UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): September 13, 2023

VIGIL NEUROSCIENCE, INC.
(Exact name of registrant as specified in its charter)

Delaware	**001-41200**	**85-1880494**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

Vigil Neuroscience, Inc.
100 Forge Road, Suite 700
Watertown, Massachusetts 02472
(Address of principal executive offices, including zip code)

(857) 254-4445
(Registrant's telephone number, including area code)

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trade Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	VIGL	The Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On September 13, 2023, Vigil Neuroscience, Inc. (the "Company") held a webcast highlighting its small molecule TREM2 agonist program for Alzheimer's disease. A copy of the presentation that accompanied the webcast is furnished as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

The information set forth under Item 7.01 and in Exhibit 99.1 attached hereto is intended to be furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933 or the Exchange Act, except as expressly set forth by specific reference in such filing.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Slide Presentation dated September 13, 2023 (Furnished herewith)
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Vigil Neuroscience, Inc.

Date: September 13, 2023

By: /s/ Ivana Magovčević-Liebisch
Ivana Magovčević-Liebisch
President and Chief Executive Officer

Exhibit 99.1


Vigil Neuroscience
Small Molecule KOL Event
September 13, 2023
(vigil)™
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Today's Agenda

7:30 – 7:35 AM (5 min)
Opening Remarks & Corporate Overview
Ivana Magovčević-Liebisch, PhD, JD
Chief Executive Officer, Vigil Neuroscience, Inc.

7:35 – 7:50 AM (15 min)
TREM2 Concept in Alzheimer's Disease
Marco Colonna, MD
Robert Rock Belliveau Professor of Pathology & Immunology
Washington University School of Medicine, St. Louis, MO
Vigil Neuroscience, Inc. Scientific Advisory Chairman

7:50 – 8:30 AM (40 min)
Overview of Vigil's Small Molecule TREM2 Agonist Program
David Gray, PhD
Chief Science Officer, Vigil Neuroscience, Inc.

Christian Mirescu, PhD
Vice President, Head of Neuroimmunology, Vigil Neuroscience, Inc.

8:30 – 8:45 AM (15 min)
Alzheimer's Disease Treatment & Unmet Need
Samuel E. Gandy, PhD, MD
Mount Sinai Professor of Alzheimer's Disease Research, Professor of Neurology & Psychiatry
Associate Director of Mount Sinai Alzheimer's Disease Research Center, NYC
Past Chairman, National Medical & Scientific Advisory Council of the Alzheimer's Association

8:45 - 8:50 AM (5 min)
Clinical Development of VG-3297, Vigil's Small Molecule TREM2 Agonist
David Gray, PhD
Chief Science Officer, Vigil Neuroscience, Inc.

8:50 – 9:00 AM (10 min)
Closing Remarks and Q&A Session

Reminders

- Webcast scheduled to end at 9:00am U.S. ET
- Presentation is available in investors section under Events & Presentations at www.vigilneuro.com
- Moderated Q&A session following prepared remarks
- To submit a written question, fill out form on webcast home page
- Webcast replay available later today on Vigil website under Events & Presentations

Forward-Looking Statements

This presentation contains "forward-looking statements," which are made pursuant to the safe harbor provisions of the federal securities laws, including the Private Securities Litigation Reform Act of 1995. Any statements that are not statements of historical fact may be deemed to be forward-looking statements. Such statements may contain words such as "may," "might," "will," "could," "should," "would," "expect," "intend," "plan," "prepare," "look," "seek," "anticipate," "believe," "estimate," "predict," "potential," "possible," "continue," "ongoing" or the negative of these terms, or other comparable words.

These forward-looking statements include, among others, statements relating to: the Company's strategy, business plans, focus and value of future milestones; the progress and timing of the preclinical development, clinical development and regulatory development of Vigil's programs, including VGL-101 and VG-3927 and the availability of data from our clinical trials involving our product candidates and expected timing of first dosing for VG-3927; our ability to discover and build a platform of precision medicine based therapies targeting the microglia; and the patient burden of Alzheimer's disease and potential therapeutic benefit of our product candidates. These forward-looking statements, which are only predictions, involve risks and uncertainties, many of which are beyond our control and are based on our current beliefs, expectations and assumptions regarding our business. As such, you should not place undue reliance on any forward-looking statements because such risks and uncertainties could cause actual results, performance or achievement to differ materially and adversely from those anticipated or implied in the forward-looking statements. Factors that could cause actual results to differ from those predicted in our forward-looking statements include, among others, risks and uncertainties related to conducting and reporting data analyses; product development, including delays or challenges that may arise in the development and regulatory approval of our current and future product candidates or programs; uncertainties as to the availability, analyses and timing of results and data from preclinical and clinical studies and whether results from preclinical studies and early interim data will be predictive of the results of later preclinical studies and data readouts, and other clinical trials; the timing of our ability to submit and obtain regulatory clearance for investigational new drug applications and initiate additional clinical trials; our ability to work with the FDA to successfully remove the partial clinical hold on VG-3927; our ability to initiate and complete our current and expected clinical trials; whether our cash resources will be sufficient to fund our foreseeable and unforeseeable operating expenses and capital expenditure requirements; our ability to raise additional funding on favorable terms, or at all; the rate and degree of market acceptance and clinical utility of our product candidates; the accuracy of our data analyses or estimates for the potential and market for our products; our ability, and the ability of our collaborators, to protect our intellectual property and to conduct activities for the development and commercialization of our candidates in view of third party intellectual property positions; our financial performance; our ability to retain and recruit key personnel, as well as the potential contribution of our employees and board to our growth and success as a Company; developments and projections relating to our competitors or our industry; changes in general economic conditions and global instability, in particular economic conditions in the markets on which we or our suppliers operate; changes in laws and regulations; and those risks and uncertainties identified in our filings with the Securities and Exchange Commission (SEC), including under the heading "Risk Factors" in Quarterly Report on Form 10-Q for the quarter ended June 30, 2023, and such other risks and uncertainties that may be described in other filings we make with the SEC.

You should not rely upon forward-looking statements as predictions of future events or performance, or as a representation or warranty (express or implied) by us or any other person that we will achieve our objectives and plans in any specified time frame, on such specified terms, or at all. Although our management believes that the expectations reflected in our statements are reasonable, we cannot guarantee that the future results, performance or events and circumstances described in the forward-looking statements will be achieved or occur. These forward-looking statements speak only as of the date such statements are made. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.


(vigil)™
NEURO
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Corporate Overview
Ivana Magovčević-Liebisch, PhD, JD
Chief Executive Officer
Vigil Neuroscience, Inc.
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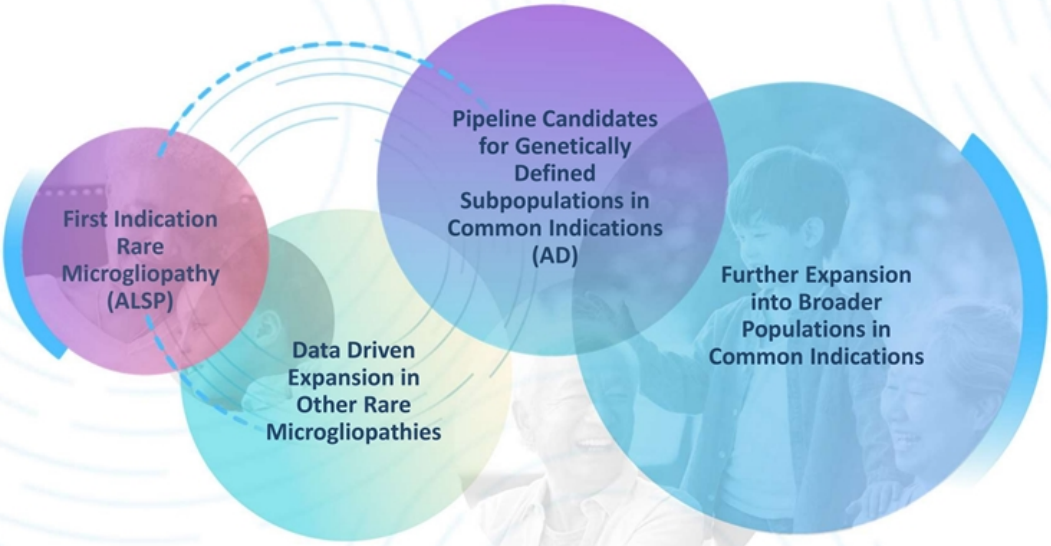
Vigil Neuroscience

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

- Founded ~3 years ago in July 2020
- Our purpose: to treat rare and common neurodegenerative diseases by restoring the vigilance of microglia, the brain's sentinel immune cells
- Precision-based strategy for developing microglia therapeutics
- Only company known to have 2 modalities for TREM2 agonism – monoclonal antibody and small molecule
- Highly experienced, execution-focused management team and Board of Directors
- >60 highly dedicated team members

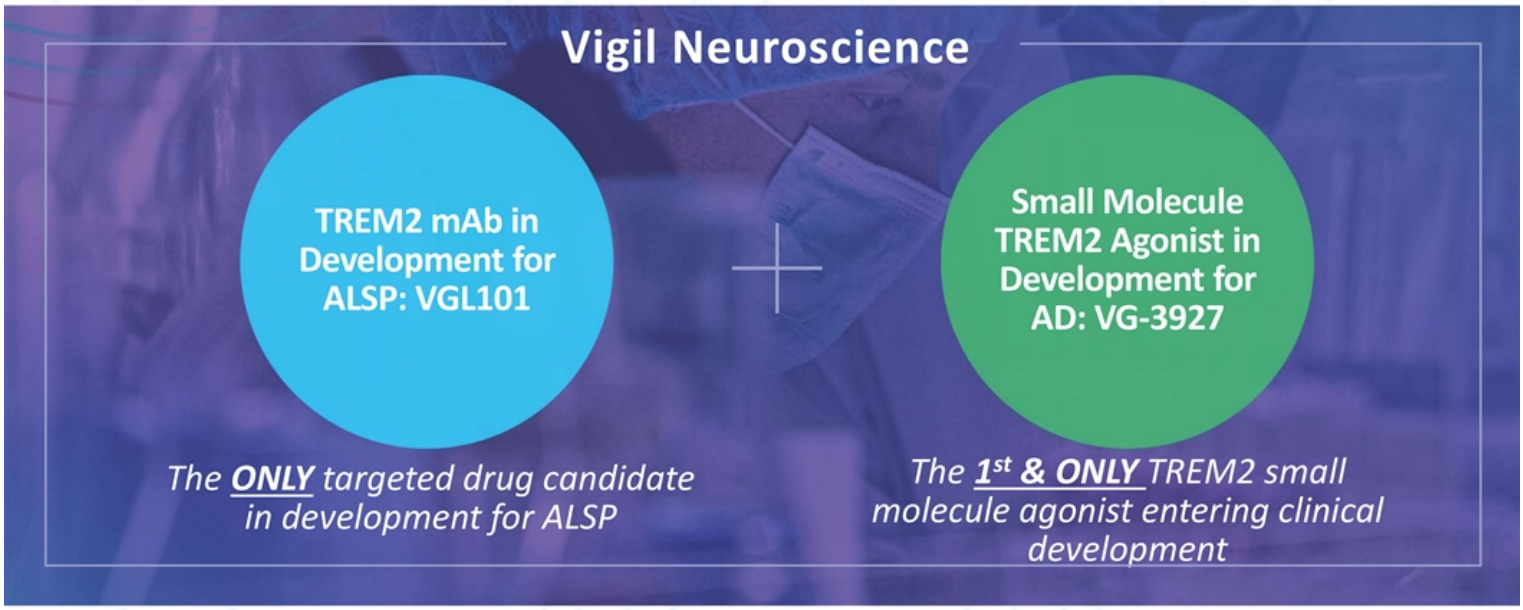
Vigil's Precision Medicine Strategy to Target Broad Range of Neurodegenerative Diseases



Apply learnings from genetically defined subpopulations to larger indications

ALSP: Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia; AD: Alzheimer's Disease

Vigil TREM2 Agonists: Differentiated Strategy & Multiple Modalities



VG-3927: Small Molecule TREM2 Agonist Well-Positioned for AD

- **First & only small** molecule TREM2 agonist entering clinical development
- **Excellent profile** as potential treatment for Alzheimer's Disease (AD):
  - Oral dosing
  - **Superior** brain penetration & **differentiated** pharmacokinetics & MoA vs antibody-based therapeutics
    - > Novel MoA potentiates TREM2 response to natural damage ligands may enable
      - **Improved potency & specificity** in active disease state
      - Potentially **more favorable safety profile**
  - Absence of Fc effector domain may **limit observations of ARIA**
- Investigational New Drug (IND) is now **open**
  - Phase 1 clinical trial in healthy volunteers **allowed to proceed** with partial clinical hold related to maximum exposure limit
- **Dosing in Phase 1** clinical trial in healthy volunteers to commence in **Oct 2023**

Featured Key Opinion Leaders (KOLs)

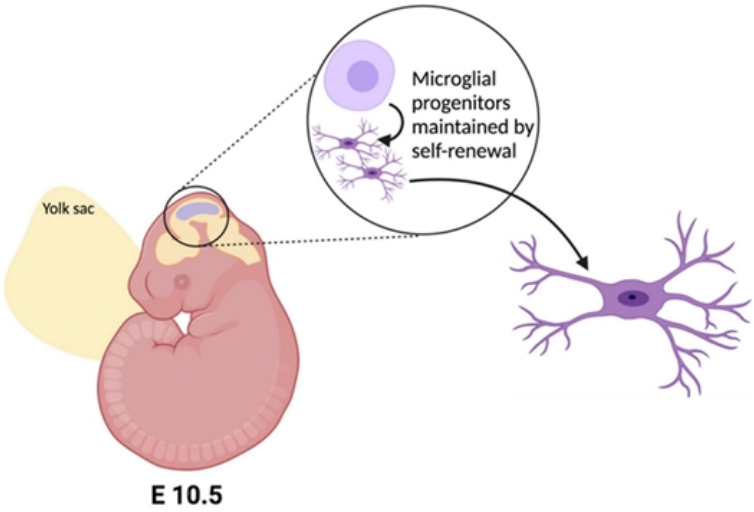
Marco Colonna, MD
Robert Rock Belliveau Professor of Pathology & Immunology
Washington University School of Medicine, St. Louis, MO
Vigil Neuroscience, Inc. Scientific Advisory Board Chairman

Samuel E. Gandy, MD, PhD
Mount Sinai Professor of Alzheimer's Disease Research,
Professor of Neurology & Psychiatry
Associate Director of Mount Sinai Alzheimer's Disease Research Center, NYC
Past Chairman, National Medical & Scientific Advisory Council of the Alzheimer's Association

TREM2 Concept in Alzheimer's Disease (AD)

Marco Colonna, MD
Robert Rock Belliveau Professor of Pathology & Immunology
Washington University School of Medicine, St. Louis, MO
Vigil Neuroscience, Inc. Scientific Advisory Board Chairman

Unique Developmental Origin of the Brain Resident Immune System



Microglial-specific Markers:

CD11b

$CD45^{low}$

$Cx3cr1^{high}$

Tmem119

FCRLS

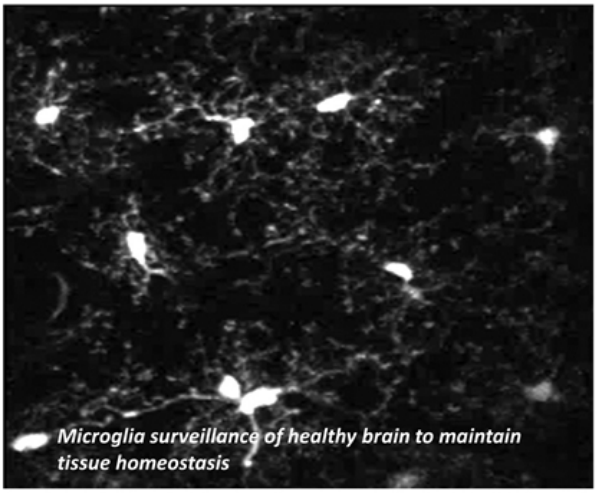
P2RY12

Sall1

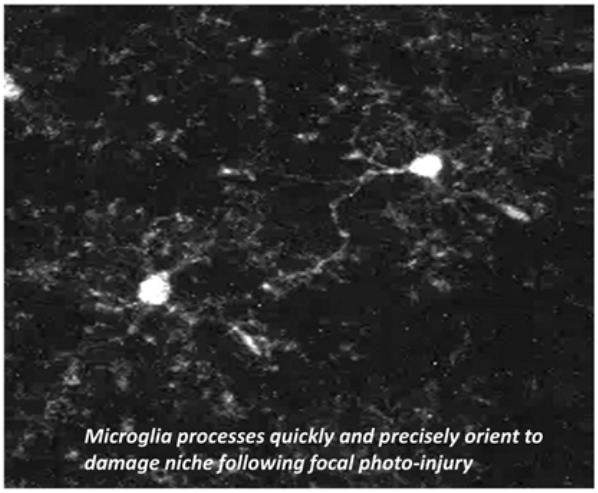
https://www.mdpi.com/1422-0067/22/18/9706

Microglia in Healthy & Disease States

Microglia are Key to Maintaining Normal Brain Homeostasis and Neuronal Function



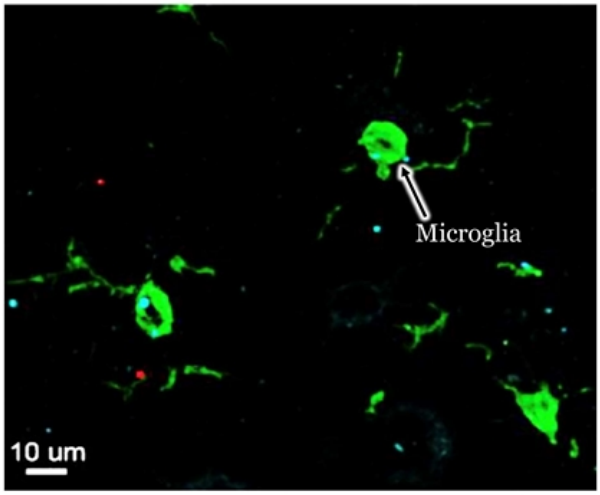
Microglia are Brain-resident First Responders to Acute Brain Injury



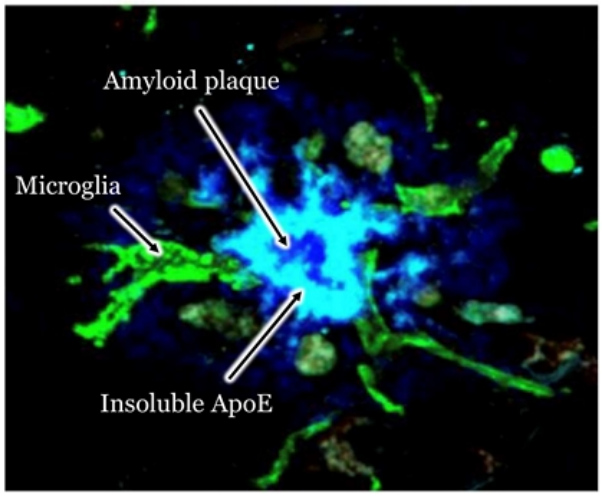
Nimmerjahn, A et al. (2005) Science

Microglia Migration into AD's Neuropathological Amyloid Plaque Microenvironment

Healthy Control Brain



Alzheimer's Disease Brain

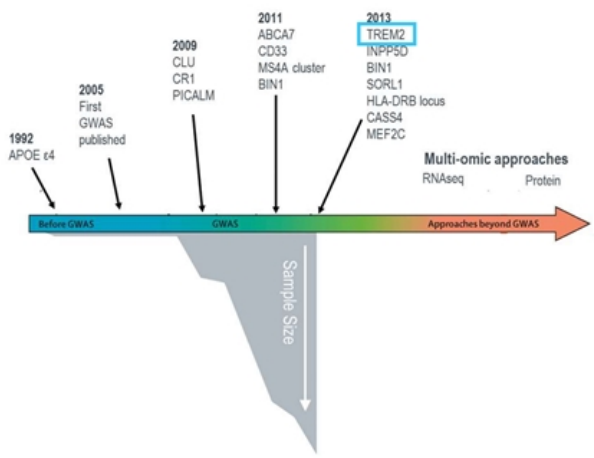


Microglia marker Amyloid plaque Aggregated ApoE

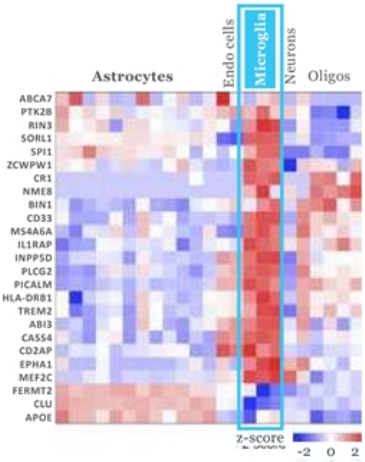
Colonna Lab, unpublished data

Genetics of AD Inspire the Next Generation of Microglia-Targeted Therapeutics

Expansion of AD Sequenced Genomes Identifies Rare And Novel Causal Genetic Risk Factors



AD Genetics-identified Genes Enriched in Microglia

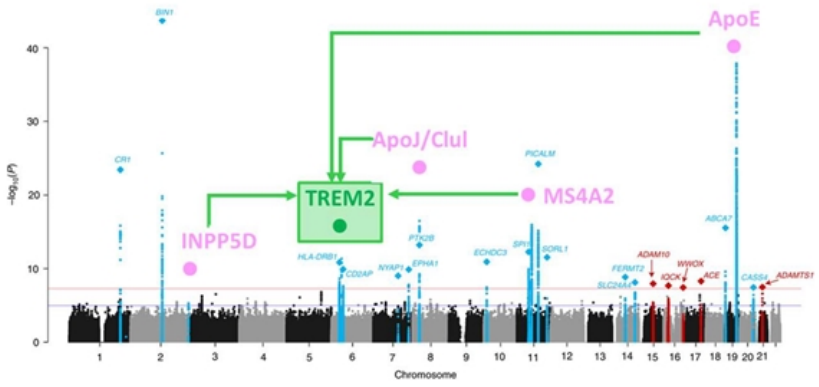


Cuyvers, E and Sleegers, K (2016) Lancet Neurology; Hansen, DV et al. (2018) J Biol Chem

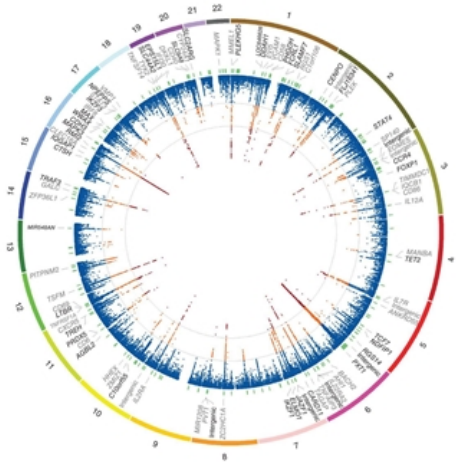
Targeting Neuroimmunology Specifically for Alzheimer's Disease

Distinct Genetic Links vs Inflammation Disease States

Human Genetic Underpinnings of Alzheimer's Disease Point Directly to TREM2 with Further Validation by Multiple Pathway Interactors



Biological Substrates of Multiple Sclerosis Points to a Distinct Signature

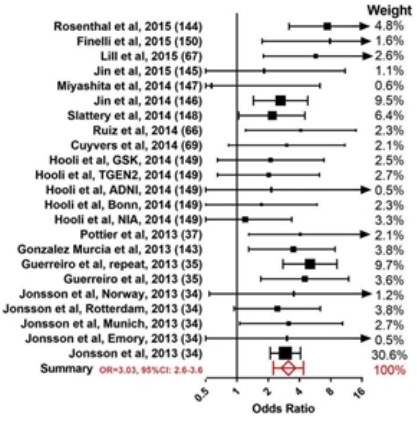


Adapted from Kunkle, BW et al (2019) Nature Genetics; International Multiple Sclerosis Genetics Consortium (2013) Nature Genetics

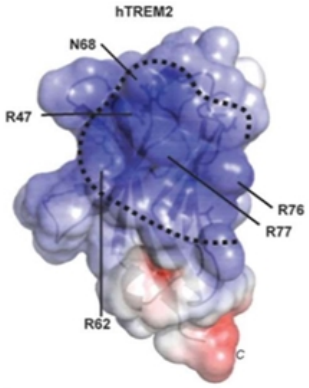
Why All the Focus on TREM2?

Overwhelming Human Data Point to AD-risk Associated Gene, Protein & Cellular Dysfunction

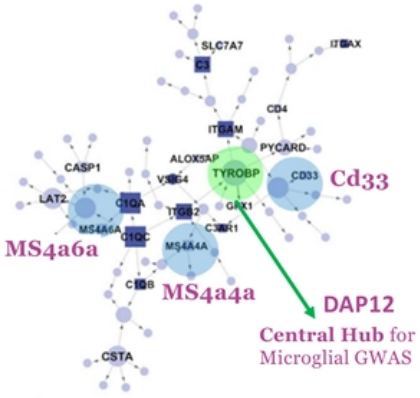
Association of TREM2 Variants with AD Risk is Robust and Highly Replicated



TREM2 Mutations in AD Suggest Loss of Ligand Binding and Loss of Microglia Function



Gene Expression in Sporadic AD Further Validates Involvement of the TREM2 Pathway

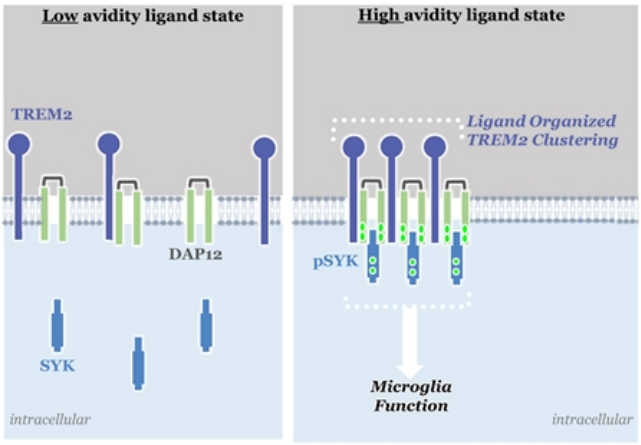


Condello, C et al. (2018) Biol Psychiatry; Kober, D et al. (2016) eLife; Zhang, B et al. (2013) Cell

Microglial Loss-of-Signaling Hypothesis for TREM2

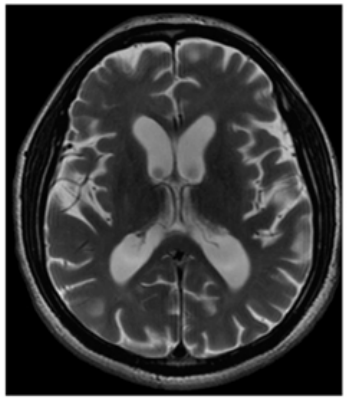
TREM2-DAP12 Pathway & Its Importance Beyond AD

TREM2-DAP12 Signaling Transduction and Cellular Function in Microglia

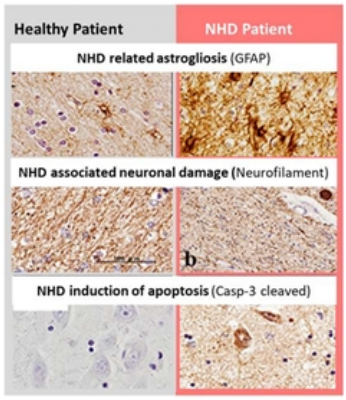


TREM2 and DAP12 Mutations Cause Rare Early-onset Familial Microgliopathy Called Nasu-Hakola Disease (NHD)

MRI manifestations of NHD



Neuropathology in NHD patient

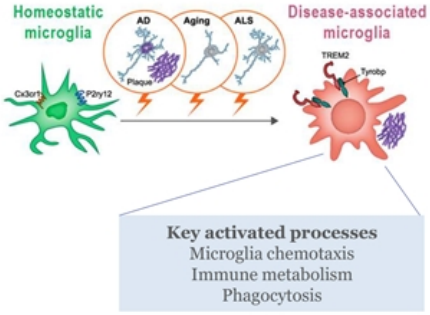


Satoh et al. (2010) Neuropathology; Kilic et al. (2012) Clinical Imaging

TREM2's Role in Microglial Activation Disease State

Molecular Evidence

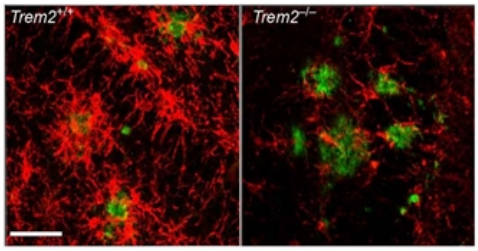
TREM2 promotes non-inflammatory, neuroprotective microglia state



Key activated processes
Microglia chemotaxis
Immune metabolism
Phagocytosis

AD Mouse Models

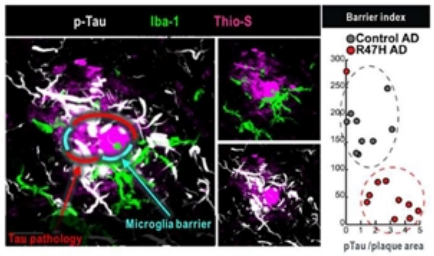
TREM2 is required for neuroprotection within the amyloid plaque niche



Amyloid plaque Microglia

Human AD Validation

Plaque-associated microglia protect neighboring neurons



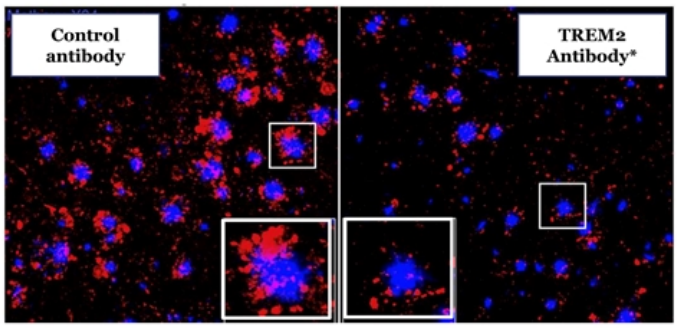
Amyloid plaque Neuronal damage
Microglia

Keren-Shaul, H et al. (2017) Cell ; Wang, Y et al. (2015) Cell; Yuan, P et al. (2016) Neuron

Preclinical Proof-of-Principle via TREM2 Agonist Antibodies

Target Validation via Pharmacological Modulation

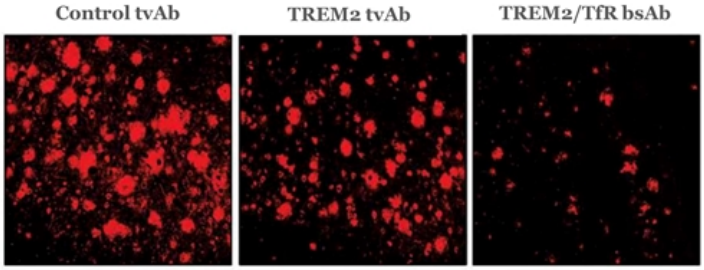
TREM2 Agonist Antibody Reduces Neuronal Damage Locally Around Aβ Plaques



*AL002

Amyloid plaque Neuronal damage

Enhanced Brain Penetration Leads to Increased Amyloid Reduction



Amyloid plaque

TREM2 tvAb: TREM2 tetravalent antibody
TREM2/TfR bsAb: TREM2 tetravalent antibody engineered for enhanced brain penetration
TfR: transferrin receptor epitope

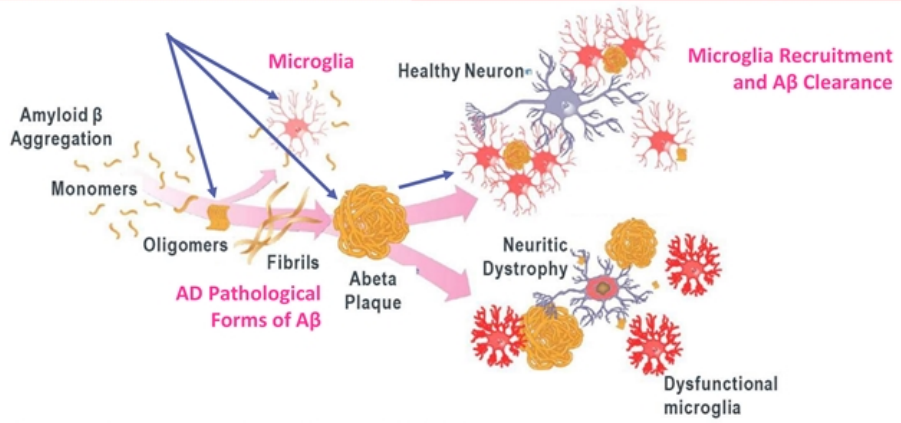
Wang, S et al. (2020) J Exp Med

Leveraging Microglia to Restore Tissue Homeostasis in AD

Evidence from Recent Anti-Aβ Therapeutics

Anti-Aβ dual binding to AD substrate and microglia

Antibody full effector function drives microglial Aβ clearance



Effector inactivated mAbs fail to engage microglia and lack efficacy

Chauraslya, A et al. (2023) Nanomedicine-Based Approaches for the Treatment of Dementia

Breakthroughs in Neuroimmunology Seed a Promising New Outlook for AD Therapeutics

Summary of Key Concepts

- Genetics of AD point to microglia as the next generation therapeutics
- TREM2 is both directly implicated as a causal gene as well as indirectly as a genetic hub
- Extensive research points to their protective role in the amyloid plaque microenvironment
- Preclinical genetic and pharmacological studies validate the TREM2 agonism for AD concept
- Recently approved anti-Aβ therapeutics provide clinical precedent that leveraging microglia can restore tissue homeostasis in AD

Acknowledgements

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Ido Amit
Hadas Keren-Shaul

Brain research Institute Niigata, Japan
Akiyoshi Kakita
Mari Tada
Masaki Takao

Mayo Clinic Rochester
Aivi Nguyen
Rachel Larsen
Eleni Costantopoulos

University of Brescia
Luigi Poliani
William Vermi
Mattia Bugatti
Andrea S Omodei

CST, Boston
Tyler Levy
Sean Beausoleil
Richard Cho

Vigil Neuroscience
David Gray
Christian Mirescu
Borislav Dejanovic
Kelley Larson

Amgen
Daniel C. Ellwanger
Samuel A. Hasson
Menno van Lookeren Campagne

Alector
Tina Schwabe
Meer Moustafa
Ilaria Tassi
Herve` Rhinn
Adiljan Ibrahim
Arnon Rosenthal


VG-3927: First & Only Small Molecule TREM2 Agonist Entering Clinical Development for Alzheimer's Disease
David Gray, PhD
Chief Science Officer, Vigil Neuroscience, Inc.
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VG-3927: First & Only Clinical Oral Small Molecule TREM2 Agonist

We Are Microglia Experts

Outstanding & differentiated clinical candidate from world-class R&D

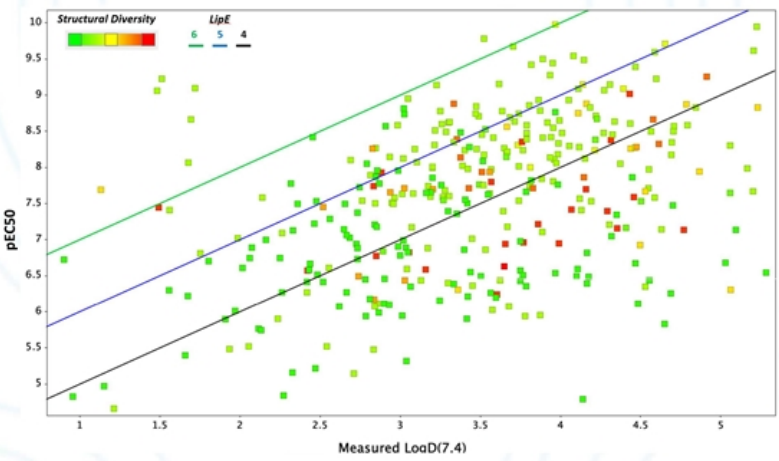
Potent TREM2 agonism synergizes with natural damage ligands

Broad and favorable modulation of neuropathology

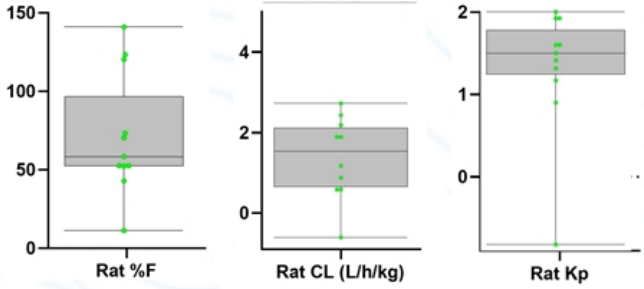
VG-3927 Selected from High Quality Chemical Matter

Deep Understanding of MoA with Multiple Excellent Back-up Compounds

Highly Efficient and Structurally Diverse



Target Coverage in CNS via Oral Dosing



Strong Development Path

- Consistent PK across preclinical species
- CNS drug properties fully optimized
- Scalable and versatile synthetic route

pEC50 = log [pSYK EC50] measured in HEK293T–hTREM2 cells , LogD(7.4) = Measured water/octanol partition coefficient at pH 7.4, Rat%F = percentage oral bioavailability in Wistar-Han Rats , Rat Cl = Estimated metabolic clearance rate measured in Wistar Han rats, Rat Kp = Brain to plasma partition coefficient measures in Wistar Han rats

VG-3927: Entering Phase 1 with Excellent Product Profile

- TREM2 EC_{50}: < 0.003 µM
- TREM1 selectivity: > 50,000-fold
- Clean profile (evaluated in ~350 off-target assays)

- PK consistent with QD dosing
- CSF exposure ≈ free plasma
- No CYP inhibition liability
- No TDI risk

- SIF solubility: 83 µM
- MDCK Papp: >10 cm^{-6}/s
- MDCK PGP ER: ~0.5

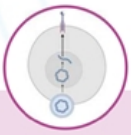
- Well tolerated with sufficient safety margins to support Ph1
- hERG margin: > 3,500-fold

EC_{50}: half maximal effective concentration; PK: pharmacokinetics; QD: once-daily; CSF: cerebrospinal fluid; CYP: cytochrome P450 enzymes; TDI: time-dependent inhibition; hERG: human ether-a-go-go-related gene; SIF: stimulated intestinal fluids; MDCK Papp: Madin-Darby canine kidney apparent permeability; PGP ER: P-glycoprotein efflux ration

Establishing VG-3927 for Development in AD

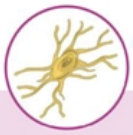
Pharmacological & Clinical Translation

VG-3927 Pharmacological Profile



TREM2 engineered systems

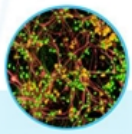
High-throughput profiling



Human iPSC microglia monocultures

Therapeutically relevant target cells

VG-3927 Functional & Model System Profile



Human CNS tri-culture platform

Biologically diverse human CNS model system

Mouse neurodegenerative disease models

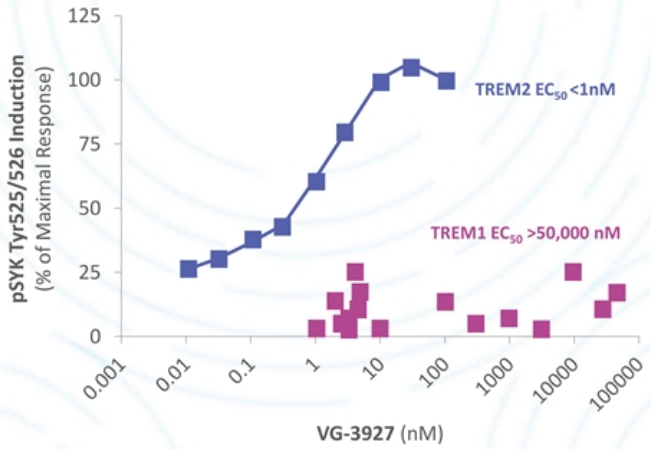
Established preclinical AD transgenic mice

Nonhuman primate profiling

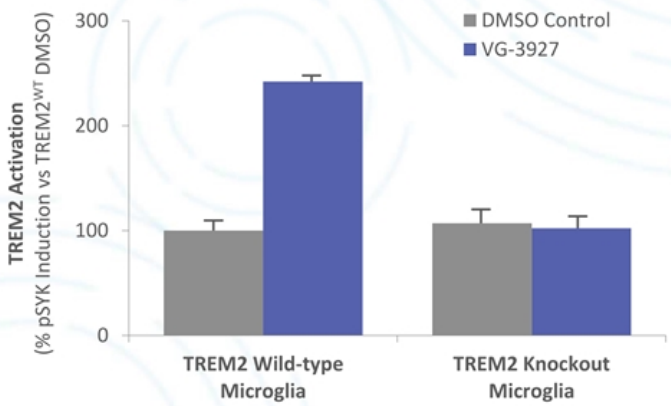
ID and validation of translational biomarkers

VG-3927: Potent & Selective TREM2 Agonist

VG-3927 – Highly Selective Agonist for TREM2 Over TREM1



VG-3927 Signaling in Human Microglia is Fully Dependent on TREM2

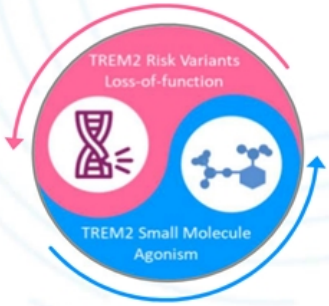


DMSO: dimethyl sulfoxide

VG-3927: Potent TREM2 Agonist in Neurodegenerative Disease-Associated TREM2 Variants

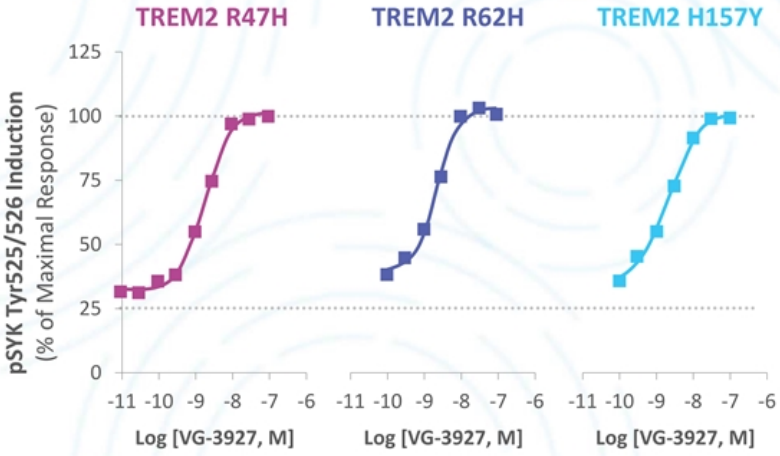
Supports Precision-based Clinical Development

Vigil Precision AD Strategy



Accelerated Path to Successful Clinical POC

VG-3927 Potency Across Notable AD-risk Variants of TREM2

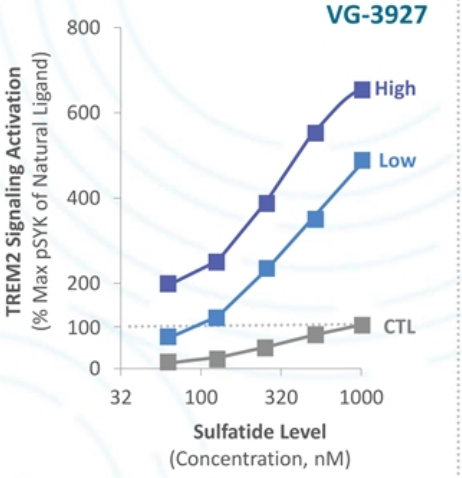


TREM2 Variant	Highly Potent
Common Variant	✓
R47H	✓
R62H	✓
H157Y	✓
T96K	✓

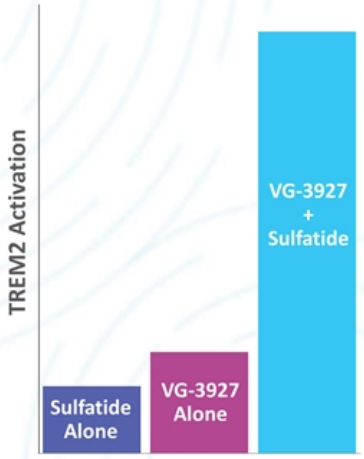
VG-3927 Potentiates Signaling of Damage-associated Ligands

Damage-associated Ligand: Sulfatide

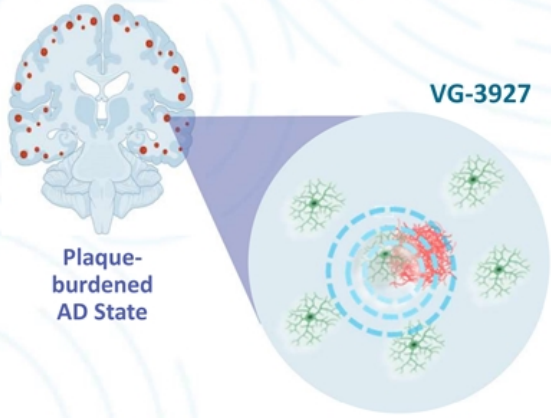
TREM2 Signaling Activation



Potentiation of TREM2 Activation



Focusing Efficacy in Pathological Microenvironments



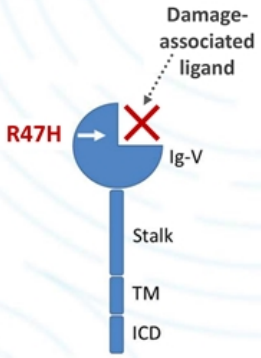
CTL: control; Low: VG-3927 at 2 nM; High: VG-3927 at 125 nM

TREM2 AD-risk Variants Are Loss of Function & Impact Signaling

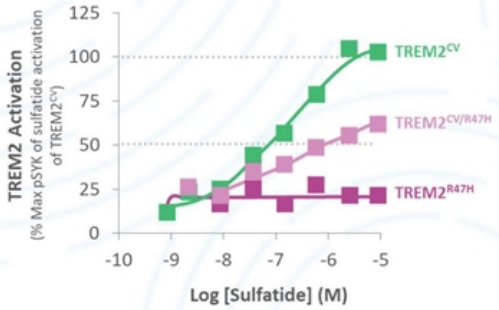
Example: R47H Leads to Defective Sensing of Sulfatide

TREM2^{R47H} Variant

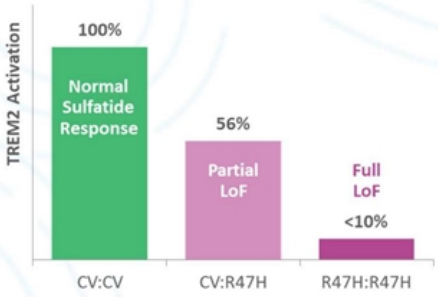
Mutation Impact:
- Missense in ligand binding domain
- Loss of TREM2 response to sulfatide (damage-associated ligand)



TREM2 Activation (CV vs R47H Variants)
Based on pSYK Activation



Genotype Impact on TREM2 Activation



TM: transmembrane domain; ICD: intracellular domain; CV: common variant; LoF: loss of function

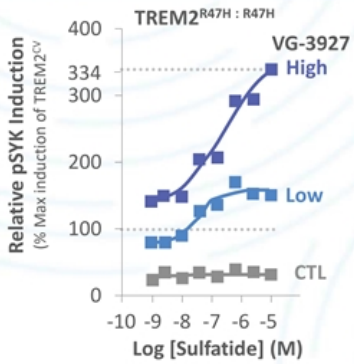
VG-3927 Restores TREM2 Response to Damage-associated Ligand in R47H

Rescues Signaling Impairment in AD-risk Variant

VG-3927
TREM2 SM for AD

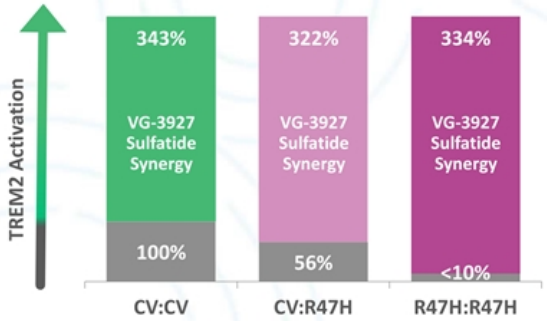
- TREM2-R47H defective response to damage-associated ligand (sulfatide)
- VG-3927 rescues signaling and response to sulfatide
- Similar effects observed in TREM2 R62H AD-risk variant

VG-3927 Fully Restores Compromised Signaling in AD-risk Variant



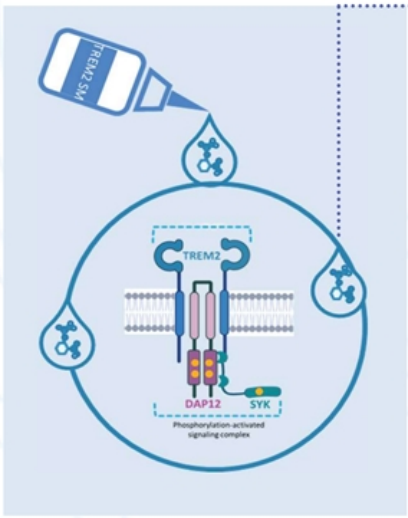
CTL: control; Low: VG-3927 at 1 nM; High: VG-3927 at 100 nM

VG-3927 Fully Restores TREM2 R47H Defect

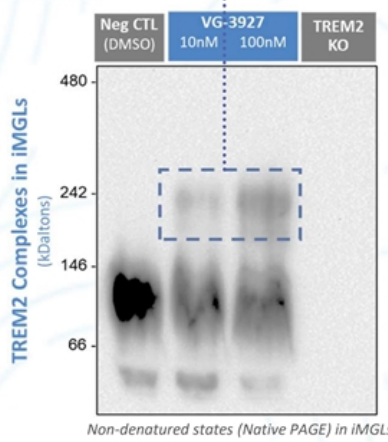


VG-3927 Acts as a Molecular Glue to Stabilize TREM2 Complex

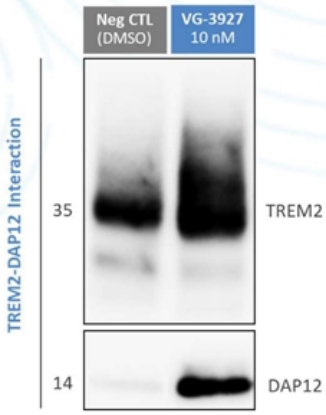
Novel Mechanism of Action



Higher molecular weight band reveals novel receptor ligand complex



Non-denatured states (Native PAGE) in iMGLs

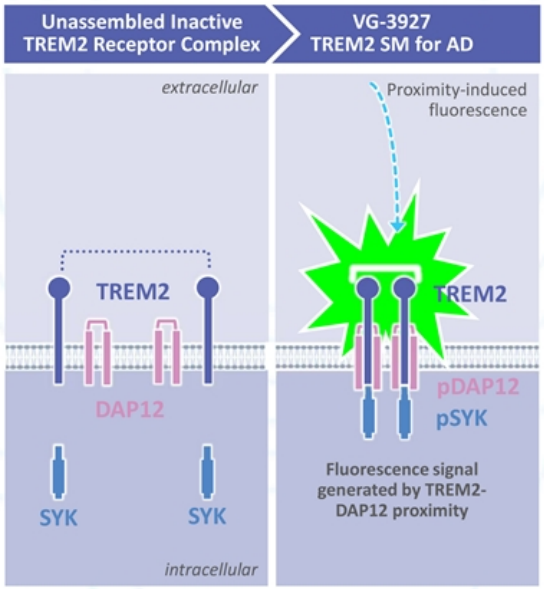


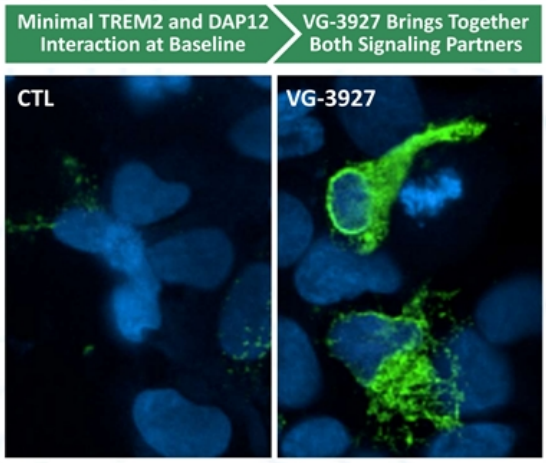
TREM2 immunoprecipitation in HEK system

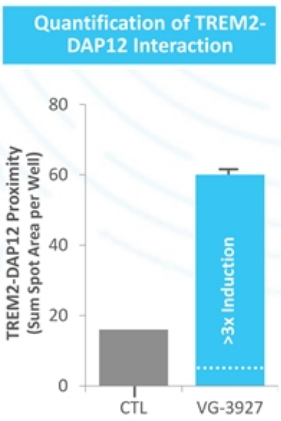
Neg CTL: negative control; DMSO: dimethyl sulfoxide; KO: knock-out; PAGE: polyacrylamide gel electrophoresis; iMGLs: induced pluripotent stem cell-derived microglia; HEK: human embryonic kidney

VG-3927 Orchestrates Multi-Protein Interaction to Trigger Signaling

Unique Molecular Glue Mechanism of Action





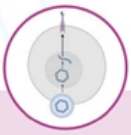


- TREM2 clusters and utilizes DAP12 to initiate downstream signaling
- VG-3927 coordinates these protein-protein interactions

Establishing VG-3927 for Development in AD

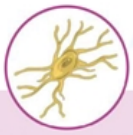
Pharmacological & Clinical Translation

VG-3927 Pharmacological Profile



TREM2 engineered systems

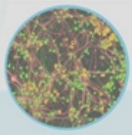
High-throughput profiling



Human iPSC microglia monocultures

Therapeutically relevant target cells

VG-3927 Functional & Model System Profile



Human CNS tri-culture platform

Biologically diverse human CNS model system

Mouse neurodegenerative disease models

Established preclinical AD transgenic mice

Nonhuman primate profiling

ID and validation of translational biomarkers


VG-3927: First & Only Small Molecule TREM2 Agonist Entering Clinical Development for Alzheimer's Disease
Christian Mirescu, PhD
Vice President, Head of Neuroimmunology, Vigil Neuroscience, Inc.
vigil™
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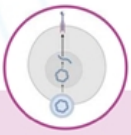
Establishing VG-3927 for Development in AD

Pharmacological & Clinical Translation

VG-3927 Pharmacological Profile



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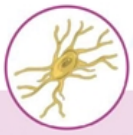

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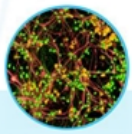

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Biologically diverse human CNS model system

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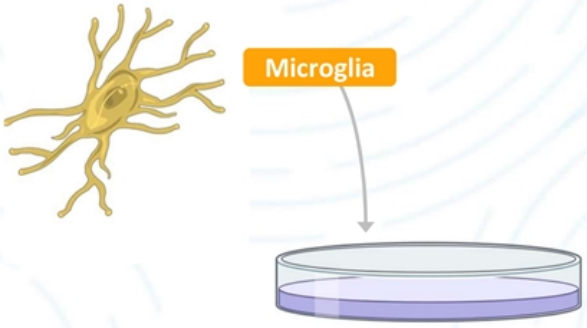
Vigil Human CNS Platform Combines Neurons, Astrocytes & Microglia

Human iMGL Monoculture Platform

Pharmacology in disease-relevant human cells

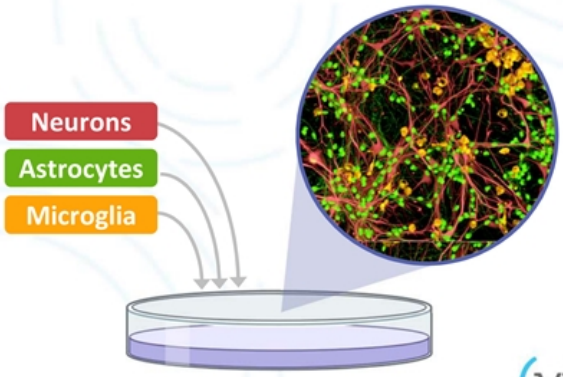
- Microglial pharmacology
- Target selectivity
- Fine mapping agonism



Human CNS Tri-culture Platform

Bridge to a predictive human translational system

- Vigil's fully human translational cell model
- Understand interactions between diverse CNS cells
- Complementary with mono-culture applications

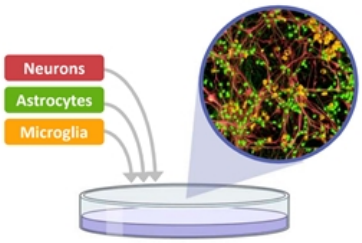


iMGL: induced pluripotent stem cell (iPSC)-derived microglia

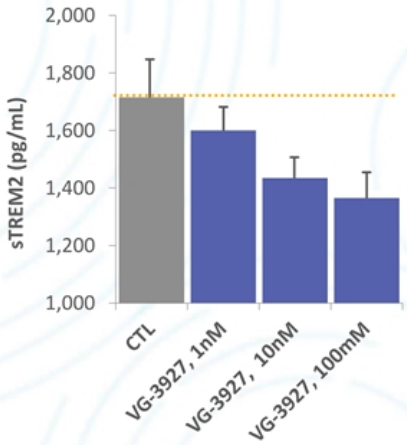
(vigil)

VG-3927 Functional Profiling in CNS Tri-Culture Platform

Platform Application: Understand VG-3927 Downstream Biology & Human Neuroprotective Actions



VG-3927 Modulates Established Target Engagement Biomarker



VG-3927

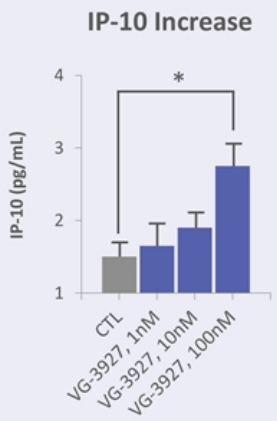
Mobilizing microglia response with a favorable, non-inflammatory profile

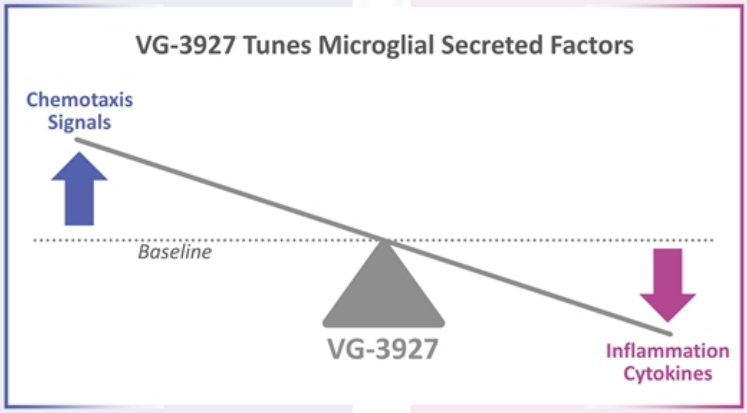
- Boosting of neuroprotective markers
- Plus countering inflammation-induced neurodegeneration

VG-3927: Enhances Signals of Microglia Mobilization

Favorable, Non-inflammatory Profile

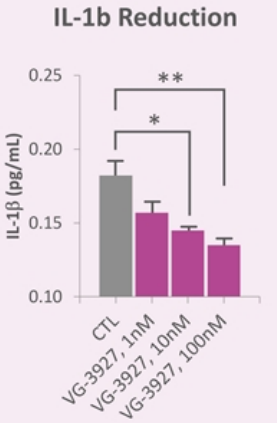
Enhancement of Microglia Migration Signal





* *denotes p<0.05*

Suppression of Pro-inflammatory Cytokines

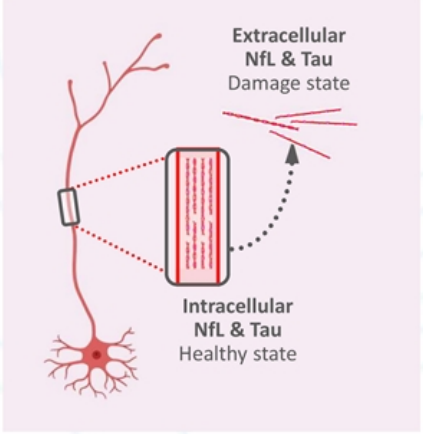


* *denotes p=0.01; ** denotes p=0.001*

VG-3927 Reduces Established Neurodegeneration Biomarkers

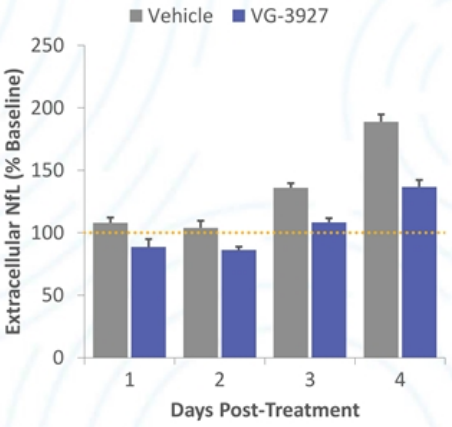
Reduction of Extracellular NfL & Tau

VG-3927's Impact on Key Neurodegeneration Biomarkers in Humans



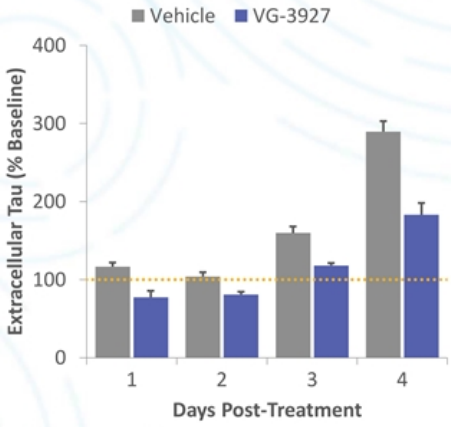
NfL: neurofilament

VG-3927 Reduces Extracellular NfL Accumulation in Human Tri-cultures



ANOVA$_{Treatment}$, p<0.0001

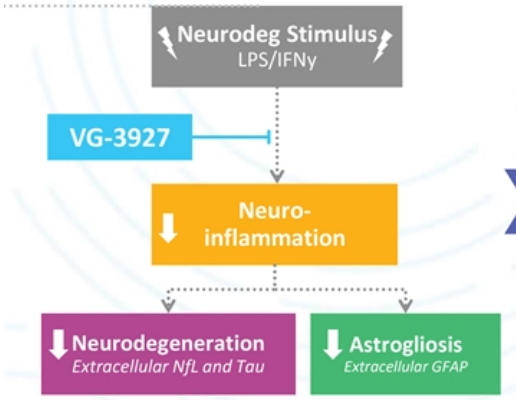
VG-3927 Reduces Extracellular Tau Accumulation in Human Tri-cultures



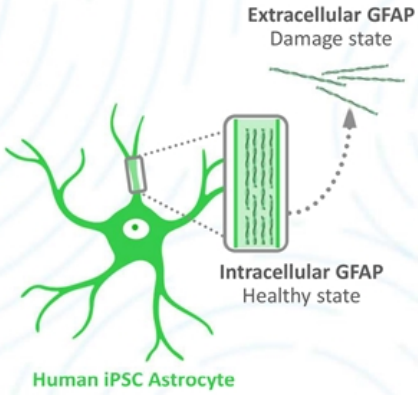
ANOVA$_{Treatment}$, p<0.0001

VG-3927 Protects Against Inflammation-Induced Astrogliosis

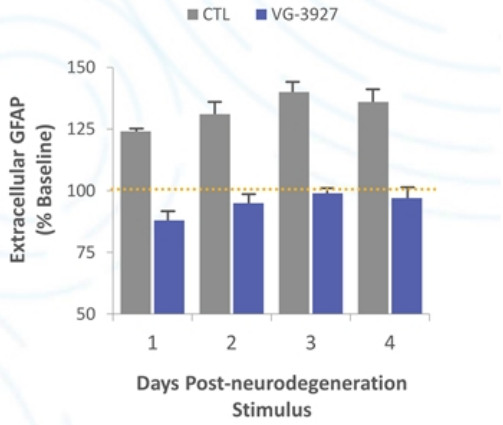
TREM2 Agonism Activates Anti-inflammatory Benefit



GFAP: Marker of Astrogliosis



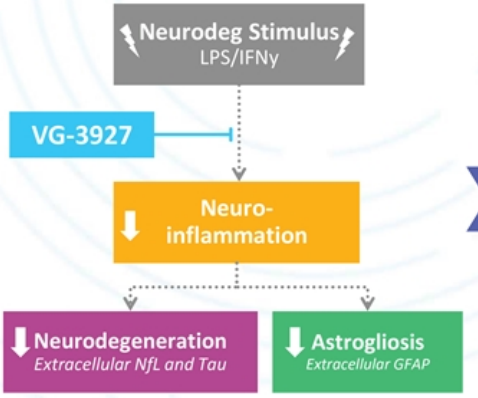
VG-3927 Reduces Astrogliosis Biomarker (GFAP) in Human CNS Tri-cultures



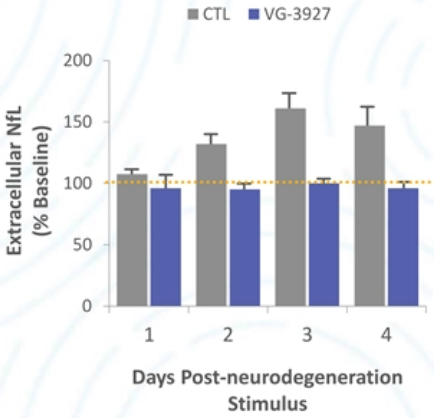
LPS: lipopolysaccharide; IFNY: interferon-gamma; GFAP: glial fibrillary acidic protein

VG-3927 Protects Against Biomarkers of Inflammation-Induced Neurodegeneration

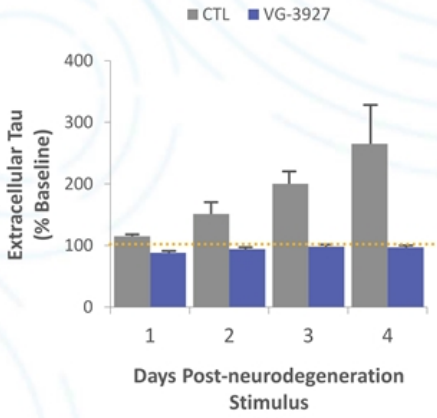
TREM2 Agonism Activates Anti-inflammatory Benefit



VG-3927 Suppresses Extracellular NfL & Tau Accumulation in LPS Model



$ANOVA_{Treatment}$ $p<0.05$

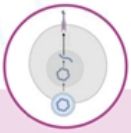


$ANOVA_{Treatment}$ $p<0.05$

Establishing VG-3927 for Development in AD

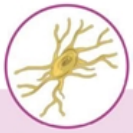
Pharmacological & Clinical Translation

VG-3927 Pharmacological Profile



TREM2 engineered systems

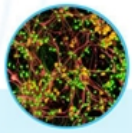
High-throughput profiling



Human iPSC microglia monocultures

Therapeutically relevant target cells

VG-3927 Functional and Model System Profile



Human CNS tri-culture platform

Biologically diverse human CNS model system

Mouse neurodegenerative disease models

Established preclinical AD transgenic mice

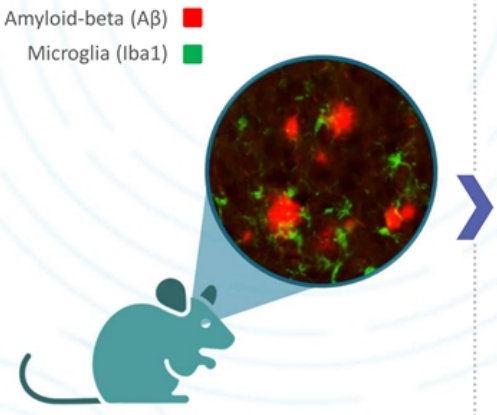
Nonhuman primate profiling

ID and validation of translational CSF biomarkers

VG-3927: Functionally Active in AD State

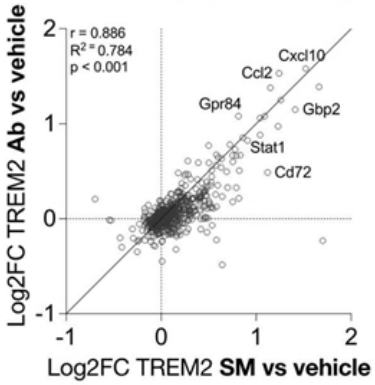
VG-3927 & VGL101 mAb Activate Neuroprotective Genes Similarly

Mouse Amyloidosis Model VG-3927 Oral Dosing

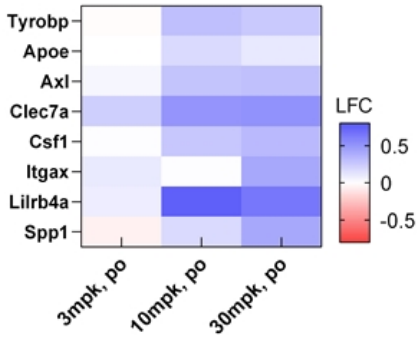


Model: 5xFAD AD (mut APP/PS1) + hTREM2

VG-3927 Recapitulates TREM2 Antibody Gene Signatures



VG-3927 Activates Protective Microglia Gene Signatures



Exploring VG-3927 Therapeutic Effects in Aβ Plaque-bearing Mice

Initial Pilot Study

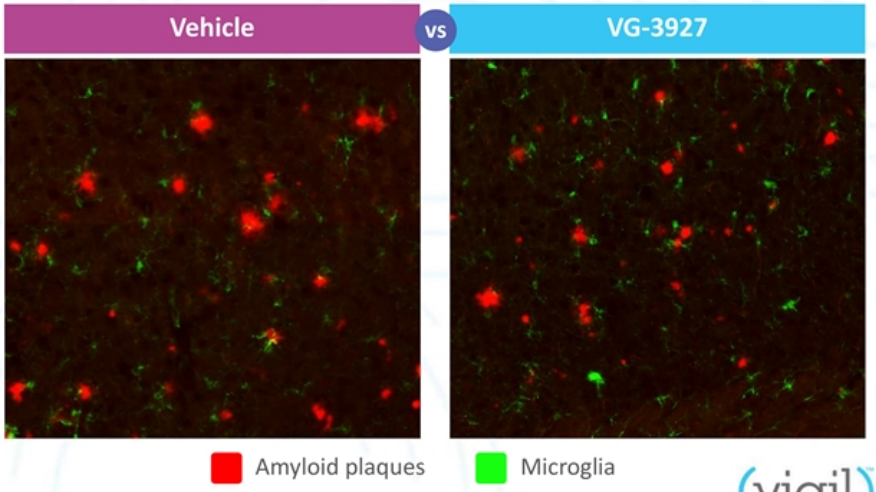
VG-3927 Effects in Humanized TREM2 AD Mouse Model

Intervention: Post-plaque deposition
Initial age: 4.5 month-old 5xFAD-hTREM2 mice

Daily Dosing for 6 Weeks

VG-3927
10mpk
QD

Disease-modifying Effects of VG-3927 on Aβ Pathology & AD-related Hallmarks



VG-3927 Reduces Aβ Pathology in Plaque-bearing Mice

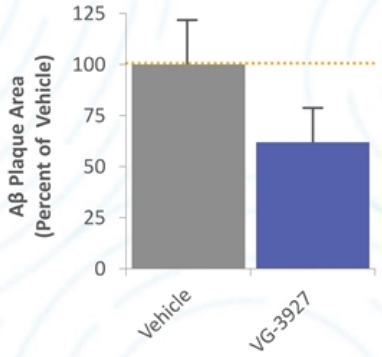
Preliminary Effects Following 6 Weeks of Oral Dosing

VG-3927

- Trend toward reducing plaque area and insoluble Aβ
- Additional potential to reduce plaque-associated ApoE

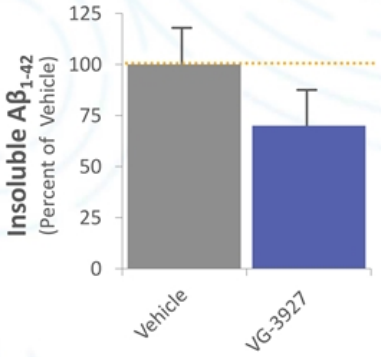
VG-3927 Effects on Aβ Plaque Area

Immunohistology from Brain Slices



VG-3927 Effects on Insoluble $A\beta_{1-42}$

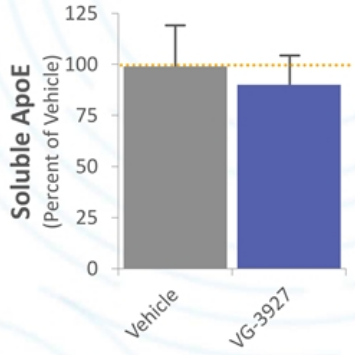
Biochemistry of Brain Homogenates



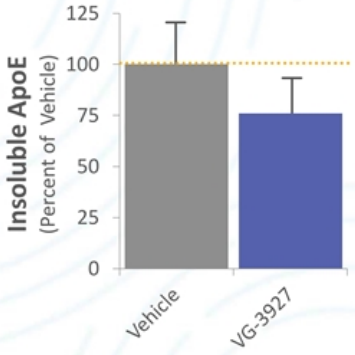
VG-3927 Reduces Neuropathology-associated Aggregated ApoE

Preliminary Effects Following 6 Weeks of Oral Dosing

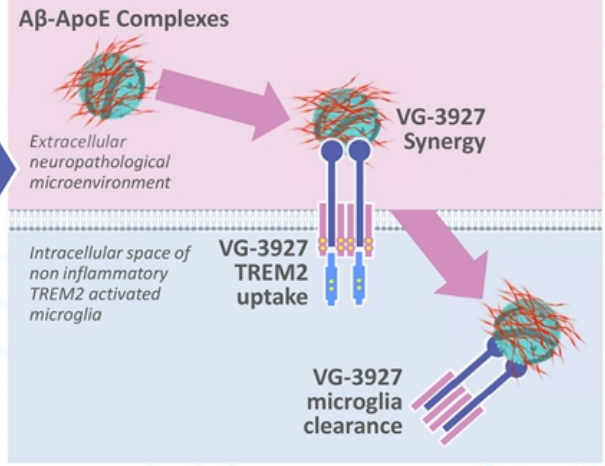
No Change in Soluble ApoE
Functional Form



Reduced Aggregated ApoE
Pathological Form



Working Model of VG-3927 Modulation of AD-related Pathology



Confirmation of Oral Bioavailability, Brain Penetrance & CNS Target Engagement

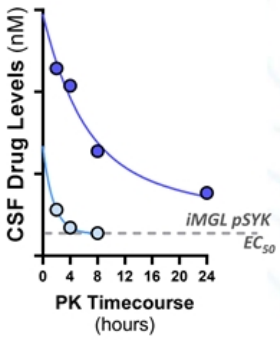
Favorable PK & PD Demonstrated in Non-Human Primates (NHPs)

Translation Biomarker Path to Clinic

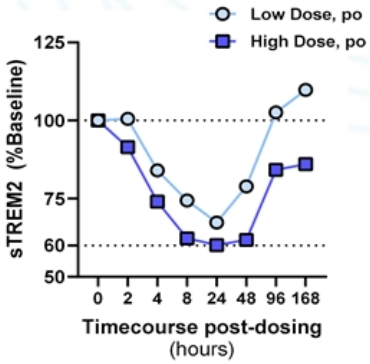
Cynomolgus Monkey

CSF Biomarker of TREM2 Target Engagement

VG-3927 CNS Exposures
PK Following Single Oral Dose



Reduction of sTREM2 in NHP CSF
Relative Change from Pre-dose Levels

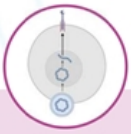


po: "per os" or oral dosing

Establishing VG-3927 for Development in AD

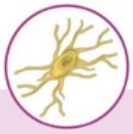
Pharmacological & Clinical Translation

VG-3927 Pharmacological Profile



TREM2 engineered systems

High-throughput profiling



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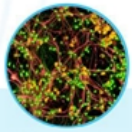

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Biologically diverse human CNS model system

Mouse neurodegenerative disease models

Established preclinical AD transgenic mice

Nonhuman primate profiling

ID and validation of translational CSF biomarkers

VG-3927: First & Only Clinical Small Molecule TREM2 Agonist for AD

Broad modulation of neuropathology by harnessing microglia

VG-3927, TREM2 SM for AD

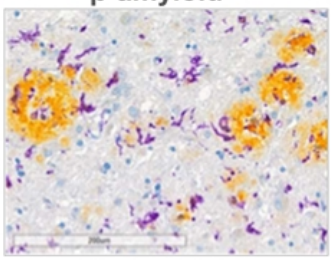
- Phase 1 dosing in healthy volunteers to commence in Oct 2023
- Differentiated TREM2 agonist
  - Highly potent and selective
  - Orally bioavailable and brain penetrant
- TREM2 natural ligand boosting
- Broad modulation of neuropathology

Alzheimer's Disease Treatment & Unmet Need

Samuel E. Gandy, PhD, MD
Mount Sinai Professor of Alzheimer's Disease Research,
Professor of Neurology & Psychiatry
Associate Director of Mount Sinai Alzheimer's Disease Research Center, NYC
Past Chairman, National Medical & Scientific Advisory Council of the Alzheimer's Association

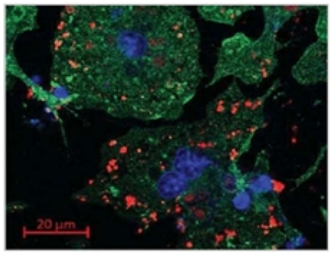
Alzheimer's Disease (AD)

β-amyloid



Tau

Inflammation



Neurodegeneration

- Progressive degenerative disease
- Most common cause of dementia in elderly
- Progressive memory loss, impaired thinking, disorientation, language problems, mood disturbances
- Complete dependence in advanced stages

Multiple Pathophysiological Mechanisms Underly Alzheimer's Disease

β-amyloid Plaques
Tau Tangles
Inflammation
Neurodegeneration

→ Clinical Decline

Plowey E et al, *Acta Neuropathol* (2022); https://www.nlm.nih.gov/medlineplus/magazine/issues/fall10/articles/fall10pg20-21.html
https://step1.medbullets.com/neurology/113089/alzheimer-disease; https://www.ahajournals.org/doi/10.1161/STROKEAHA.119.027315

AD Presents a Significant Unmet Medical Need

- An estimated 6.7 million Americans are living with Alzheimer's disease[1]
  - 1 in 9 people, age 65 and older has AD
  - Accounts for 60-80% of all dementia cases
  - Increasing incidence due to an aging population
  - 7th leading cause of death
- Enormous societal and economic burden
  - Long duration of illness and time spent in a state of severe disability & dependence
  - >11 million Americans provide unpaid care for a family member or friend with AD & other dementia
- Delaying the onset and progression of AD by 1 year may result in 9.2 million fewer cases in global burden by the year 2050[2]

1. Alzheimer's Disease Facts & Figures 2023 Alzheimer's Association; 2. Brookmeyer R, et al. *Alzheimer's Dement*. 2007;3(3):186-19

Current Treatment Options for AD

Symptomatic Treatment

- Cholinesterase inhibitors and NMDA antagonists to improve symptoms
- Does not impact brain pathology or modify the disease course
- Offers modest clinical benefit but effects wane over time due to disease progression

Anti-Aβ Monoclonal Antibodies

- Aβ lowering immunotherapies
- 22-30% slowing in clinical decline
- Administered by intravenous infusion once or twice a month
- Can cause ARIA (brain edema, microbleeds), a common side effect that requires MRI monitoring

Unmet need remains for therapeutics with improved safety and efficacy that address broader AD disease pathophysiology

ARIA - Amyloid-Related Imaging Abnormalities

Anti-Aβ mAbs with Efficacy Are Associated with ARIA

- Transient radiographic finding, occurs early in the treatment course
- Monitorable by MRI surveillance
- Managed by dose titration and dose suspension

Anti-Aβ mAbs	Efficacy on CDR-SB	Aβ plaque removal	ARIA
Effective at Lowering Aβ Plaques[1-3]	~22-30% slowing	✓	✓
Do Not Lower Aβ Plaques[4-5]	X	X	X

Small Molecule Modality Offers the Potential to Mitigate ARIA Liability

CDR-SB: Clinical Dementia Score Sum-of-Boxes; ARIA - Amyloid-Related Imaging Abnormalities

1. van Dyck et al. *NEJM* (2023); 2. Haeberlein et al. *JPAD* (2022); 3. Sims et al. *JAMA* (2023); 4. Honig et al. *NEJM* (2018); 5. Ostrowitzki et al. *JAMA Neurol* (2022)

Unmet Needs & Key Opportunities in AD Therapeutics

- Efficacy limited to ~30% slowing in clinical decline

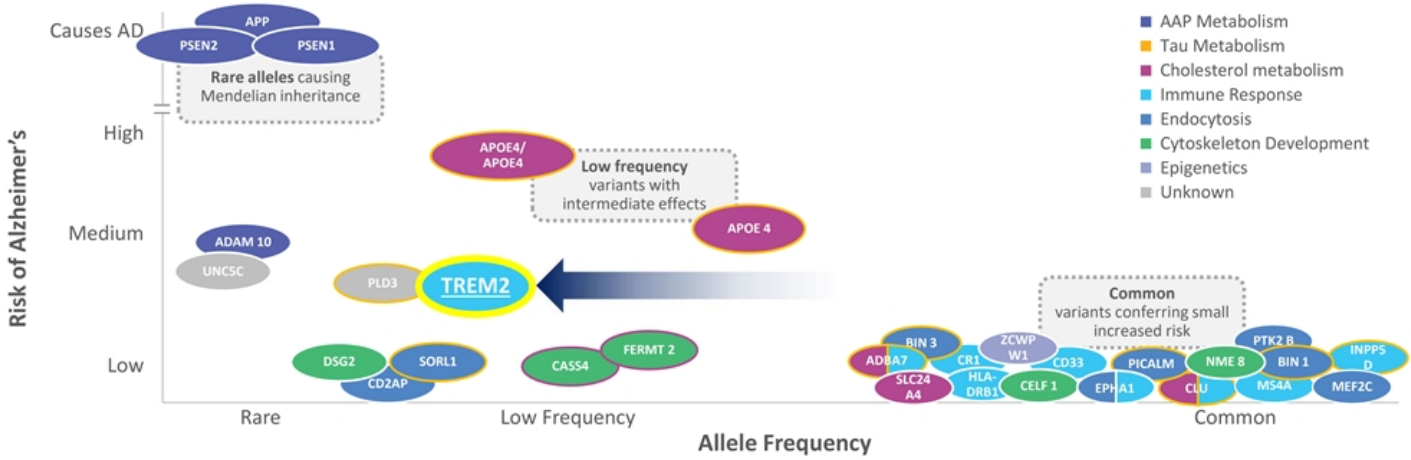
- ARIA a common side effect, requires MRI monitoring
- Immunogenicity

- Intravenous infusions once/twice monthly

- Address broader biology of the disease beyond Aβ

Human Genetics Motivates Targeting Microglia for Next-gen AD Therapeutics

>30% of AD-risk Genes Are Expressed by Microglia



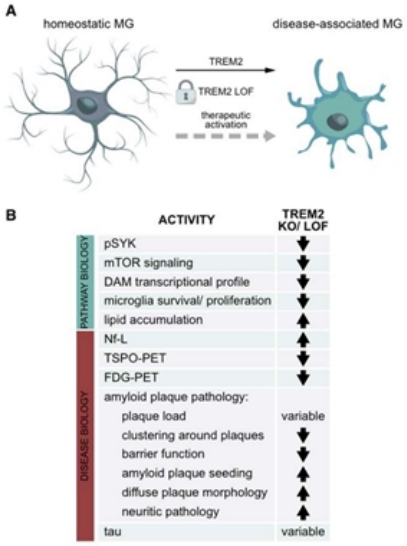
Lane et al *European Journal of Neurology* (2017)

Human Genetics & Disease Models Suggest Optimizing Microglia Function May Be Beneficial

- AD-related TREM2 variants exhibit impaired ligand binding & partial loss-of-microglia function
- Genetic mutations associated with reduced microglia function also implicated in other genetic forms of neurodegeneration

Gene	Condition Associated with Gene Mutation
TREM2	NHD/PLOSL Increase risk for AD
TYROBP/DAP12	NHD/PLOSL
CSF1R	ALSP

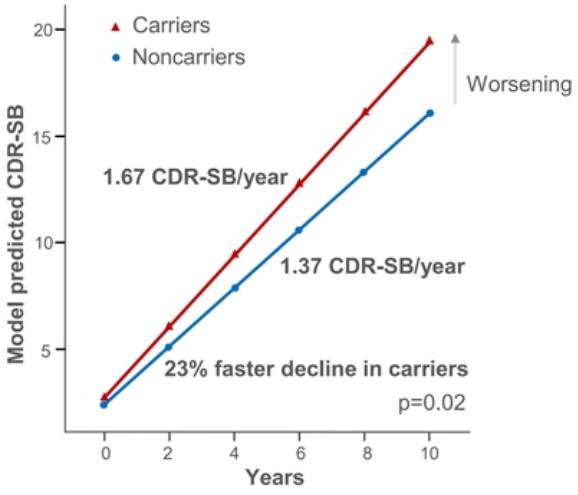
TREM2 Agonism Enhanced Barrier Function and Phagocytosis Resulting in Reduced Neuronal Loss in *in vitro* and Animal Models of AD



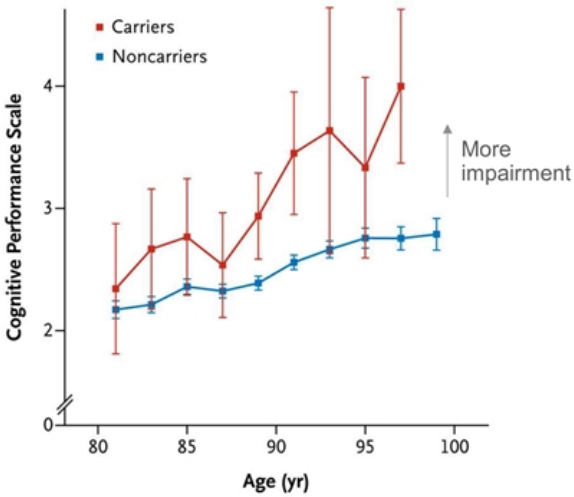
NHD – Nasu Hakola; PLOSL - Polycystic Lipomembranous Osteodysplasia; FTD – Frontotemporal Dementia; ALSP - Adult-onset Leukoencephalopathy with Axonal Spheroids Pigmented Glia
Golde T. *Neuron* (2019); Lewcock JW et al. *Neuron* (2020); Wang S et al *JEM* 2020

TREM2-R47H Variant Carriers Exhibit Faster Decline & Worse Cognition Compared to Non-Carriers

Individuals with AD



Cognitively Normal Elderly



Jonsson T et al. *NEJM* (2013); Del-Aguila JL et al. *J Alzheimer's Dis.* (2018)

VG-3927: Well-Positioned for Clinical Development in AD

- Orally bioavailable brain penetrant small molecule
- Potent and highly TREM2-specific
- Potentiates TREM2 response to natural damage ligands across different AD-associated genetic TREM2 variants
- Optimal balance of promoting neuroprotective function and suppressing proinflammatory activity of microglia
- Preliminary data showing impact on AD pathophysiology in an animal model of AD
- Clear target engagement in non-human primates

VG-3927 Has Potential to Address Unmet Needs & Opportunities in AD

Drive greater efficacy

- Boosting microglial repair functions
- Impact broader disease pathophysiology

Mitigate ARIA

- No Fc-mediated interactions
- Specificity of response to disease microenvironment
- Favorable kinetic profile vs mAbs

- **Convenient oral option** vs i.v. infusion of immunotherapies

- **Small molecule** optimal for combination therapy and AD prevention paradigms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NEURO
Clinical Development of VG-3297, Vigil's Small Molecule TREM2 Agonist
David Gray, PhD
Chief Science Officer
Vigil Neuroscience, Inc.
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VG-3927 Phase 1 Trial in Healthy Volunteers

Trial Population	▪ Healthy volunteers (HVs) including an elderly cohort
Trial Design	▪ Double-blind, placebo-controlled ▪ Single (SAD) & multiple (MAD) ascending dose cohorts
Treatment Duration	▪ VG-3927 or placebo (oral dosing) ▪ SAD – single dose ▪ MAD – once daily for 14 days
Treatment Duration	▪ Safety and tolerability ▪ Pharmacokinetics (PK) ▪ Pharmacodynamics (PD) based on CSF biomarkers (sTREM2, sCSF1R, osteopontin)

VG-3927: Early-stage Clinical Strategy to De-risk Development for AD

Phase 1 *Healthy Volunteers*	▪ Safety, tolerability, PK & PD ▪ SAD/MAD in healthy volunteers includes an elderly cohort in MAD ▪ Target engagement: based on CSF levels of sTREM2; downstream PD: based on sCSF1R and osteopontin in CSF ▪ Dosing to commence in Oct 2023 ▪ Interim data on SAD/MAD cohorts in mid-2024
Phase 1b *AD Patients*	▪ Safety and proof-of-pharmacology in symptomatic AD patients ▪ Characterize pharmacology in genetic subpopulations including disease associated TREM2 variant carriers to inform patient population for future clinical development
Phase 2/PoC *AD Patients*	▪ Phase 1b to inform on target AD population and study design to assess safety and proof-of-concept in symptomatic AD patients


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Closing Remarks
Ivana Magovčević-Liebisch, PhD, JD
Chief Executive Officer
Vigil Neuroscience, Inc.
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VG-3927: Differentiated Oral TREM2 Agonist with De-risked Precision-based Clinical Strategy for AD

- **First & only** small molecule TREM2 agonist entering clinical development
- Harnesses **neuroprotective activity of microglia** via highly-potent & specific TREM2 agonism
- **Differentiated** profile to potentially address AD therapeutic needs:
  - **Unique MoA** (potentiation of TREM2 response to natural damage ligands) for **improved efficacy & safety**
  - Activates microglia with **broad non-inflammatory profile**
  - Absence of Fc-effector domain & **favorable PK for ARIA mitigation/management**
  - **Amenable** to future combination treatment regimens
  - **Convenient & patient-friendly** oral dosing
- Genetically guided precision-based clinical strategy to **de-risk** drug development

VG-3927 Small Molecule TREM2 Agonist Milestones

☑ Submit IND for VG-3927, oral small molecule TREM2 agonist	**Q3 2023**
☐ Begin Phase 1 dosing of VG-3927 in healthy volunteers	**Oct 2023**
☐ Report interim Phase 1 SAD/MAD data of VG-3927 in healthy volunteers	**Mid-2024**

Vigil is Well-positioned to Execute on Our Mission


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