blood®

625. LYMPHOMA: PRE-CLINICAL - CHEMOTHERAPY AND BIOLOGIC AGENTS: POSTER II | DECEMBER 03, 2015

Preclinical Results Supporting Therapeutic Development of Mrg-106, an Oligonucleotide Inhibitor of Mir-155, in CTCL

Anita G Seto , PhD,[*,1] Xuan T Beatty , BS,[*,1] Linda A Pestano , PhD,[*,1] Brent A Dickinson , BA,[*,1] Marshelle S Warren , MD,[*,1] David M Rodman , MD,[*,1] Aimee L Jackson , PhD[*,1]

[1]miRagen Therapeutics, Boulder, CO

Blood **(2015) 126 (23) : 2758.**

http://doi.org/10.1182/blood.V126.23.2758.2758

Abstract

Treatment-resistant hematological malignancies remain an area of high unmet need and novel therapeutic approaches will be required. microRNAs are small (~ 22 nt) non-coding RNAs that act as negative regulators of gene expression. These small RNAs impact expression of a substantial fraction of the genome, and have powerful effects on cellular phenotypes and physiological processes. miR-155-5p is a well-described oncomiR associated with poor prognosis in multiple malignancies, particularly lymphoma and leukemia. Cutaneous T-cell lymphoma (CTCL) is a rare hematological malignancy with limited treatment options and a strong mechanistic link to increased miR-155-5p. Because of the accessibility of cutaneous lesions, CTCL provides a unique opportunity to determine if inhibition of miR-155-5p has therapeutic potential in lymphomas associated with elevated miR-155-5p.

We optimized a LNA-modified oligonucleotide inhibitor of miR-155-5p, MRG-106, based on the ability to de-repress canonical miR-155-5p targets in multiple cell types *in vitro*. In mycosis fungoides (MF) cell lines, MRG-106 does not require additional formulation to achieve maximum pharmacodynamic efficacy. Inhibition of miR-155-5p resulted in transcriptome changes consistent with miR-155-5p target gene modulation, reduction in cell proliferation, and activation of the programmed cell death pathway. The gene expression and phenotypic effects were inhibitor dose-dependent and sequence-specific. Based on an informatics approach for the expression profiling of MF cell lines treated with MRG-106, a set of 600 genes was identified to represent the translational pharmacodynamic biomarker signature, both direct and downstream of miR-155-5p.

GLP preclinical safety studies have been completed in rats and non-human primates, demonstrating an acceptable safety profile for MRG-106. We plan to initiate a 4-week first-in-human clinical trial in CTCL (MF) patients. The trial design is two-part, with Part A testing the effect of direct intra-tumoral injection of MRG-106 into plaque and nodular skin lesions, and Part B testing the effect of systemic (subcutaneous) administration of higher doses of MRG-106. The primary objective of Part A is to profile the pharmacodynamic effect of MRG-106 on the miR-155-5p gene expression signature, establishing a PK/PD model to guide future development. The primary objective of Part B is to establish the safety, tolerability, PK and skin deposition of MRG-106 after systemic delivery. Exploratory objectives include measures for clinical response, immune system effects, and biomarker validation.

Disclosures

Seto: *miRagen Therapeutics:* Employment, Equity Ownership. **Beatty:** *miRagen Therapeutics:* Employment, Equity Ownership. **Pestano:** *miRagen Therapeutics:* Employment, Equity Ownership. **Dickinson:** *miRagen Therapeutics:* Employment, Equity Ownership. **Warren:** *miRagen Therapeutics:* Consultancy. **Rodman:** *miRagen Therapeutics:* Employment, Equity Ownership. **Jackson:** *miRagen Therapeutics:* Employment, Equity Ownership.

Author notes

*Asterisk with author names denotes non-ASH members.