DIA Oligonucleotide-Based Therapeutics Conference
North Bethesda | MD October 25-27
Translating PD Biomarkers From Preclinical Studies to Clinical Trials:

MRG-106, an Oligonucleotide Inhibitor of miR-155, Coordinately Regulates Multiple Survival Pathways to Reduce Cellular Proliferation and Survival in Cutaneous T-Cell Lymphoma

Aimee L. Jackson, Ph.D.
October 26, 2017
Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to DIA, its directors, officers, employees, volunteers, members, chapters, councils, Communities or affiliates, or any organization with which the presenter is employed or affiliated.

These PowerPoint slides are the intellectual property of the individual presenter and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved. DIA and the DIA logo are registered trademarks or trademarks of Drug Information Association Inc. All other trademarks are the property of their respective owners.
microRNA Therapeutics Regulate Systems Biology to Modify Disease

- microRNA-targeted therapy is focused on disease modification by restoring homeostasis to dysregulated processes
- microRNAs regulate complex biological systems
- microRNA-targeted therapies are intrinsically focused on disease-relevant pathways
- microRNA therapeutics particularly suited for complex, multigenic disorders
Regulating Systems Biology to Modify Disease

miR-155 is an OncomiR and a Pro-inflammatory microRNA

↑ miR-155

- CEBPβ
  - Inflammation M1→M2
- SOCS
  - Cytokines T cell activation
- SHIP-1
  - IL-6, TNFα
  - PI3K/AKT/MAPK Proliferation
- Jarid2
  - Leukemic transformation
- PU.1
  - Myeloid differentiation
- Wee1
  - DNA repair

Inflammation / Immunity

Cancer
Increased miR-155 Has Been Implicated in Multiple Oncology and Inflammatory Indications

- Cutaneous T-cell lymphoma
- Acute myelogenous leukemia
- B-cell lymphoma (DLBCL)
- B-cell lymphocytic leukemia (CLL)
- Adult T-cell Leukemia/Lymphoma
- Neurofibromatosis
- Glioblastoma
- Triple negative breast cancer
- Graft-vs-host disease
- Ulcerative colitis
- Rheumatoid arthritis
- ALS
- Lupus
Cutaneous T-cell Lymphoma

- CTCL: Malignant T cells in the skin
- Mycosis Fungoides (MF)
  - Most common form of CTCL
  - United States MF prevalence of 16,000-20,000 cases
  - Initially indolent but with serious quality of life detriment
  - Disease progresses from patch → plaque → tumor
  - 10-20% progress to tumor stage
  - Elevated miR-155 expression
Inhibition of miR-155 Reduces Cell Number and Increases Apoptosis in CTCL Cell Lines

Cell Number

Apoptosis

miR-155 High cell line

miR-155 Low cell line
MRG-106 Target Engagement Correlates with Phenotype
MRG-106 Regulates Multiple Survival Pathways in CTCL Cell Lines

**Day 4**
- Upregulated
- Enriched for direct targets (miR-155 seeds)
- Enriched for downstream targets:
  - Cell cycle
  - Apoptosis

**Day 8**
- Downregulated

**PD biomarkers include:**
- PI3K/AKT
- JAK/STAT
- RAS/MAPK
Survival Signaling in Hematologic Malignancies

TCR/BCR → PI3K → AKT → NFκB↑

TCR/BCR → JAK

TCR/BCR → RAS → RAF → ERK → AP1

PI3K → AKT

JAK

STAT

↑ Proliferation
↓ Apoptosis
miR-155 Coordinately Regulates Multiple Survival Signaling Pathways

↑ miR-155

TCR/BCR

PI3K

JAK

RAS

STAT

RAF

ERK

AKT

AP1

NFκB

SOCS-1

SHIP1

Others
MRG-106 Inhibits Multiple Survival Pathways Simultaneously

- **pAKT**: w/o treatment, 10uM Idelalisib, 10uM MRG-106, 50uM MRG-106
  - w/o treatment: high, 10uM Idelalisib: low, 10uM MRG-106: moderate, 50uM MRG-106: high

- **pERK**: w/o treatment, 10uM U0126, 10uM MRG-106, 50uM MRG-106
  - w/o treatment: low, 10uM U0126: low, 10uM MRG-106: moderate, 50uM MRG-106: high

- **pSTAT**: w/o treatment, 10uM Ruxolitinib, 10uM MRG-106, 50uM MRG-106
  - w/o treatment: low, 10uM Ruxolitinib: low, 10uM MRG-106: moderate, 50uM MRG-106: high

*Significance levels: *p < 0.05, **p < 0.01, ***p < 0.001
miR-155 Expression and MRG-106 PD Biomarkers Translate to Historical Mycosis Fungoides Specimens
MRG-106 First-In-Human Phase 1 Study in CTCL

**Part A**
- Intra-tumoral delivery of MRG-106, 75 mg, up to 5 injections over 2 weeks
- Safety, tolerability, PK, PD

**Part B**
- Systemic SC or IV delivery up to 6 injections over 4 weeks; optional extension phase of weekly dosing
- Safety, tolerability, PK
- Biopsies for PD optional

![Diagram showing study design](image)
Intratumoral MRG-106 Inactivates JAK/STAT, NFkB, and PI3K/AKT Pathways in MF Lesions

Activated

Inhibited

Status of Canonical Pathways in MRG-106-treated Lesions

Status of Canonical Pathways in Saline-treated Lesions
22 of 23 Patients Treated Systemically with MRG-106 have mSWAT Score Improvement Independent of Treatment Duration

9/13 (69%) of patients receiving >1 month of dosing achieved ≥50% reduction in mSWAT
Systemic Administration of MRG-106 Reduces Total Skin Disease in MF Patients: Case Example

- Age: 51; Sex: Male
- Date of diagnosis: 2013
- Concomitant systemic therapy: Methotrexate (started June 2015)
- MRG-106: 300 mg IV
- Has skin (mSWAT) PR lasting > 4 months

Day 1
mSWAT: 180

Day 93
mSWAT: 68
(62% reduction)
Conclusions

- MRG-106 reduces proliferation and increases apoptosis in CTCL cell lines
- MRG-106 regulates genes associated with survival signaling in CTCL cell lines
- PD biomarker genes are dysregulated in MF biopsies, showing relevance to disease
- MRG-106 regulates PD biomarkers in MF lesions, demonstrating mechanistic proof-of-concept
- MRG-106 reduces total skin disease in MF patients
  - 69% of patients receiving >1 month of dosing with systemic MRG-106 achieved ≥ 50% improvement in total skin disease mSWAT score
- MRG-106 has therapeutic potential in additional hematologic malignancies and solid tumors with elevated miR-155