Pharmacodynamic activity of a microRNA-29b mimic (MRG-201) in human skin incisions

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Abstract
MicroRNA-29 is an anti-fibrotic miRNA whose expression is downregulated in multiple fibrotic indications including in cutaneous scars, keloids and burns. Its target genes include numerous collagen and other extracellular matrix molecules, suggesting that restoration of miR-29 expression in a skin wound or at the site of an excised scar could have a therapeutic benefit by reducing scarring and/or preventing scar regrowth. An oligonucleotide mimic of miR-29b (MRG-201) was studied in vivo in mice, rats and rabbits as well as in vitro in human fibroblasts to identify a set of conserved pharmacodynamic biomarkers in the skin. MRG-201 was then evaluated in a Phase 1 double-blinded within-patient randomized clinical trial in 53 normal healthy volunteers (NCT02603224). Expression of miR-29b and its pharmacodynamic biomarkers was assessed in untreated skin incisions and following single or multiple administrations of MRG-201 at the site of a sutured skin incision. miR-29b expression was significantly decreased and direct miR-29 target genes were significantly upregulated with incision alone. Intradermal administration of MRG-201 resulted in a high local concentration of miR-29b with low systemic exposure and good safety/tolerability at all doses tested. Pharmacodynamic activity was seen after MRG-201 treatment: single and multiple doses of MRG-201 reduced collagen mRNA expression as compared to a placebo injected incision in the same subject. Additionally, multiple administrations of MRG-201 reduced fibrosis as assessed by histopathology (p<0.01). These findings support further investigation of MRG-201 as a novel therapeutic to PHHS scar formation or prevent hypotrophic scar or keloid recurrence following excision.

MicroRNAs
- MicroRNAs regulate complex biological systems and this role is amplified in disease states and biological stress.
- The pharmacology of microRNA-targeted therapies is intrinsically focused on disease relevant pathways.
- MicroRNAs serve as a “molecular switch” that constrains differentiation and maintains adaptive and maladaptive phenotypes.
- The unique objective of microRNA-targeted therapy is to achieve disease modification by restoring systems homeostasis.

miR-29 Family: Antifibrotic microRNAs
hsa, mmu, rno-miR-29a: 5'-UAGGACACACUCUGAAUUCGAGUUA-3'
hsa, mmu, rno-miR-29b: 5'-UAGGACACACUCUGAAUUCGAGUUA-3'
hsa, mmu, rno-miR-29c: 5'-UAGGACACACUCUGAAUUCGAGUUA-3'

Seed sequence

In vivo Validated Targets
TGF-β2, TGF-β3, EGF, IFNα, IFNβ, PDGF, PDGFA, PDGFB

Pathways
- TGFB-D/P38-MAPK signaling
- FoxO signaling
- Collagen cross-linking
- TGFbeta signaling
- TGFalpha signaling

Identification of miR-29 Target Genes In Vivo

Functional Annotation (GO arm)
- ECM: Collagen, Extracellular matrix
- Function: Skin development, Epithelium development, Cell adhesion, Apoptosis

Selection of 24 Pharmacodynamic Biomarkers

Single Ascending Dose
- 0.5–14 mg Administered to Intact Skin

Clinical Trial MRG021-30001
Part A: Kinetics of miR-29b Expression and Pharmacodynamic Gene Expression in Normal Healthy Volunteers with Sutured Skin Incisions

Clinical Trial MRG021-30001
Part B: Safety, Tolerability, Pharmacokinetics and Pharmacodynamics
Assessment of MRG-201 Administered via Intradermal Injection in NHV

Part C
- Single Ascending Dose 4–7,14 mg Administered to Intact Skin

Part D
- Multiple Ascending Dose 4, 7, 14 mg Administered M.W.F to Skin Incision

MRG-201 Target Engagement Corresponds to Impact on Fibroplasia

Conclusions
- MRG-201 is well-tolerated in intact and incised skin
- No safety or injection site reaction concerns
- No adverse histologic findings
- Maximum tolerated dose not defined: maximum deliverable dose ~ 14 mg / 200 μL
- Demonstrated mPoC for MRG-201 in human incised skin
- Pharmacodynamic biomarkers that are up-regulated following incision are down-regulated by MRG-201
- Magnitude of target engagement appears dose-proportional with single administration
- Within a subject, MRG-201 target engagement correlates with the impact on fibroplasia following multiple administrations