Preclinical Results Supporting Therapeutic Development of MRG-106, an Oligonucleotide Inhibitor of miR-155, in CTCL

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Abstract

Treatment-resistant hematologic malignancies remain an area of high unmet need and novel therapeutic approaches are required. microRNAs are small (~22 nt) non-coding RNAs that act as negative regulators of gene expression. There is growing interest in the expression of a subset of microRNAs (miRs) that play a role in pathogenesis of hematologic malignancies (HMs) and solid tumors. miR-155 is a well studied miR associated with poor prognosis and resistance to treatment in a variety of HM subtypes including mycosis fungoides (MF) and Sézary syndrome. We sought to establish the safety and tolerability of MRG-106, an oligonucleotide modified miRs-155 inhibitor.

miR-155 plays a key role in inflammation and oncogenesis

miR-155 is upregulated in MF cell lines and skin biopsies

miR-155 inhibition results in direct target gene regulation

Microarray profiling identifies a translational pharmacodynamic gene signature of MRG-106 activity

Gene signature of MRG-106 activity normalizes gene expression changes in mycosis fungoides lesions

The biogenesis and therapeutic modulation of microRNAs

microRNAs are novel therapeutic targets that act through the regulation of systems biology

miR-155 is elevated in mycosis fungoides cell lines and skin biopsies

Inhibition of miR-155 results in reduction in cell number and activation of programmed cell death

Direct target regulation correlates with phenotypic changes

Inhibitor design can influence uptake properties

miR-155 targets a role in inflammation and oncogenesis

Direct target gene regulation is specific for miR-155 inhibition

Figure 1. The unique objective of microRNA-targeted therapy is achieving disease-modification by restoring systems function and reducing disease burden. This is accomplished through the biogenesis of microRNAs and by modulation of their biologic activity in diseased tissues.

Figure 2. MicroRNAs are transcribed from unique loci or as exons within genes of protein-coding genes. After transcription in the nucleus, the pre-microRNA is cleaved by the Drosha enzyme. Drosha is composed of a 90-kD protein and an RNA helicase, CED-4, that acts as a slicer. The mature miRNA is loaded onto the Dicer/RNA helicase complex. This complex functions to guide the RNA-induced silencing complex (RISC) to the target mRNA.

Figure 3. The mature miR-155 can be upregulated in a variety of cancers, including chronic lymphoid leukemia and mycosis fungoides (CTCL). The overexpression of miR-155 is driven by STAT3 and restores systems homeostasis.

Figure 4. Several publications have shown that miR-155 is overexpressed in patients with mycosis fungoides (Ref. 1-4). Cleared miR-155 is selectively relevant to NF pathologies (Ref. 5). One publication showed that miR-155 is upregulated in unclassified cells of patients with Sézary syndrome (Ref. 7).

Figure 5. The primary MF cell line was treated with miR-155 inhibitors MRG-106 or MRG-107 and cell proliferation was determined by cell count. Cells treated with miR-155 inhibitors MRG-106 and MRG-107 showed a 50% decrease in cell number compared to the untreated control.

Figure 6. miR-155 and miR-106 were tested in cells with unfacilitated or facilitated uptake. The RNAi response to MRG-106 was substantially enhanced in cells treated with facilitated uptake. In contrast, MRG-106 showed similar activity in both uptake groups, suggesting that MRG-106 is optimized with regard to uptake.

Figure 7. The indicated MF cell lines were treated with miR-155 inhibitors in the absence of agents to enhance cellular penetration such as cationic lipids or peptide conjugates (unfacilitated uptake). TMiR-106 and TMiR-107 are inhibitors of miR-155. After treatment for four days with the indicated compound, cells were harvested and RNA was isolated for analysis. The gene target was measured by real-time PCR and normalized to the unblocked cell control. MRG-106 appeared to have a greater magnitude of target gene expression compared to TMiR-107.

Figure 8. Microarray profiling identifies a translational pharmacodynamic gene signature of MRG-106 activity.

Figure 9. Gene signature of MRG-106 activity normalizes gene expression changes in mycosis fungoides lesions.

References

Disclosures: All the authors are employed by and have equity ownership in miRagen Therapeutics, Inc.