Harnessing the power of novel RNA-targeted oligonucleotide therapeutics

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Building an RNA-directed oligonucleotide therapeutics platform company

- Founded on unique insights into RNA binding protein biology
  - First-in-class molecular therapeutic with novel mechanism
  - Drugging the undruggable (HuR interactions)
- Scientific platform for broad target expansion
  - Technology platform applicable to multiple high impact indications
    (e.g., Bcl-2, KLF5, PDL-1, IFNγ, IL-1β, IL-12A, IL-22, IL-23A, TNFα, LIF, VEGF-A)
- Lead oligonucleotide compound partially de-risked (MS, psoriasis models, favorable tox)
  - Autoimmune uveitis is current clinical (disease) target
Our team has extensive expertise in translational research, neuroinflammation, microRNA biology, pre-clinical/clinical drug development and business development.
Destabilizing miRNAs (conventional)

Novel class of E-miRNAs

TSB oligos inhibit E-miRNAs

mRNA decay and/or translation block

HuR-miRyyy cooperative mRNA stabilization and/or effective translation

TSB interference with E-miRNA-HuR interaction resulting in mRNA decay

Blocking the cooperative, translation-promoting HuR-miRNA-3’UTR interaction with sequence-specific modified oligonucleotides can greatly and selectively dampen gene expression.
# Competitive advantage of the TSB approach

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<th>Parameters</th>
<th>TSB</th>
<th>Anti-miR</th>
<th>siRNA</th>
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<tbody>
<tr>
<td>Specificity</td>
<td></td>
<td>✗</td>
<td>✗</td>
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<tr>
<td>Efficacy</td>
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<td>No off-target effects</td>
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**Advantage TSB vs anti-miR**

TSBs inhibit 1 miRNA binding to 1 mRNA target, whereas anti-miRs inhibit binding of 1 miRNA to all targets.

- Lead TSB targets IL-17A mRNA
- Platform development for other mRNAs
IL-17A-miRyyyy TSB specifically destabilizes human IL-17 mRNA

- IL-17A and GM-CSF mRNA decay in human primary T cells
- T cells transfected with 25 nM TSB or CNTA (control) oligo after transcriptional arrest (time 0)
- miRyyyy-IL17A TSB prevents HuR-dependent protection of IL-17A but not GM-CSF mRNA
IL-17A TSB modulates rat Experimental Autoimmune Uveitis (EAU)

**Previous in vivo studies with IL-17A TSB:**
1) Proof of concept IL-17 inhibition studies in mouse and rat
2) Prevention of progressive EAE and skin plaque formation (murine multiple sclerosis and psoriasis models)

**IL-17A TSB delays onset of Autoimmune Uveitis (IRBP model)**

![Graph showing EAU score over time with different treatment groups](chart.png)
For a targeted biologic/small molecule with great specificity and better efficacy, the market could be significantly higher (up to $10 billion)
• **Efficacy study**: Proof of concept in rat model of autoimmune uveitis

• **PK**: Specific Assay development for detection of TSB oligos; detection of TSB in plasma, CNS homogenates, spleen cells, peripheral blood cells in multidose studies

• **Single and multidose toxicology studies show no deleterious effects on**:
  - Metabolism (body weight and glucose)
  - Peripheral blood cell counts
  - Hepatic and renal function
  - Organ pathology (necropsy)

• **Incorporation and establishment of leadership group**

• **Patent submitted on lead compound (5/19), additional provisional patent for numerous additional cytokine, chemokine, oncogene and growth factor RNA-directed TSBs submitted (11/19)**
We are seeking:

• Funds to optimize timing, dosage, routes of administration and formulation in the rat uveitis model (CRO Powered Research, $100K)

• Funds for PK, tolerability and tox studies in larger (rabbit) model (Powered Research, $100K)

• Funds to further develop platform and define additional enhancing miR targets, with initial IL-23 and Bcl-2 TSB generation for use in tumor and autoimmunity models ($100K)

Our goals include:

• Further TargetSite Therapeutics development as a company based on a first-in-class RNA-targeted oligo drug approach

• TargetSite Therapeutics IP for lead compound and new TSB-RNA combinations

• Establishing a new generation of highly specific, well-tolerated drugs for a wide range of diseases, including autoimmunity and cancer
Autoimmune Uveitis Therapeutic Development Plan
[including 2020 Blavatnik Support]

Goal 1: Establish efficacy and tox
- Bioanalytical methods, biomarker assay
- Efficacy in 2nd species

Goal 2: Complete IND-enabling Toxicology Program
- PK, tolerability, tox studies in rabbits, formulation, and route of administration
- Formulation development and 1-month stability
- Mfg dev
- Process dev/GMP mfg

Goal 3: Complete DP Mfg & 1-Month Stability Testing
- GMP DP Mfg
- Pre-IND meeting

Goal 4: IND Submission
- Pre-pre-IND Meeting

Budget reflects development costs only and excludes personnel, G&A

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