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

The Team

- **Jeffrey R. Bender, MD**

Robert I. Levy Professor Cardiology
Professor of Medicine and Immunobiology
Director, Yale Cardiovascular Research Center

Contact: 203-737-2223 (w)
203-980-9585 (c)
jeffrey.bender@yale.edu

- **Vinod Ramgolam, Ph.D.**

Associate Research Scientist, Internal Medicine

- Timur Yarovinsky, Ph.D

Associate Research Scientist, Internal Medicine

- Nancy Ruddle, Ph.D.

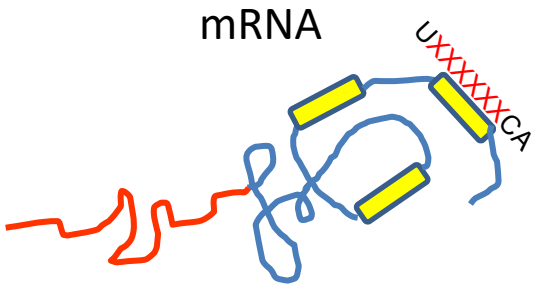
Professor Emeritus and Senior Research Scientist, Epidemiology (Microbial Diseases)

Target Site Blocker (TSB) of the IL-17A-miR466l-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 stablization

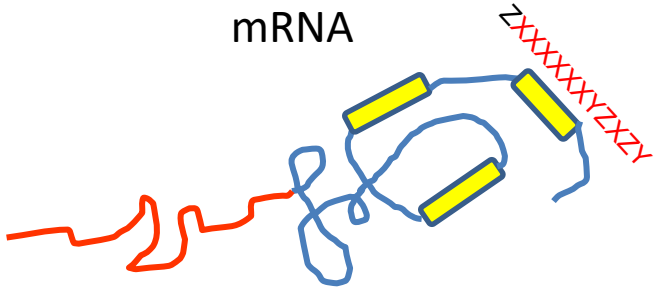
Conventional function of miRNA



miRxxx

mRNA decay or translation block

Enhancing role of miR466l-3p



miR466l-3p

IL-17A mRNA stabilization and/or effective translation

Target site

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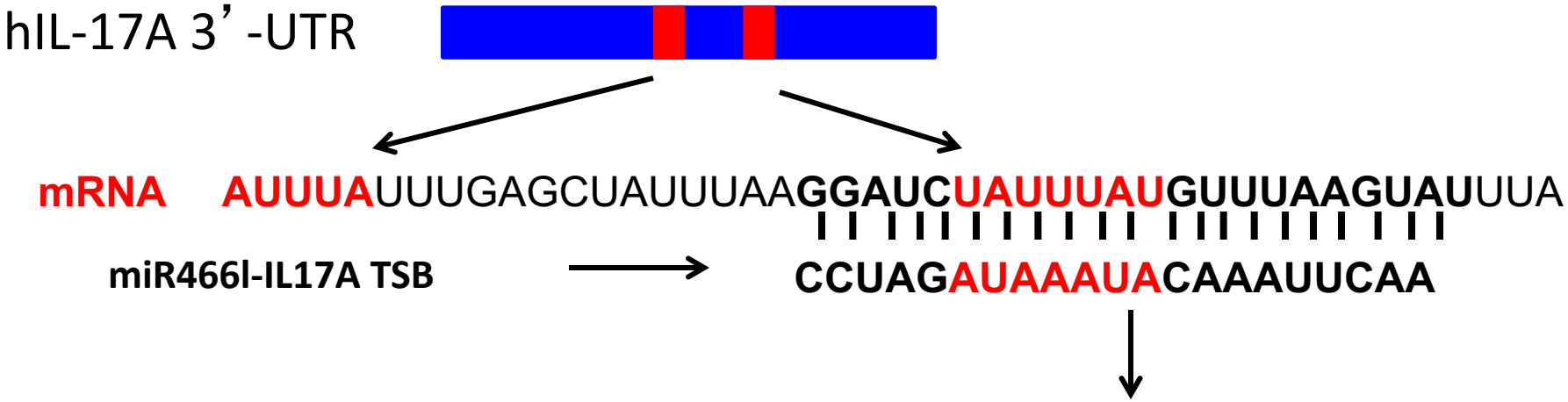
- Concept: Enhancing miRNAs augment gene expression
- Concept: Beyond the seed sequence, there is specificity to a miR-mRNA 3'UTR interaction
- Concept: A target site blocking oligonucleotide (TSB) can achieve that specificity and reduce individual gene expression, without off-target effects/toxicity
- **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

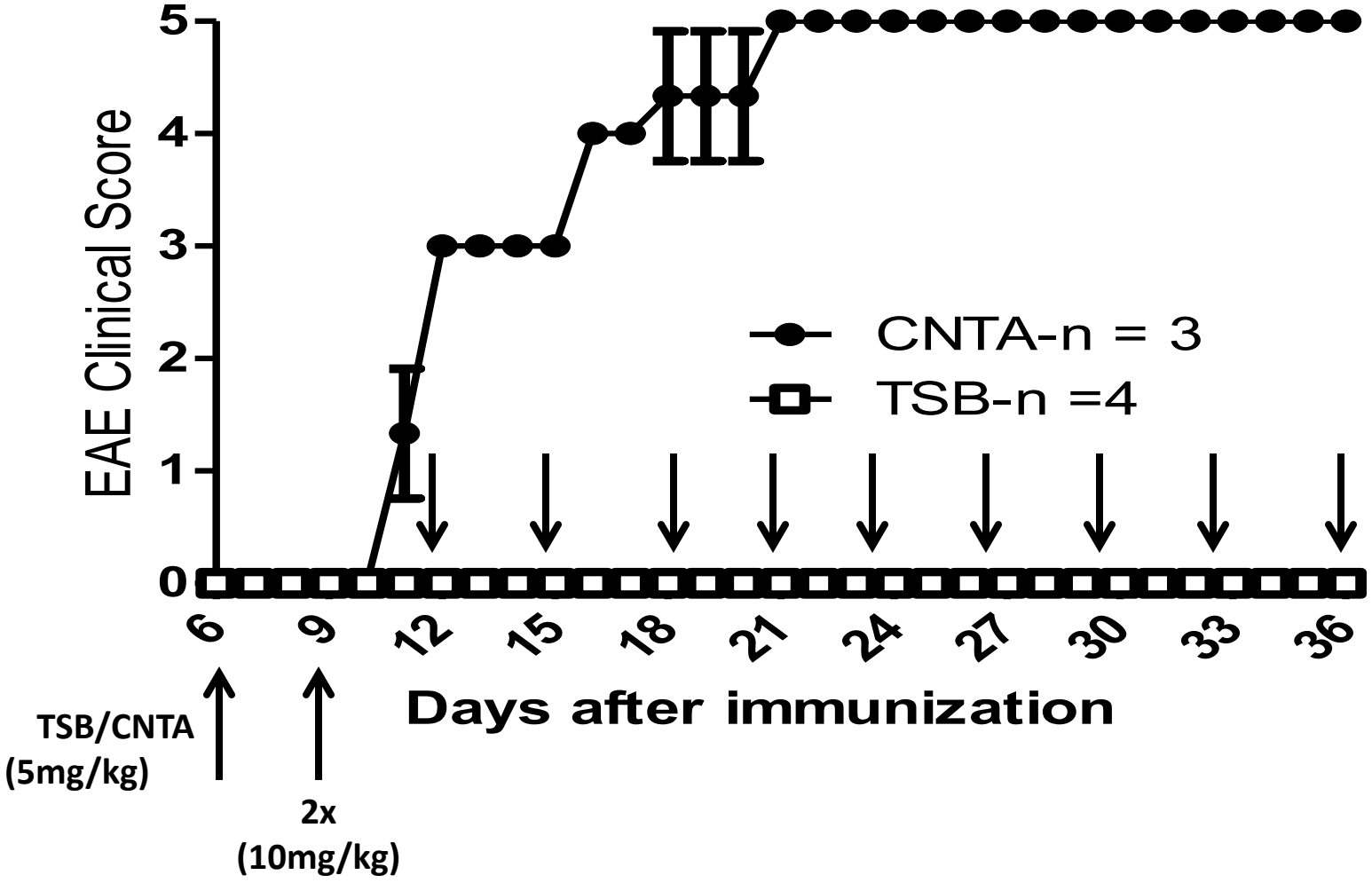
mir466l-IL17A Target site blockers (TSB)



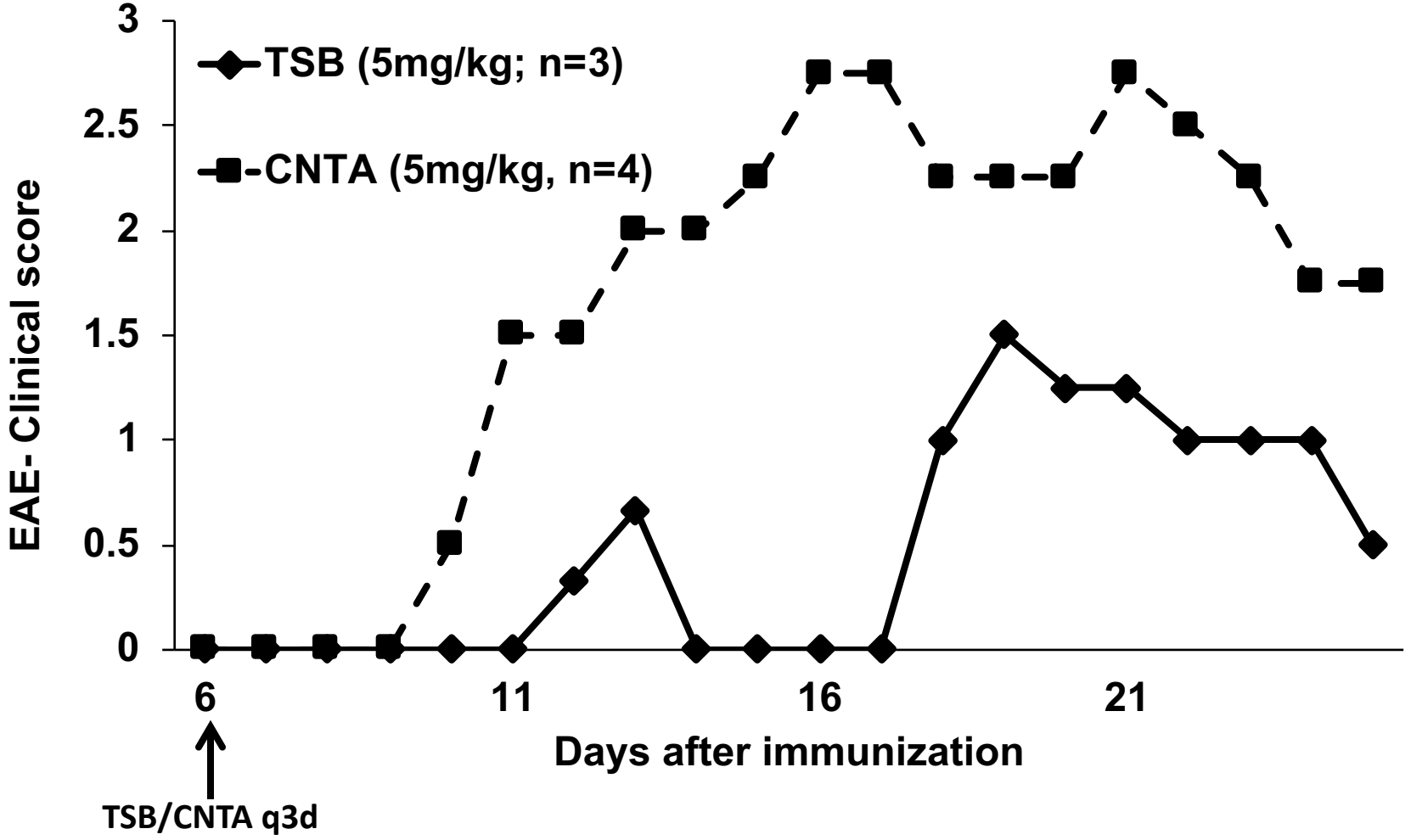
Advantage TSB vs anti-miR

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)



miR466l-3p/IL-17A TSB in relapsing remitting EAE mouse model



GD Genesis Drug Discovery & Development Proposal

- 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