**UNIQUE MECHANISM OF ACTION**

**OF HIGHLY POTENT, ORALLY BIOAVAILABLE**

**AND BRAIN PENETRANT SMALL MOLECULE TREM2 AGONISTS**

**FOR THE POTENTIAL TREATMENT OF ALZHEIMER’S DISEASE**

Matthew D. Figley¹, Kelley C. Larson¹, Abigail Renoux¹, Daria Tchessalova¹, Frederick W. Gergits¹, Bhaumik Pandya¹, Jonathan Houze¹, Evan A. Thackaberry¹, Marco Colonna², David Gray¹, Christian Mirescu¹, Borislav Dejanović¹

Vigil Neuroscience, Inc., Watertown, MA, USA¹; Washington University School of Medicine in St. Louis, St. Louis, MO, USA²

---

**INTRODUCTION**

- TREM2 is a lipid-sensing receptor upregulated by microglia in neuropathological microenvironments
- Loss-of-function TREM2 variants increase the risk for Alzheimer’s disease (AD)
- Upon ligand engagement, TREM2’s adaptor protein DAP12 recruits the signaling kinase SYK
- Small molecule TREM2 agonists represent a significant advancement for patients as they provide broader dosing options, superior brain penetration and potentially orthogonal mechanisms of action versus monoclonal antibodies

---

**RESULTS**

**Figure 1. VGL-SM is a nanomolar TREM2 agonist**

- Cells were treated for 45 minutes (Fig. 1A) or 7.5 minutes (Fig. 1B).
- Mean of 28 (TREM2, Fig. 1A), 3 (TREM1, Fig. 1A), or 6 (Fig. 1B) independent experiments is shown +/- SEM

**VGL-SM potentiates signaling from sulfatides (TREM2 lipid agonist)**

- 25 min with VGL-SM + 20 min sulfatides
- Mean of 4 independent experiments is shown +/- SEM

- 7.5 min with VGL-SM + 5 min sulfatides
- Mean of 3 independent experiments is shown +/- SEM

**Figure 3. VGL-SM treatment causes TREM2 receptor internalization and reduced sTREM2 shedding in iMGLs**

- Cultured iMGLs were treated for 21 h.
- Cells were transfected to 0.6 and stained with anti-TREM2 antibody and run on an Attune Flow Cytometer (ThermoFisher) (Fig. 3A)
- sTREM2 was measured from media of cultured iMGLs by ELISA (Fig. 3B)
- Mean of 2 independent experiments is shown +/- STD

---

**CONCLUSIONS**

Vigil’s TREM2 small molecule agonists:

- Highly potent and potentiate signaling from lipid ligands in vitro
- Cause TREM2 receptor internalization and reduce sTREM2 shedding
- Induce unique TREM2-DAP12 complex formation compared to lipid agonists
- Engage TREM2 in mouse and non-human primate brains

---

**CONTACT**

- Matthew Figley, Senior Scientist – mfigley@vigilneuro.com
- Borislav Dejanović, Director of Translational Sciences & External Innovation – bdejanovic@vigilneuro.com
- Corporate Communications & Investor Relations – investors@vigilneuro.com