Oligonucleotide-Based Therapeutics Conference
October 28-30 | North Bethesda, MD
Clinical Development of microRNA Inhibitors

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microRNAs have been evolutionarily selected to regulate networks of genes.

- microRNAs are dysregulated in many diseases.

Dysregulation of microRNAs is associated with alteration of downstream gene networks and disease.

- microRNA-targeted therapy is focused on disease modification by restoring homeostasis to dysregulated processes.

- microRNA therapeutics may be particularly suited for complex, multigenic disorders.

Conventional Therapies
(Small molecules, Antibodies, siRNA, etc)
Single molecule as target

microRNA-based Therapies
Network (pathway) as target
Many diseases are multigenic, complex disorders. Modulation of miRNAs may offer multiple opportunities to intervene in disease-relevant pathways.

miRNAs are homeostatic and therefore miRNA therapeutics do not appear to adversely affect normal tissues/systems.

miRNA therapeutics can be administered without exotic formulations, thereby potentially improving their safety profile.

Safety of formulated miRNA therapeutics has been poor to date.
  • Safety concerns may be mitigated with unique chemistry and delivery approaches.

PD biomarker identification efforts are required to identify genes and networks affected by a miRNA therapeutic.
  • Identification of translatable PD biomarkers.
  • Proving selectivity for disease specific pathways and not normal physiology.
  • Exclude candidate molecules that affect off-target biomarkers/gene signatures.

Translatability from cells → animal models → patients.
  • Need to demonstrate proof of concept early in clinical trials.
miRagen has developed miRNA inhibitors that to date have better safety profile than other miRNA inhibitors and many other oligonucleotide drugs, by addressing:

- **Chemistry**
  - LNA/DNA mixmer design appears to blunt acute inflammatory responses, hepatotoxicity, renal toxicity
  - Chemical stabilization allows for long tissue half lives and relatively infrequent dosing

- **Delivery**
  - miRNA inhibitors can be delivered without the use of viral vectors, liposomes, or nanoparticle formulation, reducing immunogenicity and potential for off-target toxicity
  - Molecules can be developed that are either broadly taken up by cells or that have targeted delivery conjugates

- **Relative specificity**
  - Target miRNAs and their regulated gene networks selected for development are dysregulated only in disease circumstances, thereby potentially limiting exacerbated pharmacology
  - Therapeutic objective is restoration of homeostasis – miRNA therapeutics modulate but do not obliterate their targets, thereby potentially preventing toxicities associated with a complete repression of target protein expression
miRagen believes it has addressed the challenges of identifying PD biomarkers for miRNA inhibitors that result in relatively minor expression changes for many genes simultaneously by:

- Focusing on miRNAs that are highly evolutionarily conserved and whose target gene networks/pathways are biologically relevant to disease
- Identifying the PD biomarker “fingerprint” for each miRNA inhibitor
  - Assess PD biomarkers in stressed settings that mimic disease
  - Using unbiased screening approaches (e.g. RNAseq) to identify pharmacodynamic targets that are reciprocally regulated by promiRs and antimiRs for the same miRNA
  - Pathway analysis to identify pharmacodynamic targets that are conserved within a network or pathway
  - Utilization of kinetics experiments to identify both direct and indirect downstream targets within the same pathway
  - Identification of lead candidates that are potent, selective

- Select the most disease relevant genes for translation to mechanistic proof of concept studies in early stage clinical trials
miRagen believes it has addressed the challenges in the translation going from cells → animal models → patients by:

- Improving translatability from preclinical to clinical studies
  - Perform research in the most relevant species or disease model
  - Identify the pharmacodynamic “fingerprint” using preclinical studies
  - Validate assays (Nanostring, QRT-PCR, ISH, IHC or other) for translation to the clinic

- Derisking the clinical program by incorporating mechanistic and/or clinical proof-of-concept studies in first-in-human trials:
  - Incorporate mPOC endpoints such as PD biomarker regulation into first in human trials to confirm biological activity in humans
  - Assess disease-relevant endpoints (e.g. CAILS and mSWAT assessments) to address cPOC early in the clinical program
  - Initially focus on localized delivery (e.g. intradermal administration) and collect target tissue samples to assess compound activity in humans
  - Follow with IV or SC administration to assess safety, efficacy
  - Conduct comparative PK for each route of administration
miRagen Clinical Development Programs

MRG-106/Cobomarsen
MRG-110
Cobomarsen, a miR-155 Inhibitor for Potential Treatment of Hematologic Malignancies
miR-155 Regulates Gene Pathways Implicated in Mycosis Fungoides

**↑ miR-155**

- PI3K/AKT
- JAK/STAT
- RAS/MAPK
- NF-κB

**Multiple survival and immune pathways activated**
- ✓ Proliferation
- × Apoptosis
- ✓ T-cell activation

**Conventional Therapy**
(e.g., idelalisib)

- PI3K/AKT
- JAK/STAT
- RAS/MAPK
- NF-κB

**One survival pathway inactivated**
- ✓ Proliferation
- × Apoptosis
- ✓ T-cell activation

**Cobomarsen**

- PI3K/AKT
- JAK/STAT
- RAS/MAPK
- NF-κB

**Multiple survival and immune pathways inactivated**
- × Proliferation
- ✓ Apoptosis
- × T-cell activation
miR-155 is overexpressed in CTCL skin lesions and is involved in tumor progression

The miR-155 inhibitor cobomarsen impacts proliferation and cell survival in MF cells

*In collaboration with Madeleine Duvic (MD Anderson)
T cell activation, survival signaling, and cytokine signaling genes ↑ in MF lesions
REDUCED by cobomarsen
Cell cycle checkpoint genes ↓ in MF lesions
INCREASED by cobomarsen
Cobomarsen Clinical Program in Hematological Malignancies

Dose, Schedule Optimization and Response Durability in CTCL

**Ph 1 CTCL**
- mPoC
- PART A
  - LOCAL
- Parallel Indication Expansion in Ph1
  - ATLL
  - DLBCL
  - CLL

**Ph 2 CTCL**
- cPoC
- PART B/C
  - SYSTEMIC
- Futility Analysis

**Ph 2 in NHL / Leukemia**

**CTCL MYCOSIS FUNGOIDES**

**MIR-155-HIGH NON-HODGKINS LYMPHOMA (NHL)/LEUKEMIA**
Cobomarsen Clinical Development Phase I Results in CTCL
Cobomarsen: Two-part Phase 1 CTCL Clinical Trial

**PART A**
Intra-tumoral delivery of cobomarsen (75 mg dose)

**PART B**
Systemic SC or IV delivery to determine optimal potential dose (300, 600 and 900 mg+ dose)

**OBJECTIVES**

- **PRIMARY** Safety and tolerability
- **SECONDARY** PK
- **EXPLORATORY** PD, histopathology, lesion morphology
Cobomarsen Shows Favorable Tolerability

- **COBOMARSEN HAS BEEN GENERALLY SAFE** and well tolerated
  - Multiple patients receiving more than a year of therapy
  - Total of 1254 cumulative doses (across 68 patients)

- **NO SIGNIFICANT LAB ABNORMALITIES** found in liver function, kidney function, thyroid function and platelet counts

- **NO EVIDENCE OF METABOLIC** or **HEMATOLOGICAL** toxicities

- **NO EVIDENCE OF GLOBAL IMMUNOSUPPRESSION**

- **NOVEL OLIGONUCLEOTIDE** drug class

In Total, **68 Patients** (CTCL, ATLL, DLBCL, and CLL from Ph1 and CTCL SOLAR) **Have Been Exposed to Cobomarsen** for up to **2.25 Years**

(Data Cutoff July 23, 2019)
Cobomarsen Observed to Reverse the Disease Gene Signature and Reduce Malignant Cell Clonality in Mycosis Fungoides Patients
Phase I CTCL  Thirty-three of Thirty-six Patients (92%) Treated Systemically with Cobomarsen Have Shown mSWAT Score Improvement

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<thead>
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<th>1A</th>
<th>2A</th>
<th>1B</th>
<th>2B</th>
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<td>10</td>
<td>27</td>
<td>32</td>
<td>9</td>
<td>33</td>
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</table>

Best Change in mSWAT Score (%)

-30
-20
-10
0
10
20
30

300 mg
600 mg
900 mg

* treatment ongoing
Phase I CTCL Cobomarsen Substantially Reduces Lesion Severity Following IV Administration
Cobomarsen Clinical Development: Phase I Results in ATLL
Cobomarsen Clinical Experience in ATLL

PART F:
Open-label, dose-ranging, multiple dose trial of cobomarsen in ATLL

OBJECTIVES
+ PRIMARY: Safety and tolerability
+ SECONDARY: PK
+ EXPLORATORY: PD, histopathology, lesion morphology

OVERALL TRIAL DESIGN
+ INCLUSION CRITERIA
  o Acute, lymphomatous, chronic, and smouldering subtypes
  o Relapsing or in PR/CR after prior therapy
  o Progressed on, or refractory to, at least one prior therapy

+ DOSING AND DURATION
  o SQ or IV
  o 3 loading doses the first week
  o Weekly dosing thereafter
  o Discontinue if subject becomes intolerant, develops clinically significant side effects, or progresses
Subject 101-008 Acute ATLL in Partial Remission

+ Diagnosed Dec 2016 with acute ATLL
+ Relapsed after treatment with zidovudine, interferon α-2b, lenalidomide and EPOCH chemotherapy
+ Cobomarsen monotherapy initiated Nov 2017
  o Stable abnormal ATL cells for > 16 mo
  o Normalization of residual enlarged lymph node after chemotherapy (1.0 to 0.8 cm), which remained normal as of last imaging Nov 2018
  o Reduction in biomarkers of cell activation and proliferation (Ki67, CD69 and HLA-DR)
+ Subject remains on treatment and has completed Cycle 18, missing only 1 dose due to sciatic pain

(Data Cutoff March 15, 2019)
Subject 101-008 Cobomarsen Appears to Decrease Activation and Proliferation Status of Circulating Tumor Cells in ATLL

FLOW CYTOMETRIC ASSESSMENT of ACTIVATION and PROLIFERATION Biomarkers’ Expression in Circulating ATLL Cells

(Data Cutoff March 15, 2019)
Cobomarsen Appears to Decrease the Activation and Proliferation of Circulating Tumor Cells

ACTIVATION MARKERS ATL TUMOR CELLS

PROLIFERATION INDEX ATL TUMOR CELLS

(Data Cutoff March 15, 2019)
SOLAR: A Phase II Clinical Trial of Cobomarsen in Mycosis Fungoides
A Randomized, Open-Label, Parallel-group, Active Comparator, Global Trial in Patients with Stage IB-III Mycosis Fungoides (MF)

**Primary Endpoint**
- Overall Response Rate of Four Months (ORR4) using Global Response Criteria

**Secondary Endpoints**
- Progression-free Survival
- Patient Reported Outcomes

**Diagram:**
- OPEN LABEL
  - RANDOMIZE TO:
  - COBOMARSEN IV INFUSION VS. VORINOSTAT
- RANDOMIZE
- COBOMARSEN (282 MG IV INFUSION) N=63 SUBJECTS
- FOLLOW UNTIL PROGRESSION
- VORINOSTAT N=63 SUBJECTS
- FOLLOW UNTIL PROGRESSION
- OPEN LABEL EXTENSION PRISM
SOLAR Study Participating Countries

126 Subjects at ~60 Sites
Across 11 Countries

+ Austria
+ Australia
+ Belgium
+ Canada
+ France
+ Germany
+ Italy
+ Netherlands
+ Spain
+ United Kingdom
+ United States
MRG-110, a miR-92a Inhibitor for Potential Treatment of Cardiovascular Disease and Wound Healing
Overexpression of miR-92a inhibits sprouting, network formation, and angiogenesis in multiple models

miR-92a mimics and inhibitors reciprocally regulate multiple angiogenesis-associated genes in endothelial cells

**Spheroid model**

Control

+ miR-92a

**Network formation**

**Matrigel plug model**

![Images showing the effects of miR-92a on network formation and Matrigel plug model]
Translatability of MRG-110 in Wound Healing: MRG-110 Observed to Increase Angiogenesis in Mice to Men

<table>
<thead>
<tr>
<th>Species</th>
<th>Data</th>
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<tr>
<td>Rodent</td>
<td>▪ Accelerated wound healing in db/db mice</td>
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<tr>
<td></td>
<td>▪ Increased CD31+ vessel formation in db/db mice</td>
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<tr>
<td>Porcine</td>
<td>▪ Improved perfusion and rate of wound closure in farm pigs</td>
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<td></td>
<td>▪ Dose-dependent decrease in contracture of healed wounds</td>
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<tr>
<td></td>
<td>▪ Accelerated wound healing in burn model</td>
</tr>
<tr>
<td>Human</td>
<td>▪ Increased angiogenesis and perfusion in treated subjects</td>
</tr>
<tr>
<td></td>
<td>▪ Decreased fibroblast/myofibroblast α-SMA expression at Day 29</td>
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</table>
MRG-110 Appears to Accelerate Wound Healing and Angiogenesis in db/db Mice

**Wound Healing**

Granulation tissue area (mm²)

<table>
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<tr>
<th></th>
<th>PBS</th>
<th>VEGF</th>
<th>PDGF</th>
<th>10 nmol MRG-110</th>
<th>30 nmol MRG-110</th>
<th>100 nmol MRG-110</th>
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**Angiogenesis**

CD31 immunostaining

PBS

MRG-110

CD31+ counts

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<tr>
<th></th>
<th>PBS</th>
<th>PDGF</th>
<th>10 nmol MRG-110</th>
<th>100 nmol MRG-110</th>
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† = p<0.05, Kruskal-Wallis

‡‡ = p<0.01, Kruskal-Wallis

†††† = p<0.0001, Kruskal-Wallis

Gallant-Behm et. al., Wound Repair Regen., 2018
MRG-110 Appears to Improve Vascularization and Decreases Contracture in Healthy Farm Pigs
Assessed on Day 49

Gallant-Behm et. al.
Wound Repair Regen
2018
MRG-110 Clinical Development Phase I Results
**TRIAL 1**
Single IV administration (0.01-1.5 mg/kg)

Objectives
+ PRIMARY Safety and tolerability
+ SECONDARY PK

**TRIAL 2**
Single or multiple (3 weekly) ID administrations around an excisional wound (0.25-2.25 mg/wound)

Objectives
+ PRIMARY Safety and tolerability
+ SECONDARY PK
+ EXPLORATORY wound healing, wound perfusion, PD, histopathology
MRG-110 Shows Favorable Tolerability

- **MRG-110 HAS BEEN GENERALLY SAFE** and well tolerated
  - IV administration up to 1.5 mg/kg
  - ID administration up to 2.25 mg/wound

- **NO INJECTION SITE REACTIONS**

- **NO SIGNIFICANT LAB ABNORMALITIES** found in liver function, kidney function, thyroid function and platelet counts attributable to MRG-110
  - One Placebo subject had a Grade 4 asymptomatic elevation in CK that was transient and did not require treatment

- **NO EVIDENCE OF DISTAL ANGIgenesis**

- **NOVEL OLIGONUCLEOTIDE** drug class

**In Total, 65 Subjects Have Been Exposed to MRG-110 for up to 3 Weeks**
MRG-110 Observed to Increase Wound Angiogenesis and Tissue Perfusion

Peri-wound perfusion intensity

Angiogenesis

ITGA5 expression (miR-92a target)
MRG-110 Observed to Decrease α-Smooth Muscle Actin Expression and Prevent Excessive Granulation Tissue Formation

α-SMA expression reduced with MRG-110 treatment

Granulation tissue volume reduced early after treatment

No appreciable difference 1 month after injury – Delayed kinetics of granulation tissue formation was not detrimental to achieving full wound closure or appropriate collagen maturation
Potential Clinical Indications

Cardiovascular indications that may benefit from angiogenic therapy
- Acute myocardial infarction
- Chronic heart failure/angina
- Vascular injury – inhibition of neointimal formation after balloon angiography
- Peripheral artery disease

Wound healing, where ischemia is a major contributing factor to slow/ineffective process
- Burn wounds
- Grafts
- Diabetic foot ulcers
- Pressure ulcers
- Acute wounds in the elderly (e.g. pretibial lacerations)
- Graft donor sites
- Complicated laparotomy closure