controls which genes are active and how active they are via targeting specific mRNAs to degradation
- **siRNA therapeutic molecules** are produced synthetically using well-established solid-phase synthesis processes and mimic endogenous RNAi triggers upon cell entry
- Use of **specific chemical modifications** in siRNA compounds ensures:
  - Stability against body exonucleases and endonucleases
  - High activity and specificity
  - Strong attenuation of pro-inflammatory effects typical for exogenously delivered oligonucleotides



# Therapeutic Hypothesis:

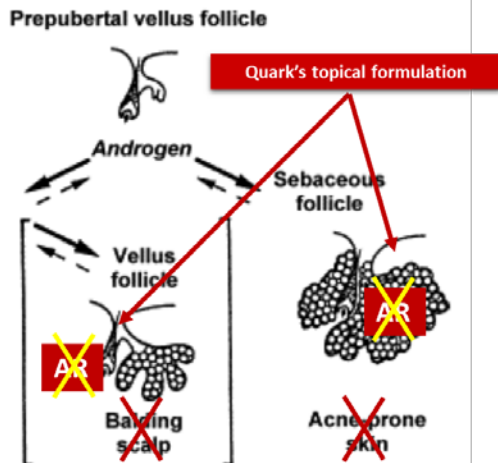
- Increased androgen production or increased androgen receptor (AR) sensitivity to androgens in the hair follicles bulbs and sebaceous glands leads to
  1. **Hair follicle miniaturization and pattern scalp balding (androgenic alopecia)**
  2. **Excessive sebum production and acne development (acne vulgaris)**
- A siRNA therapeutic designed to downregulate AR activity may result in prevention / treatment of these conditions

# Quark's Novel Topical Formulation for Management of Male and Female Pattern Hair Loss and Excessive Skin Sebum Production



- Active Ingredient: *synthetic siRNA formulated in liposomes for topical delivery specifically to hair follicle bulb and to sebaceous glands*

- Does not penetrate into the dermis
- No transdermal systemic absorption
- Once or twice a week application
- New IP

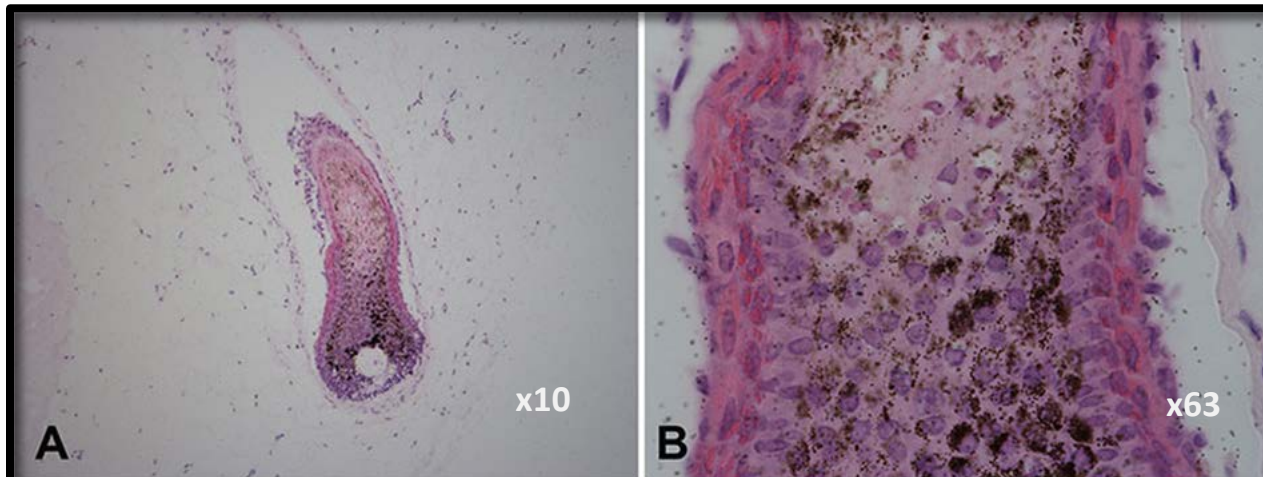




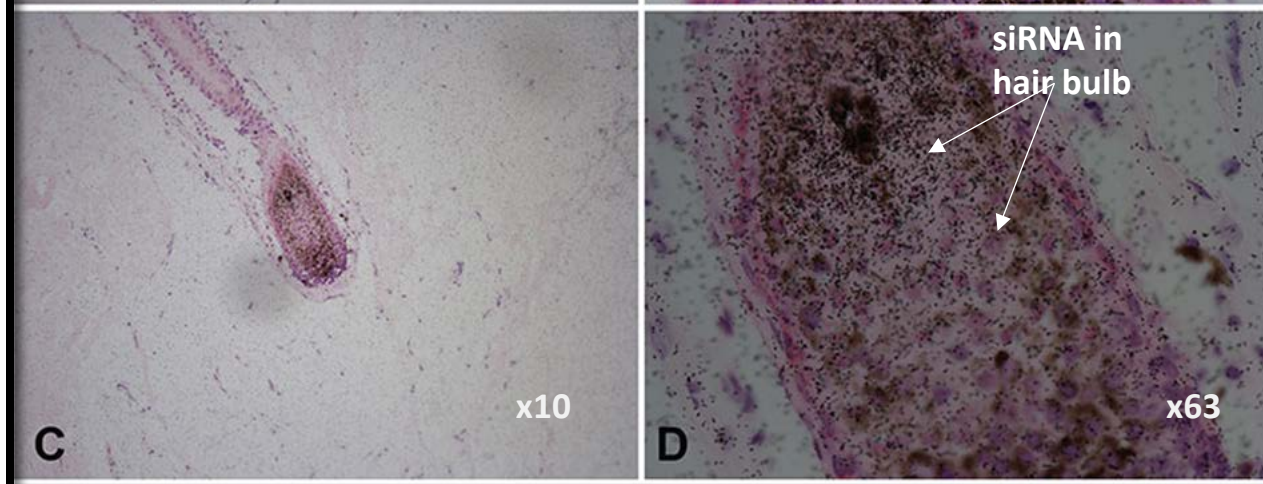
# Detection of Synthetic siRNA in Human Male Scalp Skin Explants 24 Hours After Topical Application in the Novel Formulation

*RNA is visible as black dots (by in situ hybridization technique)*

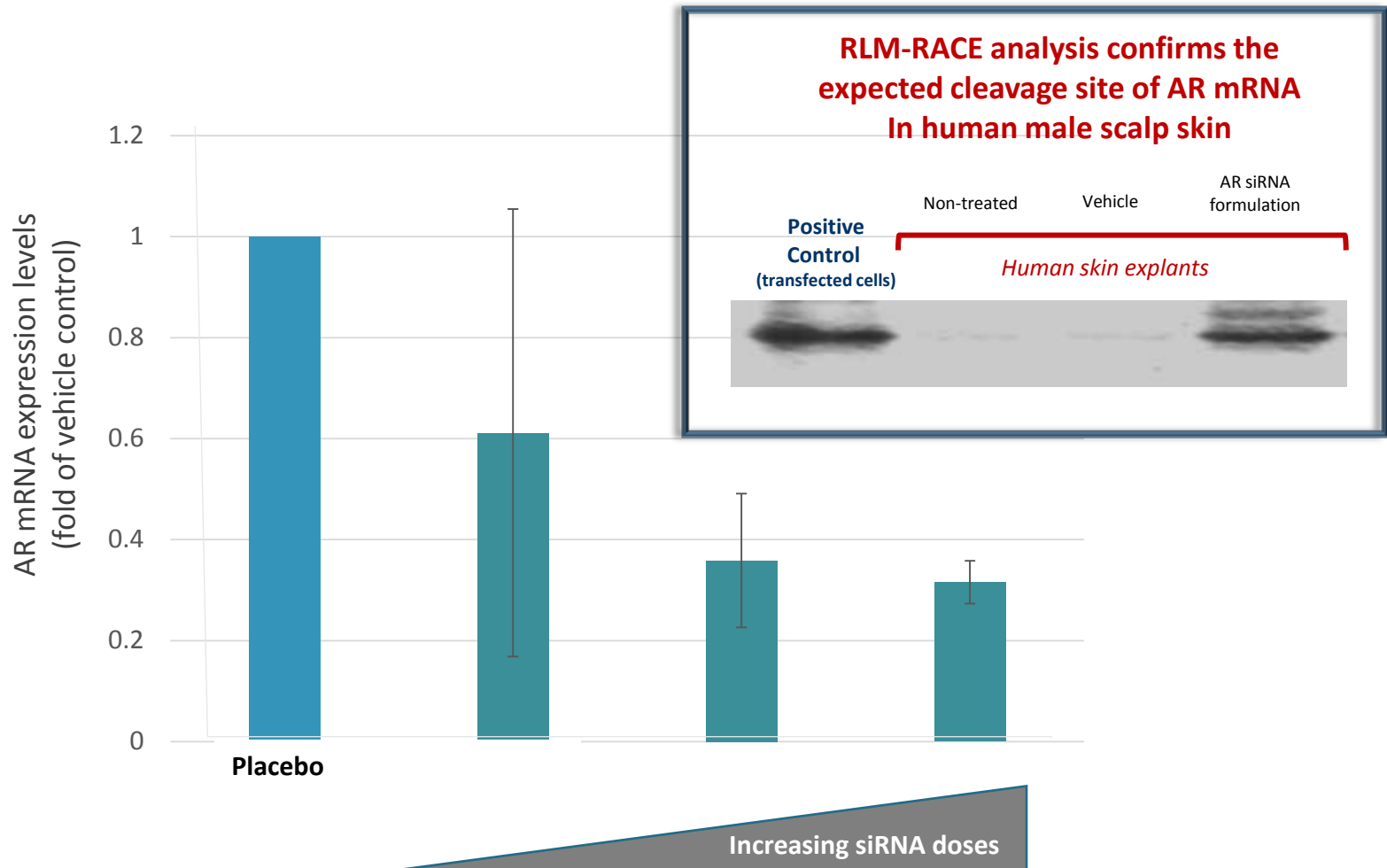
Placebo



Quark's Novel Topical Formulation



# siRNA Dose-Dependent Reduction of AR mRNA Levels in Human Male Scalp Skin Explants 24 Hours After Topical Application of the Formulation

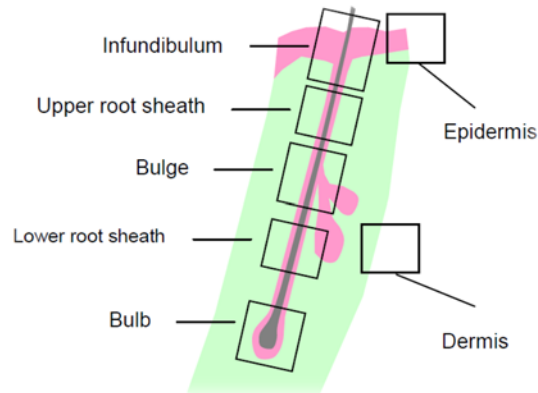


# Decrease of AR Protein Levels in Human Skin Explants 24 Hours After Topical Application of the Formulation

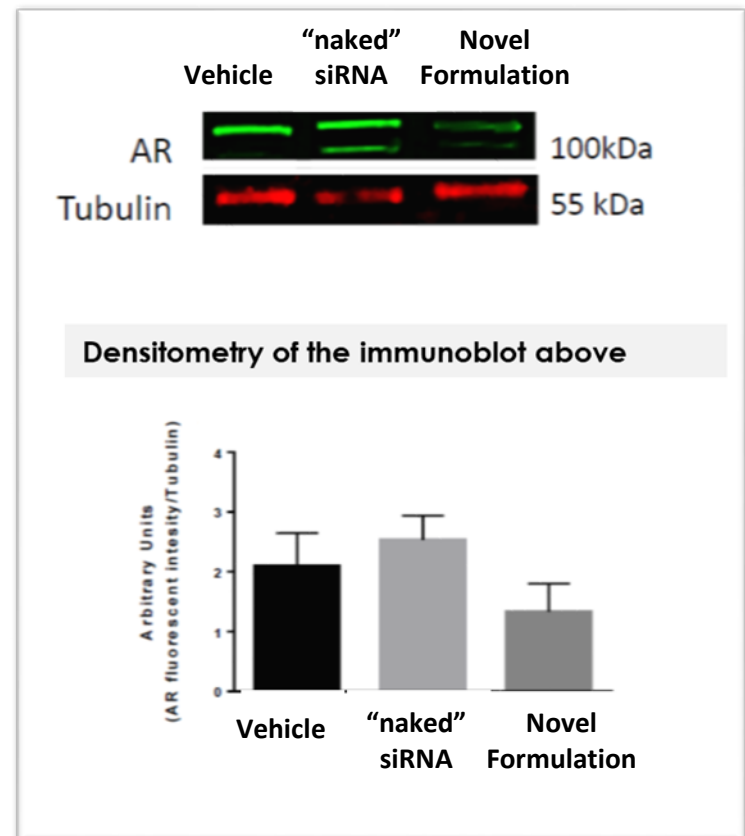
*Immunohistochemistry analysis in male skin*

Comparison vs. vehicle group	Quark's Novel Topical Formulation
Dermis	↔
Infundibulum	↘
Upper root sheath	↘
Bulge (Close to sebaceous glands)	↘↘
Lower root sheath	↔
Bulb	↘↘↘

- ↔ No Variation
- ↘ Slight decrease
- ↘↘ Moderate decrease
- ↘↘↘ Quite clear decrease
- ↘↘↘↘ Clear decrease



*Immunoblotting analysis in female skin*



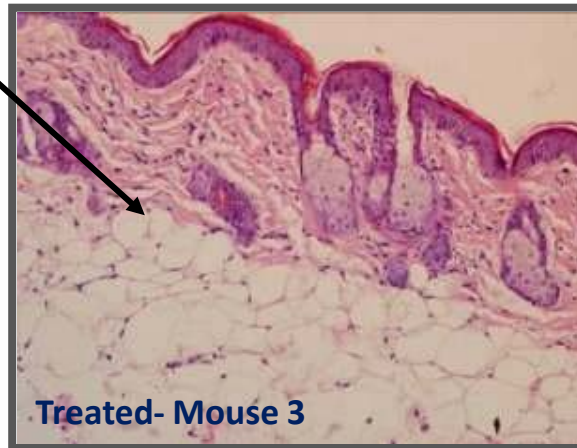
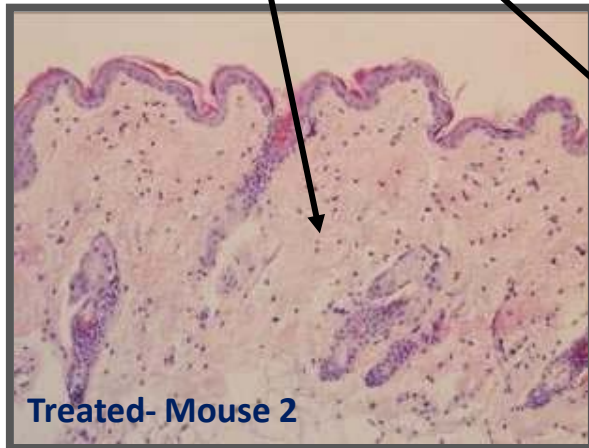
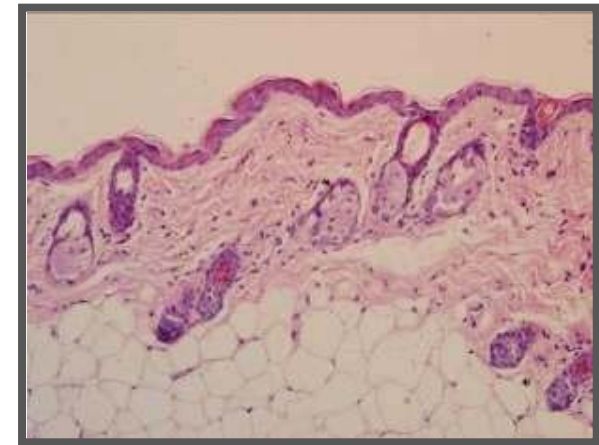
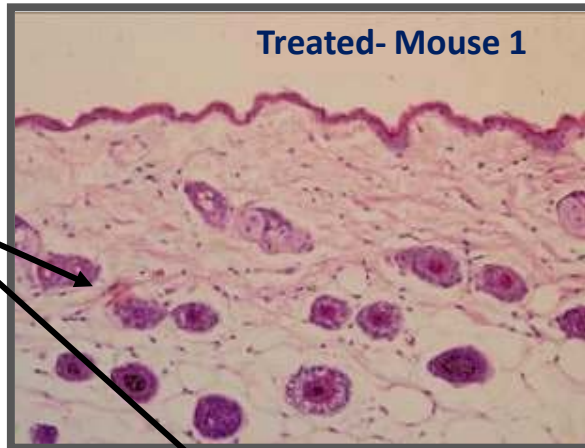


# Lack of Skin Inflammation Following Repeated Topical Application of the Liposome-Formulation on Depilated Mouse Skin

*Formulated siRNA*

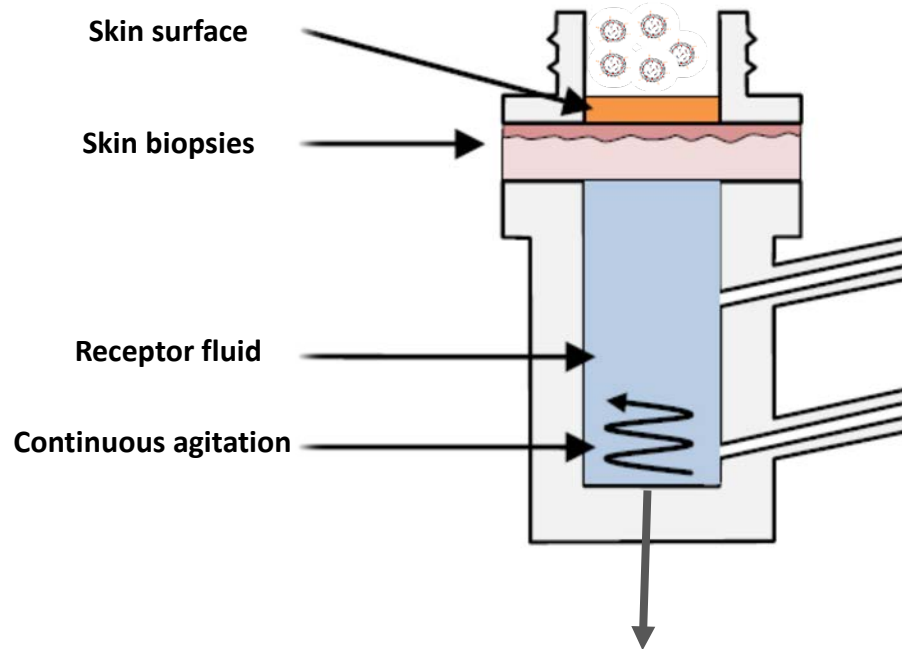
*Ctrl Saline*

*Absence of infiltrating immune cells or edema following repeated applications of the liposome formulated RNA*



# No Absorption Through Human Skin Explants (*ex vivo*) in Franz Diffusion Cells

*Apical application of formulated siRNA for 24 hours*



**No siRNA was detected in the receptor fluid**

# Demonstration of siRNA efficacy in alleviating alopecia in animal models

- There are currently no robust animal models of AGA or acne vulgaris
- A well-established chemotherapy-induced alopecia (CIA) model in mice was used as a surrogate model of AGA. In this model, the cells in the hair bulb die due to chemotherapy administration.
- Quark used topically delivered siRNA targeting p53 in its proprietary formulation in this surrogate model of hair loss model for POC efficacy studies. P53 gene was selected as a target due to the fact that P53 KO mice do not lose hair in the CIA model.

# Efficacy of Quark's Liposome-Formulated p53 siRNA in the Mouse Model of Chemotherapy-Induced Alopecia



# Summary

Following topical application on human male and female skin explants, the liposome-formulated siRNA targeting AR:

- Distributes to hair follicle including bulb and sebaceous glands
- Significantly reduction in AR mRNA levels
- Significantly reduction in AR protein levels
- No evidence of transdermal absorption

Following topical application on mouse skin in vivo, the liposome-formulated siRNA targeting AR leads to:

- No transdermal absorption into systemic circulation
- No skin irritation
- Following topical application on mouse skin in vivo, the liposome-formulated siRNA targeting AR leads to:
  - Significantly accelerated regrowth of more pigmented hair in the model of chemotherapy-induced alopecia

**BASED ON THESE DATA FURTHER EXPLORATION OF OTHER  
DISEASES OF HAIR FOLLICLES AND SEBACEOUS GLANDS  
INCLUDING AGA AND ACNE IS FEASIBLE**



# Thank you!

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