Unique MoA of Highly Potent, Orally Bioavailable and Brain Penetrant Small Molecule TREM2 Agonists for the Potential Treatment of Alzheimer's Disease

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Vigil Neuroscience is a clinical-stage microglia-focused therapeutics company

Our purpose: to treat rare and common neurodegenerative diseases by restoring the vigilance of microglia, the brain’s sentinel immune cells

We are utilizing the tools of modern neuroscience drug development across multiple therapeutic modalities as we seek to deliver precision-based therapies to improve the lives of patients and their families.
### Strength of human TREM2 genetics
- Multiple genetic variants enriched in AD
- Strong autosomal dominant impact on AD risk
- Highly replicated in meta datasets and broad populations

### TREM2 is a critical regulator of microglia functional
- Expression is essential for neuroprotective microglia state
- Regulation of microglia survival, metabolism, and lipid metabolism
- TREM2 plays an important role in phagocytosis

### TREM2 is key microglia receptor hub
- Receptor ligands implicated in disease – ApoE, ApoJ, phospholipids
- Signaling partner DAP12 is causal for rare microgliopathy
- In network with additional AD-risk genes – Cd33, Ms4a, Ship1
Vigil small molecule agonists specifically activate human TREM2

pSYK activation in stable HEK293 cells and human iPSC-induced microglia (iMGLs)

- **pSYK activation in stable HEK293 cells**
- **pSYK activation in iMGLs**

**SM TREM2 agonist (nM)**

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![Graph showing pSYK activation in stable HEK293 cells and iMGLs](image)
TREM2 SM agonists potentiate signaling response to native ligands in iMGLs

TREM2 SM potentiate signaling response to sulfatide

Sulfatide potentiate signaling response to SM

> 6x increase in sulfatide-induced activation

> 4x increase in SM-induced activation

Improved SM potency (~4x) in presence of sulfatide
TREM2 SM agonists retain activity in rare AD risk variants

SM enable precision medicine

pSYK activation in transiently transfected HEK293 cells

<table>
<thead>
<tr>
<th>TREM2 variant</th>
<th>Nanomolar potency</th>
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<tbody>
<tr>
<td>Common Variant</td>
<td>✓</td>
</tr>
<tr>
<td>R47H</td>
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</tr>
<tr>
<td>R62H</td>
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<tr>
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<tr>
<td>L211P</td>
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Evidence of SM MOA as TREM2 molecular glues

Vigil SM induce TREM2 clustering and enhance the interaction of TREM2-DAP12 complexes

TREM2 immunoprecipitation in HEK cells

Non-denatured native PAGE in iMGLs

Vigil SM coordinate signaling via molecular glue MOA
Vigil SM treatment results in TREM2 internalization and reduced sTREM2 shedding in iMGLs

**sTREM2 levels in iMGLs**

**Surface TREM2 target engagement**

**Surface TREM2+ iMGLs**
SM agonist-induced transcriptome changes recapitulate TREM2 mAb-induced alterations in 5xFAD AD mouse models

Nanostring analysis indicates microglial activation by SM

Transcriptome changes in hippocampus from 5xFAD\(^{CV}\) mice

Pathway scoring

IP10 protein levels in cortex from TREM2\(^{CV}\) mice

Innate Immunity
Inflammatory Signaling
Microglia function
Cytokine Sig.
Neuronal function
Oral dosing in Cynos demonstrates CNS TREM2 engagement

Path to translational biomarker

Small Molecule CSF Exposure

Reduction in NHP CSF sTREM2 levels

CSF Drug Levels (nM)

PK timecourse (h)

sTREM2 (%Baseline)

Timecourse post-dosing (h)

Low Dose, po
High Dose, po
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