Target Site Blocker (TSB) of the IL-17A-miR466l-3p Interaction Prevents Progressive and Relapsing Remitting EAE

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Target Site Blocker (TSB) of the IL-17A-miR4661-3p Interaction Prevents Progressive and Relapsing Remitting EAE

• **What we have:** a microRNA “target site blocking” oligonucleotide that interferes with pro-inflammatory cytokine IL-17 production

• **Where it stands:** (1) extensive *in vitro* data supporting its ability to block IL-17 production in immune cells; (2) dramatic *in vivo* data displaying prevention of EAE (mouse model of multiple sclerosis)

• **Development targets:** (1) *in vivo* pharmacokinetic (and toxicology) data with multiple delivery sites; (2) mechanistic readout analysis in EAE prophylaxis; (3) application to other disease models

• **Reason for these targets:** requirements for *in vivo* dosing, safety and widespread applicability (market)
The non-conventional role of miR466l-3p in mRNA stabilization

Conventional function of miRNA

Enhancing role of miR466l-3p

mRNA

miRxxx

mRNA decay or translation block

mRNA

miR466l-3p

IL-17A mRNA stabilization and/or effective translation

Target site
Target Site Blocker (TSB) of the IL-17A-miR466l-3p Interaction Prevents Progressive and Relapsing Remitting EAE

- Concept: Enhancing miRNAs augment gene expression
- Concept: Beyond the seed sequence, there is specificity to a miR-mRNA 3’UTR interaction
- Concept: A target site blocking oligonucleotide (TSB) can achieve that specificity and reduce individual gene expression, without off-target effects/toxicity
- **Concept: The TSB market has not been explored**
- Small (18 nucleotide, ~7 kDa) oligos gain greater access to protected sites (e.g., the CNS, across the BBB) than antibodies (~150 kDa)
- Context: miR466l-3p promotes IL-17A gene expression
- Context: IL-17A plays a critical pathogenic role in inflammatory diseases such as multiple sclerosis (MS), psoriasis, autoimmune uveitis, asthma, IBD and even atherosclerosis
- Context: A specific inflammation-dampening oligonucleotide can treat and/or diminish the burden of these inflammatory diseases
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
miR466l-3p/IL-17A TSB in a progressive EAE mouse model (2D2 Transgenic)

Days after immunization

TSB/CNTA (5mg/kg) 2x (10mg/kg)

TSB/CNTA

Days after immunization

EAE Clinical Score

- CNTA-n = 3
- TSB-n = 4
miR466l-3p/IL-17A TSB in relapsing remitting EAE mouse model

- TSB (5mg/kg; n=3)
- CNTA (5mg/kg, n=4)

Days after immunization

TSB/CNTA q3d
Phase I: $83,000
- EAE model development
- TSB quantitation (LC-MS/MS or alternative)
- PK studies (IP, IV, SC)

Phase II: $127,000
- Efficacy studies (multiple delivery routes [IP, IV, SC, ICV] and models)
  - clinical scores
  - brain, spinal cord, spleen IL-17A

Phase III: $84,000
- Efficacy studies at defined, appropriate ED
  - clinical scores
  - spinal cord cytokines
  - FACS of inflammatory cell infiltrates
  - histopathology
- Target tissue PK after the last dose

Discovery Toxicology Study: $13,000
- 10 day peripheral blood counts, clinical chemistries, body weights
  (single highest dose)
Additional IL-17A-dependent Mouse Models (and applications)

- Collagen-induced arthritis (rheumatoid arthritis)
- Experimental autoimmune uveitis (autoimmune uveitis)
- Imiquimod-induced psoriasis (psoriasis) [topical delivery]
- IBD
- Atherosclerosis
- Asthma