microRNA Therapeutics Heading Towards the Clinic

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The focus of this GEN Market & Tech Analysis Report is to frame the translation of microRNAs from research towards therapeutics.

Currently, there are two segments of the microRNA research marketplace that are translating towards the clinic:

- miR Signatures as Biomarkers with Utility in Diagnostics Development
- Modulating miRs Therapeutically as a Means to Modulate Disease

The challenge in the translation of microRNAs from research towards therapeutic utilization is that a given microRNA is known to modulate the expression of several genetic elements. Therefore, the up/down-regulation of a given microRNA is expected to broadly affect several genes in vivo.

In spite of this challenge, there is a movement of specific microRNA species towards the clinic and in this report we analyze this landscape.
The Growth of Content in the miR-Base Database has been a Driver for the identification and Validation of microRNA Signatures Associated with Disease

- Driver for: microRNA Signatures as Biomarkers → Associations have been discovered
- Driver for: microRNAs as Therapeutics to modulate targets in vivo → Modulations with therapeutic value have been discovered
microRNAs of Therapeutic Significance Currently

- The following microRNAs are being targeted for therapeutic purposes currently:
  - **miR-21**
    - Found to be up-regulated in many solid tumors
    - Being addressed as a miR to down-regulate for various solid tumors
  - **miR-34**
    - Found to have tumor suppressor properties
    - Some have referred to it as a “master tumor suppressor”
    - Ongoing phase I clinical trial focuses on miR-34 modulation in liver cancer
  - **miR-122**
    - Imperative for Hepatitis C Virus (HCV) infection
    - Down-regulation of miR-122 blocks productive HCV infection and subsequent Hepatocellular Carcinoma (HCC)
  - **miR-33**
    - Involved in cholesterol biosynthesis
    - Preclinical in vivo data suggests
miR-21

• Extensive interest in miR-21 centered around its role in “maintaining” solid tumors by way of blocking the programmed cell death pathway in vivo

• Various classes of solid tumors have miR-21 associated with them as shown in the following slides—publications on associations of specific microRNAs with different cancer classes [miR-21 illustrated with arrow]

• Regulus Therapeutics has programs modulating miR-21 in HCC and Renal Fibrosis
miR-34

- miR-34 is down-regulated in many cancers
  - Solid tumors
  - Hematological (liquid) tumors
- Therefore it is believed to be a tumor suppressor miR in vivo—some reports have referred to it as a “master tumor suppressor” given that its associated with many different cancer classes
- Mirna Therapeutics, Inc. is focused on restoring loss-of-function of miR-34 via a mimic delivered in vivo using nanoparticle-based delivery approach
  - Restoration of loss-of-function of this tumor suppressor
  - Modulate gene functionality of cancer genes addressed by this miR
- The company has begun a phase I clinical trial focusing on miR-34-based therapy in unresectable primary liver cancer or metastatic cancer with liver involvement
miR-122

- This microRNA has received by far the most attention vis-à-vis its therapeutic potential
- The source of the interest is driven by the fact that Hepatitis C Virus (HCV) requires in its life cycle cell-derived miR-122
  - Cell lines with low levels of endogenous miR-122 are refractory to HCV infection
  - Up-regulation of miR-122 via transfection makes these cell lines permissive to HCV infection
  - Furthermore, HCV infection is a prelude to HCC and therefore a strategy of miR-122 down-regulation via a therapeutic strategy is devised to therapeutically-target HCV infection and down-stream HCC event
miR-122 Therapeutic Targeting

• **Regulus Therapeutics**
  – miR-122 targeting for HCV

• **Santaris Pharma A/S**
  – Phase 2a trial of Miravirsen (blocks miR-122 via LNA-antisense molecule) completed
  – Enrollment completed for combination therapy with other anti-HCV anti-virals

First miR-Modulator to Move into Clinical Trials, albeit for an Infectious Disease
InteRNA Technologies B.V. has been focusing on several oncology programs and has disclosed that miR-3157 is their target for the B-raf/melanoma space. Their lead compound is a mimic of miR-3157.
**Beyond Cancer to Cardiovascular Disease**

- Although the majority of the interest and drive for miRs as biomarkers has been in the oncology space, this is not exclusively the case as miRs associated with cardiovascular disease are translating from research towards the clinic.
- **miRagen Therapeutics** is focused on the therapeutic targeting of miRs associated with cardiovascular disease:
  - All programs in preclinical stages
  - Disease classes addressed are presented in the table below

<table>
<thead>
<tr>
<th>miR Targeted</th>
<th>Disease Class Addressed</th>
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<tbody>
<tr>
<td>miR-208</td>
<td>Heart Failure</td>
</tr>
<tr>
<td>miR-15/-195</td>
<td>Post-Myocardial Infarction</td>
</tr>
<tr>
<td>miR-145</td>
<td>Vascular Disease</td>
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<tr>
<td>miR-29</td>
<td>Fibrosis</td>
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<tr>
<td>miR-92</td>
<td>Peripheral Artery Disease</td>
</tr>
<tr>
<td>miR-378</td>
<td>Cardiometabolic Disease</td>
</tr>
<tr>
<td>miR-206</td>
<td>Neuromuscular Disease</td>
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In Summary

• Therapeutic Targeting of microRNAs is Moving Forward Towards the Clinic

• Even Though Majority of Efforts are in Biomarker/Diagnostics Development using miR Signatures, Therapeutic Modulation of miRs in vivo Remains an Attractive Clinic Space and there are now reports of specific miRs targeted by therapeutics in defined clinical [disease] spaces—most notably cancer

• In summary, we reaffirm our position that as the microRNA space becomes populated with associations with disease, these associations can be leveraged in biomarker-based assays for LDTs/Dx, but also for Rx development