# Vigil Neuroscience
## Small Molecule KOL Event

*September 13, 2023*

vigil™ NEURO

vigilant for you®

# 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.


# Corporate Overview

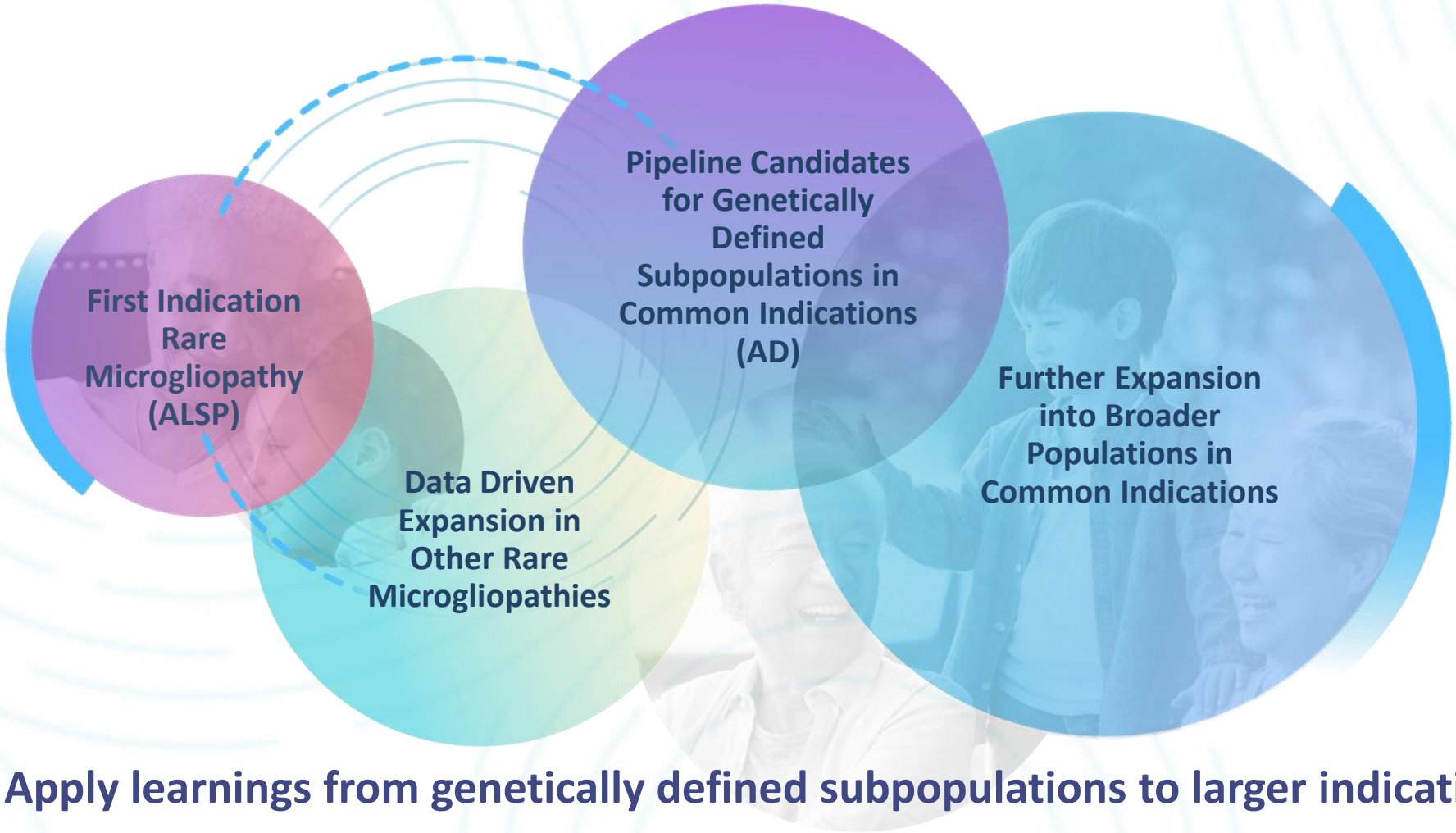
**Ivana Magovčević-Liebisch, PhD, JD**
*Chief Executive Officer*
*Vigil Neuroscience, Inc.*

# 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

## Vigil Neuroscience

**TREM2 mAb in Development for ALSP: VGL101**

*The **ONLY** targeted drug candidate in development for ALSP*

+

**Small Molecule TREM2 Agonist in Development for AD: VG-3927**

*The **1st & ONLY** TREM2 small molecule agonist entering clinical development*

# 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*

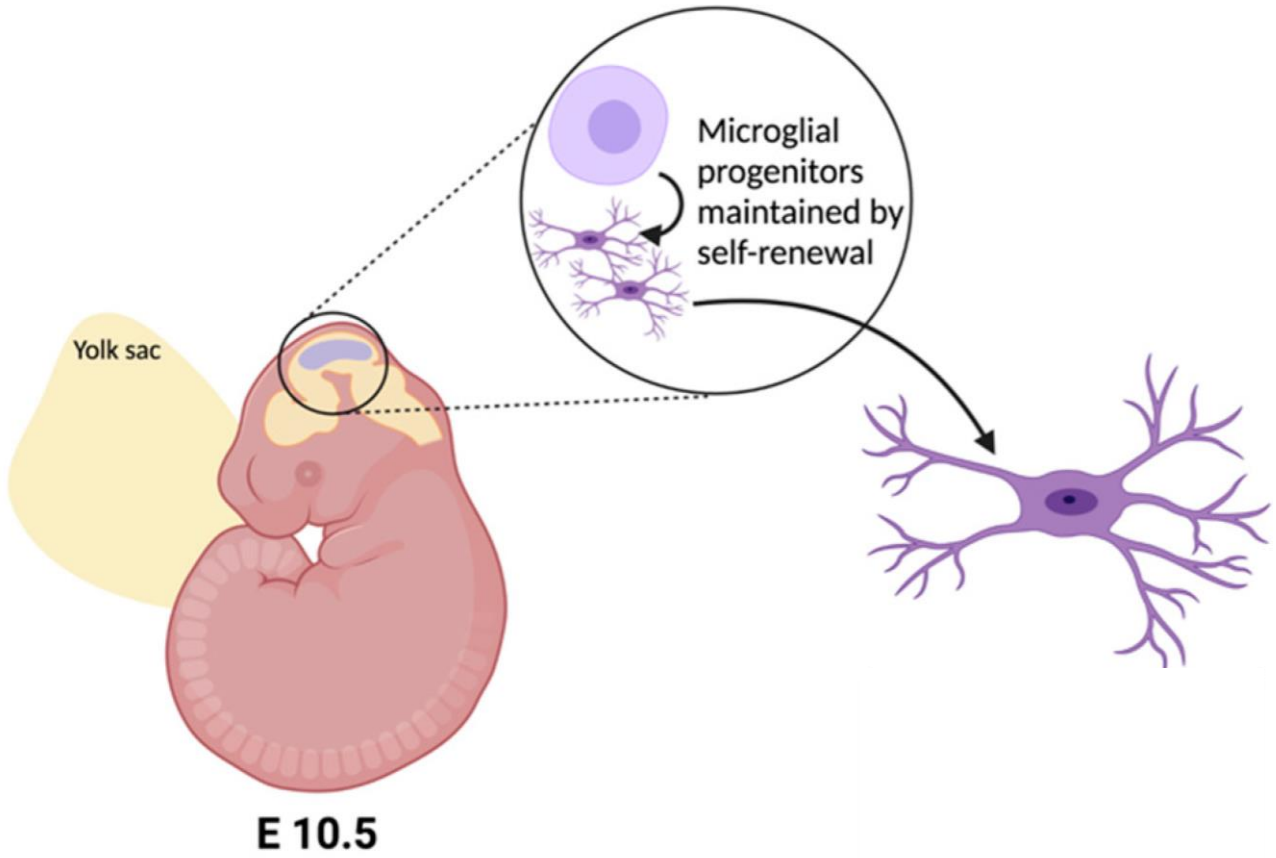
**Samuel E. Gandy, MD, PhD**
*Mount Sinai Professor of Alzheimer's Disease Research,*
*Professor of Neurology & Psychiatry*
*Associate Director of Mount Sinai Alzheimer's Disease Research Center, NYC*
*Past Chairman, National Medical & Scientific Advisory Council of the Alzheimer's Association*

# 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**

Washington University in St. Louis
School of Medicine

# Unique Developmental Origin of the Brain Resident Immune System




**Microglial-specific Markers:**

CD11b

$CD45^{low}$

$Cx3cr1^{high}$

Tmem119

FCRLS

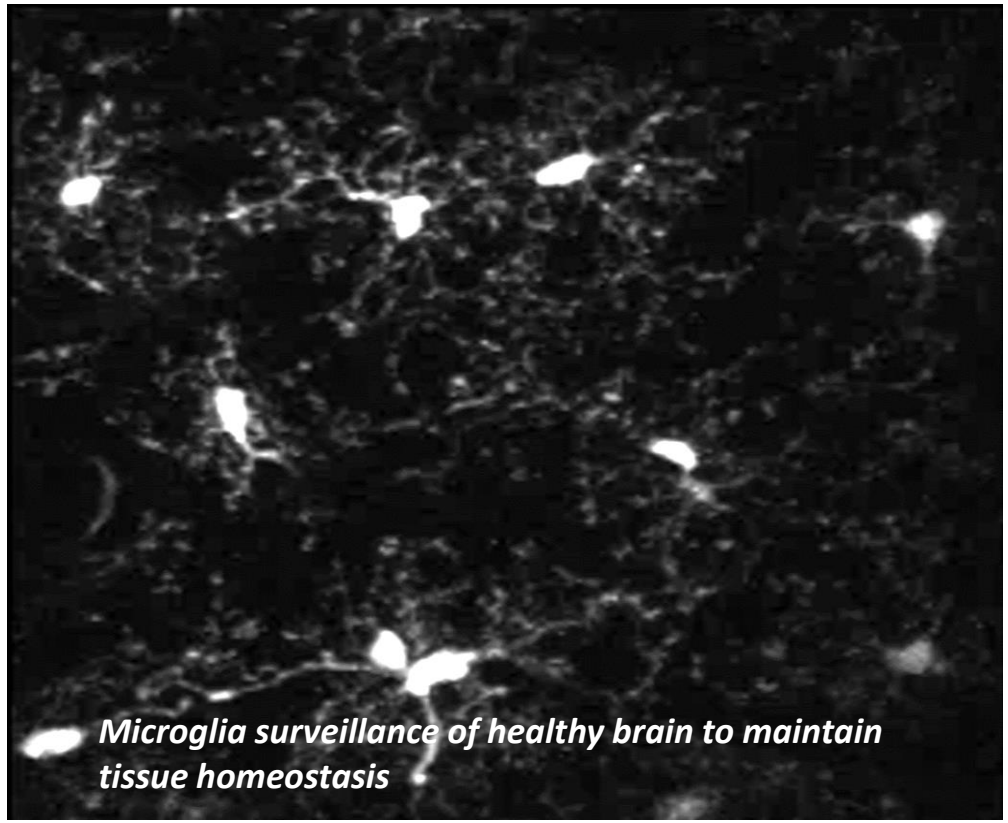
P2RY12

Sall1

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

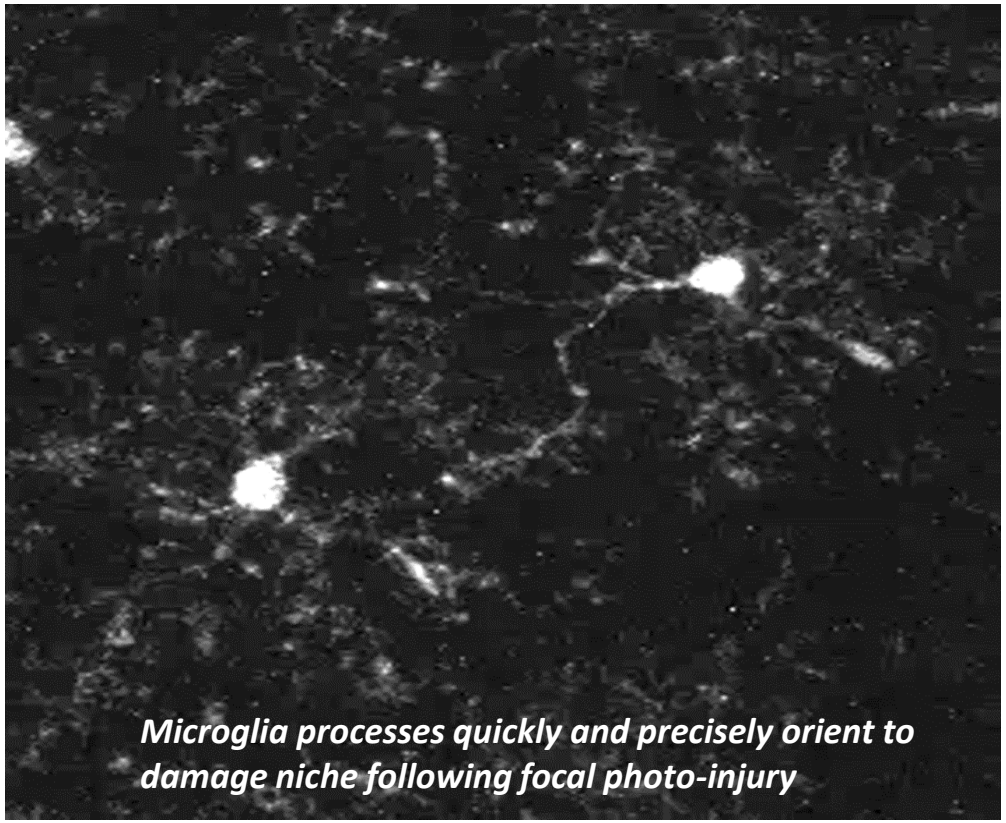
# Microglia in Healthy & Disease States

## Microglia are Key to Maintaining Normal Brain Homeostasis and Neuronal Function



*Microglia surveillance of healthy brain to maintain tissue homeostasis*

## Microglia are Brain-resident First Responders to Acute Brain Injury

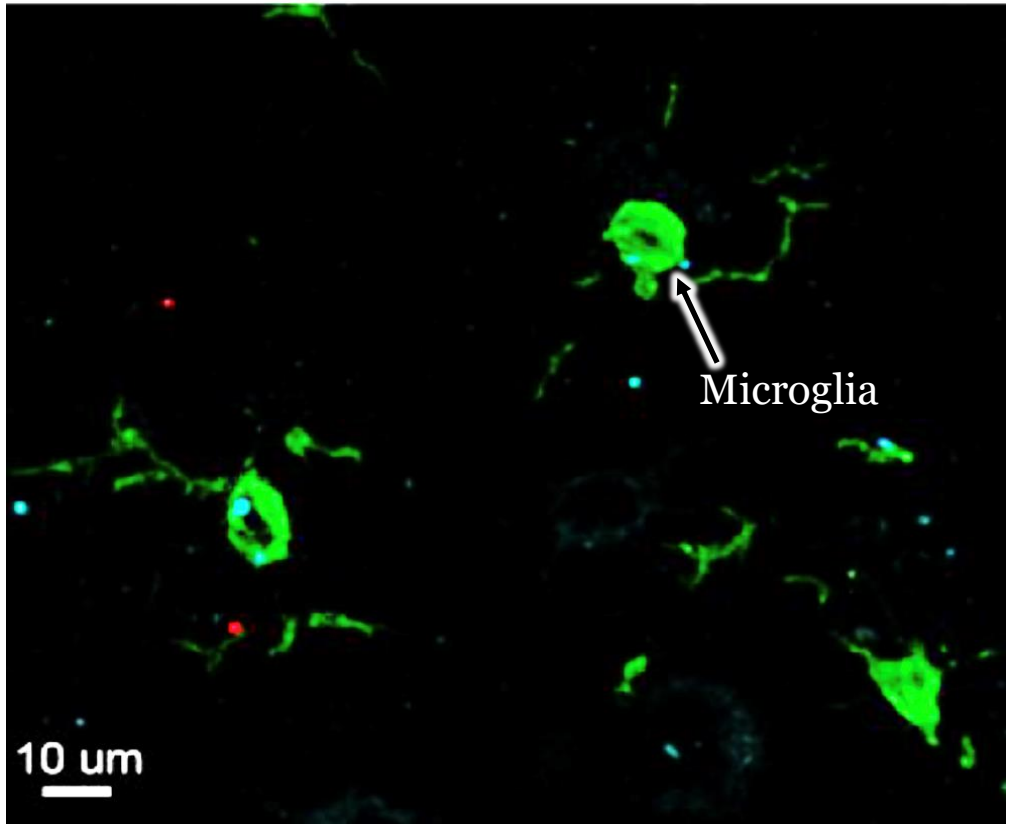


*Microglia processes quickly and precisely orient to damage niche following focal photo-injury*

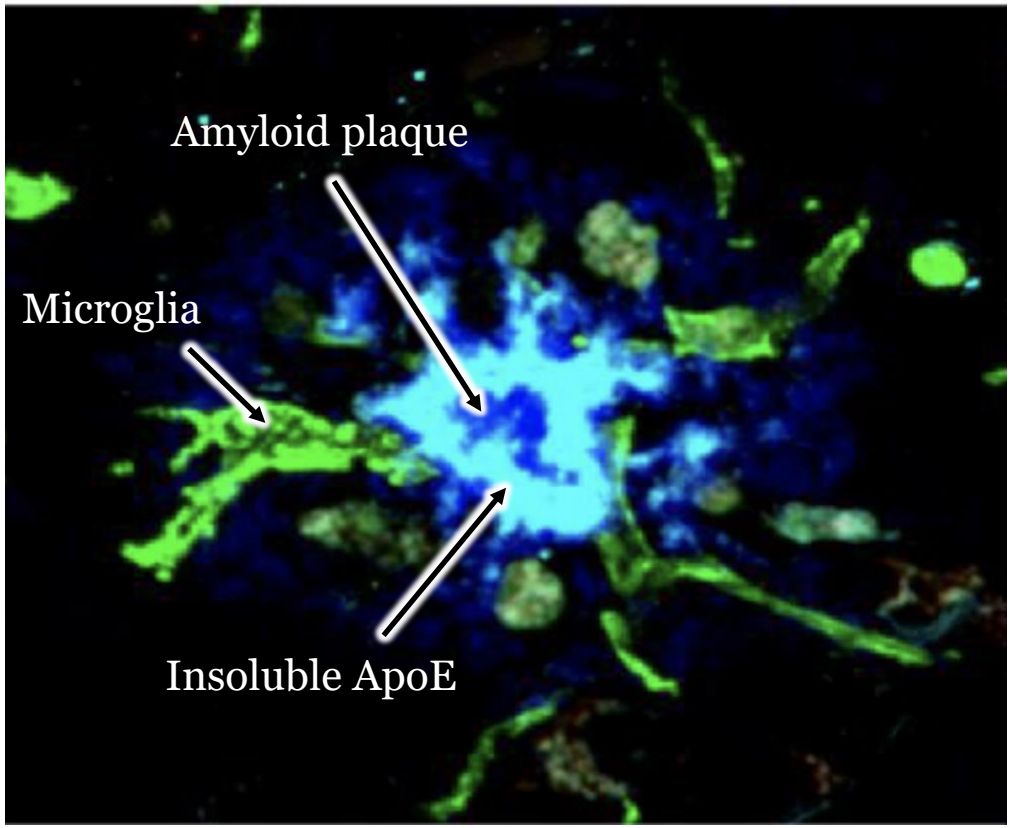
*Nimmerjahn, A et al. (2005) Science*

# Microglia Migration into AD's Neuropathological Amyloid Plaque Microenvironment

## Healthy Control Brain




## Alzheimer's Disease Brain

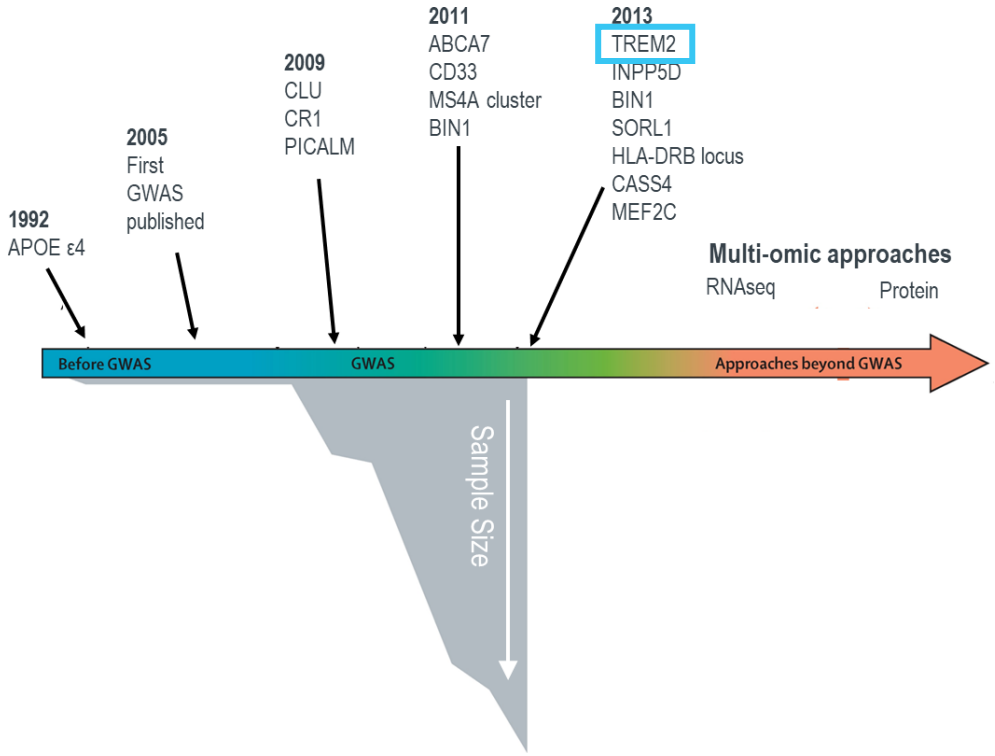



Microglia marker  Amyloid plaque  Aggregated ApoE

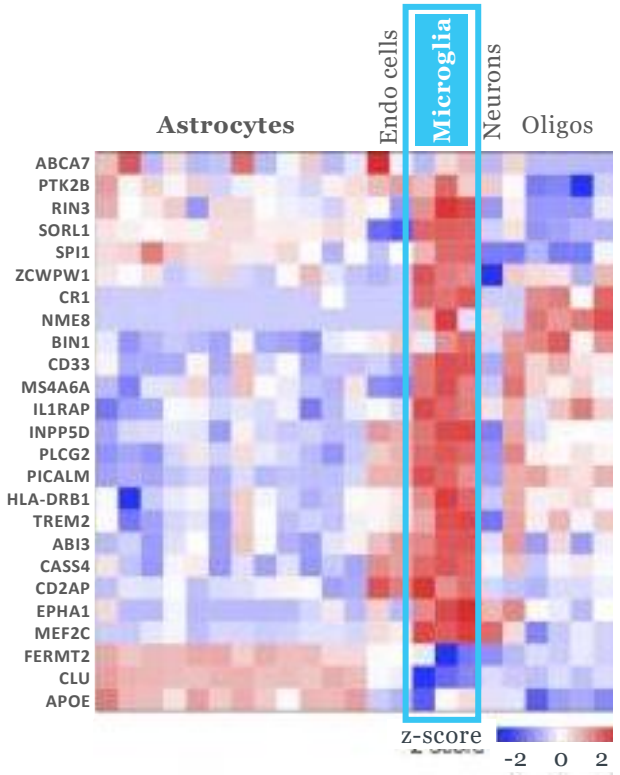
*Colonna Lab, unpublished data*

# 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

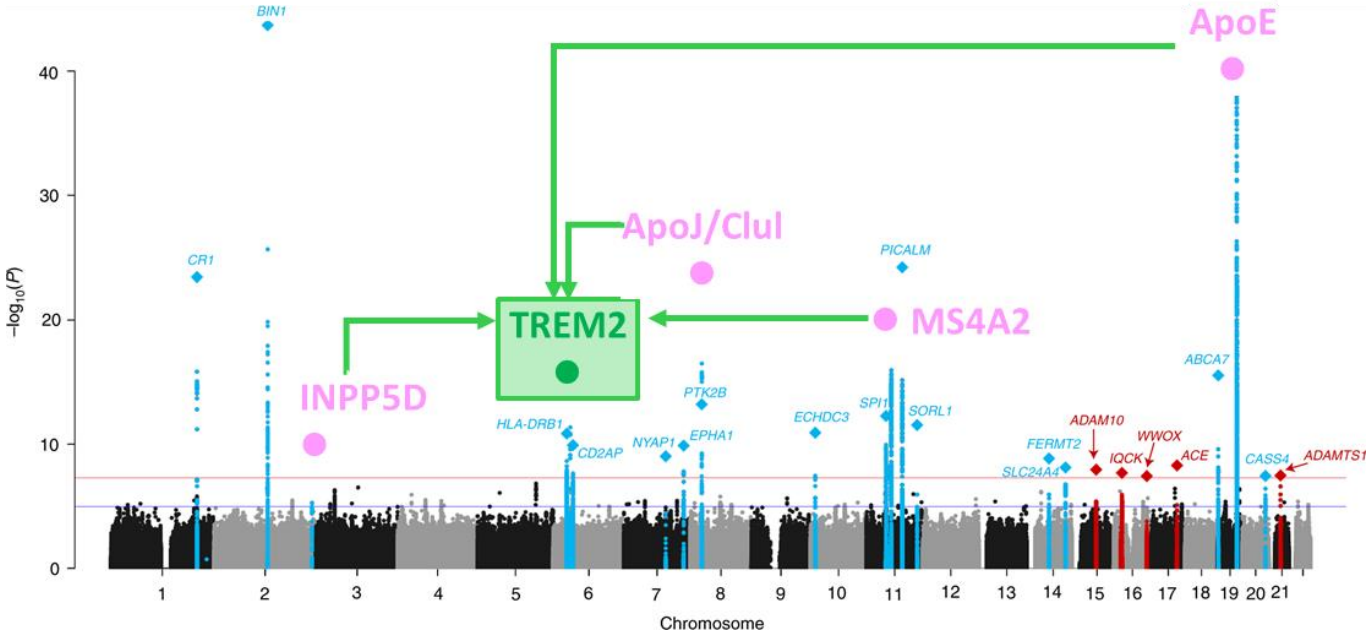



*Cuyvers, E and Sleegers, K (2016) Lancet Neurology; Hansen, DV et al. (2018) J Biol Chem*

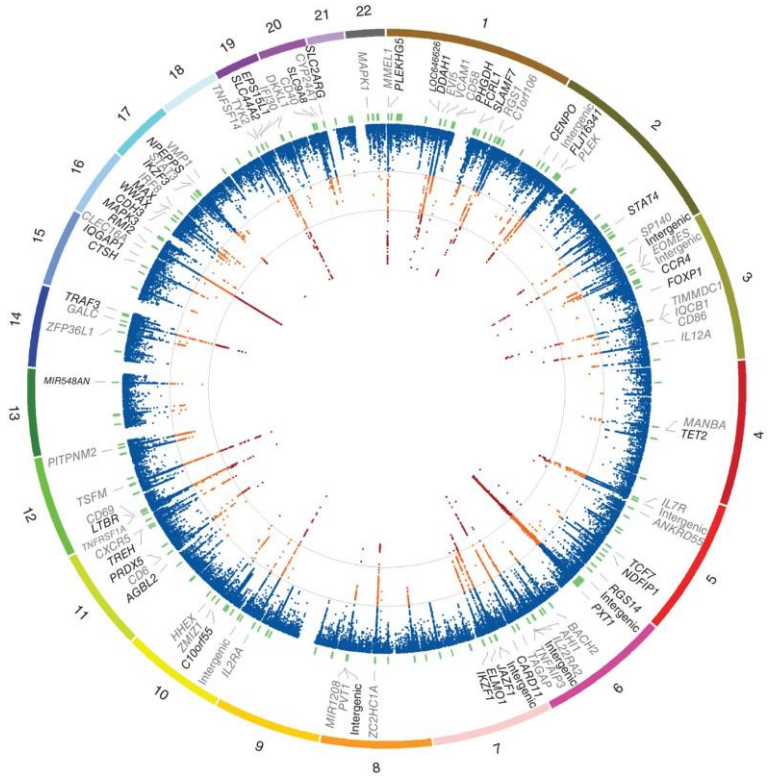
# Targeting Neuroimmunology Specifically for Alzheimer's Disease

## 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

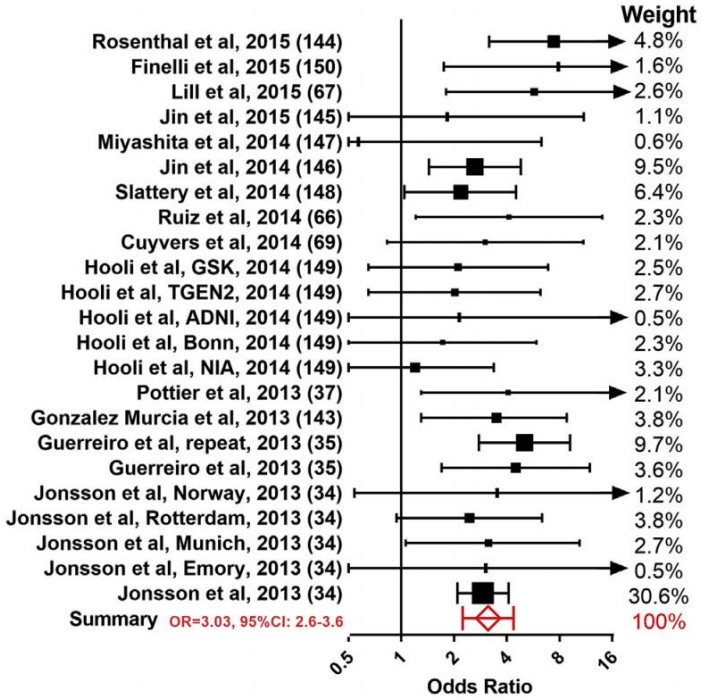


*Adapted from Kunkle, BW et al (2019) Nature Genetics; International Multiple Sclerosis Genetics Consortium (2013) Nature Genetics*

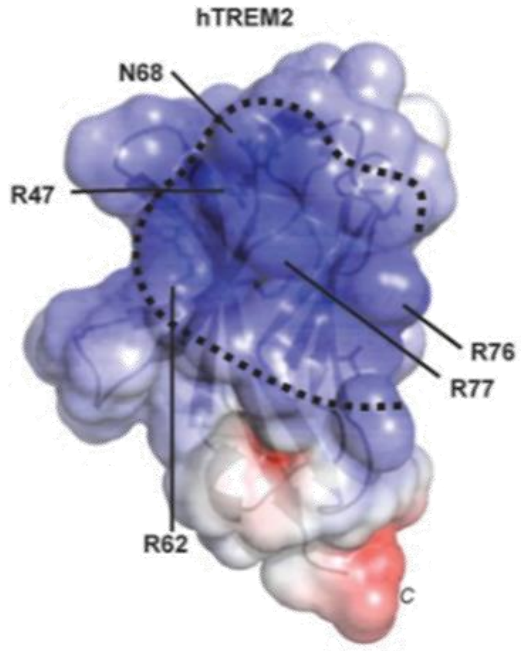
# Why All the Focus on TREM2?

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

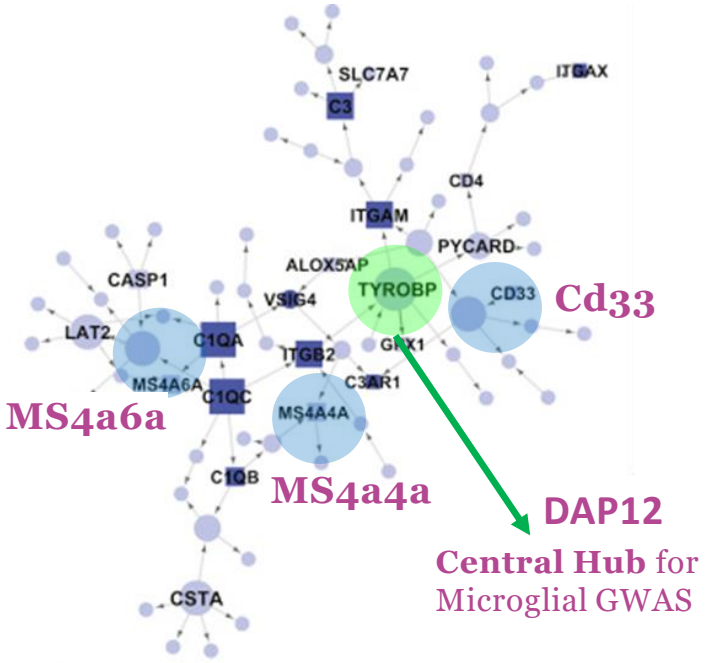
### Association of TREM2 Variants with AD Risk is Robust and Highly Replicated




### 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

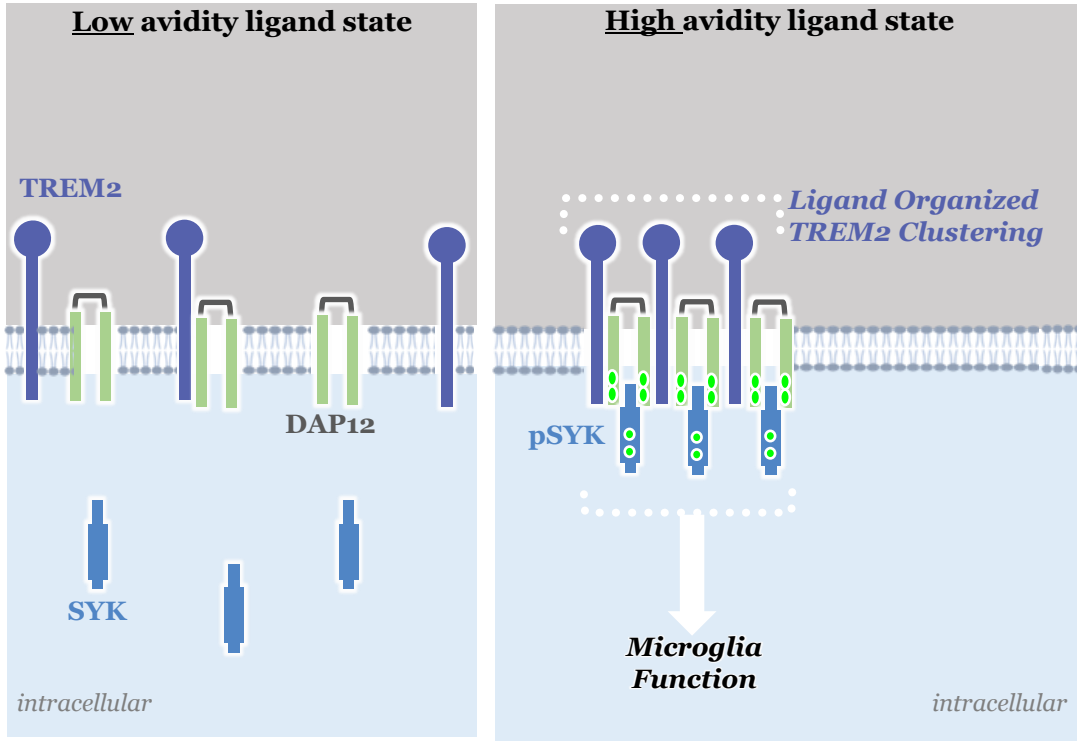



*Condello, C et al. (2018) Biol Psychiatry; Kober, D et al. (2016) eLife; Zhang, B et al. (2013) Cell*

# Microglial Loss-of-Signaling Hypothesis for TREM2

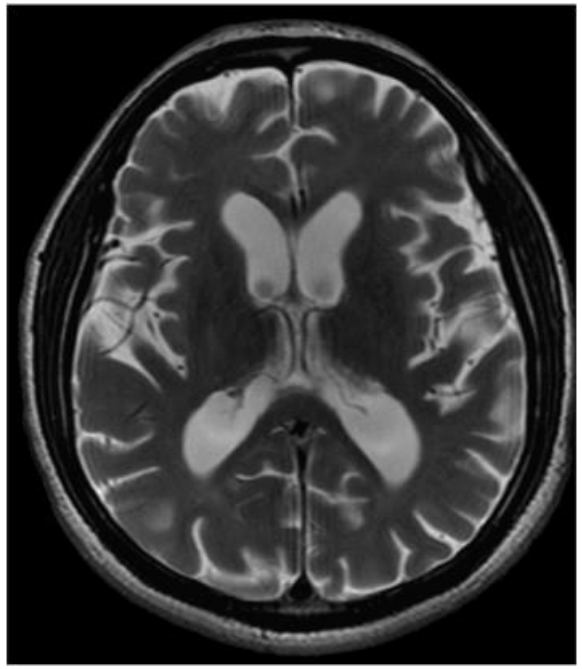
## TREM2-DAP12 Pathway & Its Importance Beyond AD

### TREM2-DAP12 Signaling Transduction and Cellular Function in Microglia

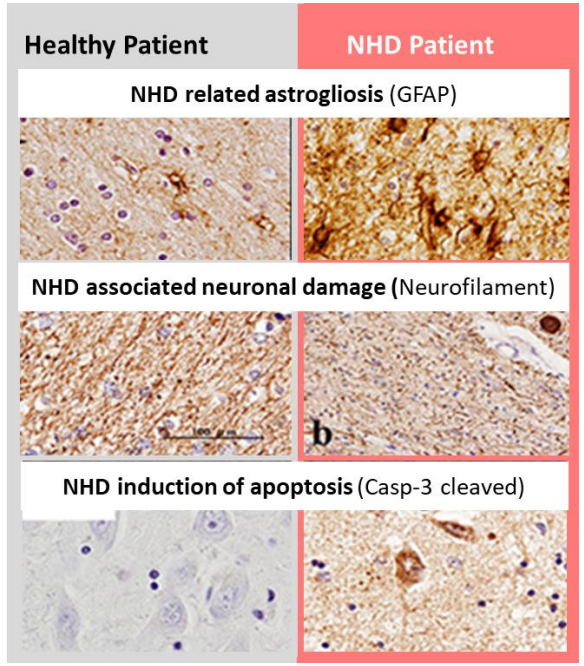



### TREM2 and DAP12 Mutations Cause Rare Early-onset Familial Microgliopathy Called Nasu-Hakola Disease (NHD)

MRI manifestations of NHD



Neuropathology in NHD patient

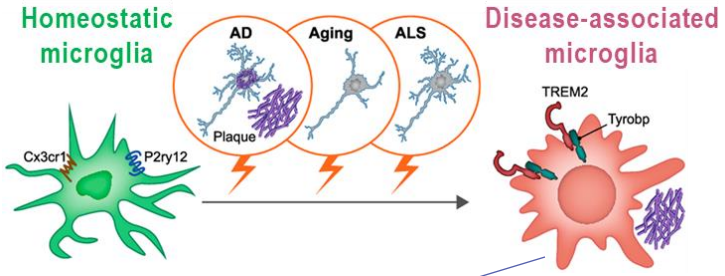



*Satoh et al. (2010) Neuropathology; Kilic et al. (2012) Clinical Imaging*

# TREM2's Role in Microglial Activation Disease State

## Molecular Evidence

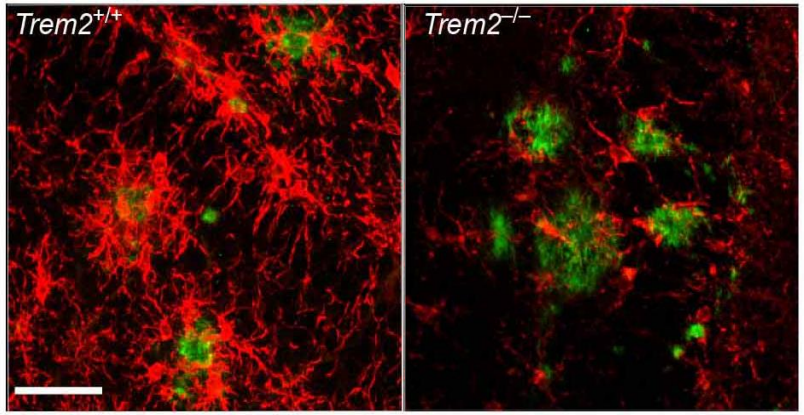
TREM2 promotes non-inflammatory, neuroprotective microglia state




**Key activated processes**
Microglia chemotaxis
Immune metabolism
Phagocytosis

## AD Mouse Models

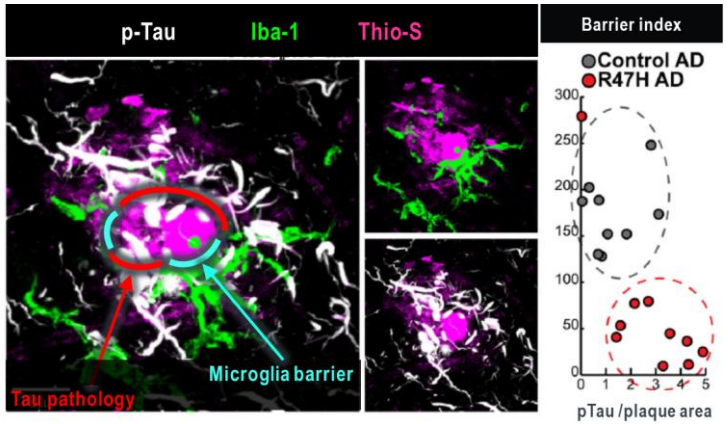
TREM2 is required for neuroprotection within the amyloid plaque niche




**Amyloid plaque** **Microglia**

## Human AD Validation

Plaque-associated microglia protect neighboring neurons




**Amyloid plaque** **Neuronal damage**

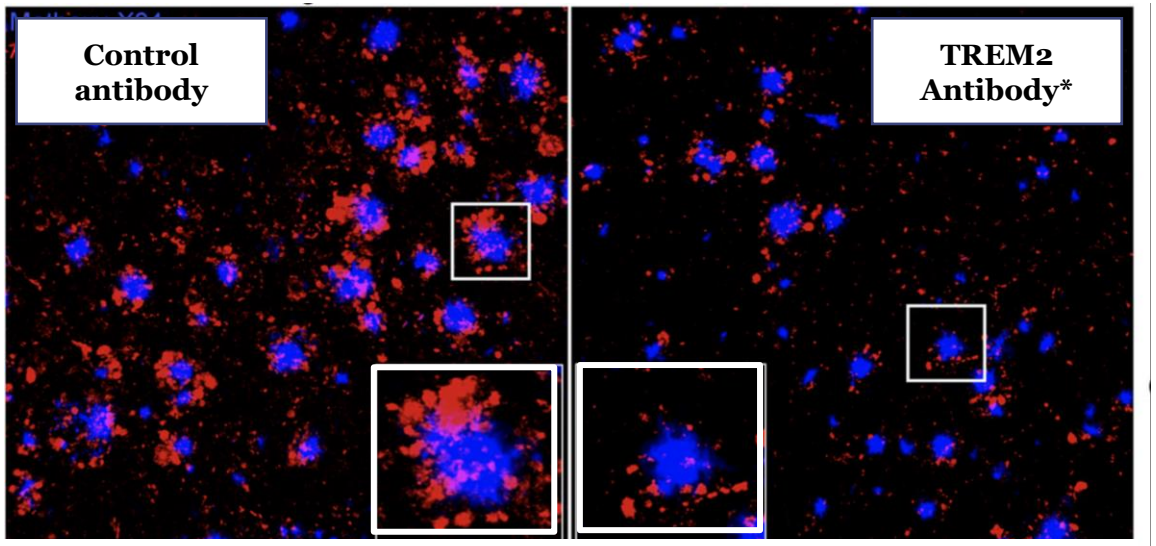
**Microglia**

*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

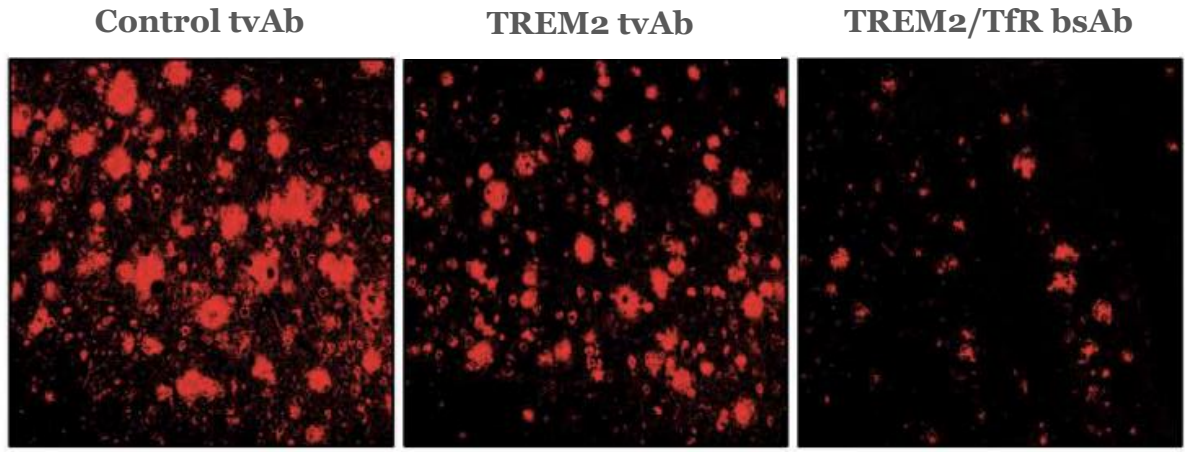
### TREM2 Agonist Antibody Reduces Neuronal Damage Locally Around Aβ Plaques




*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

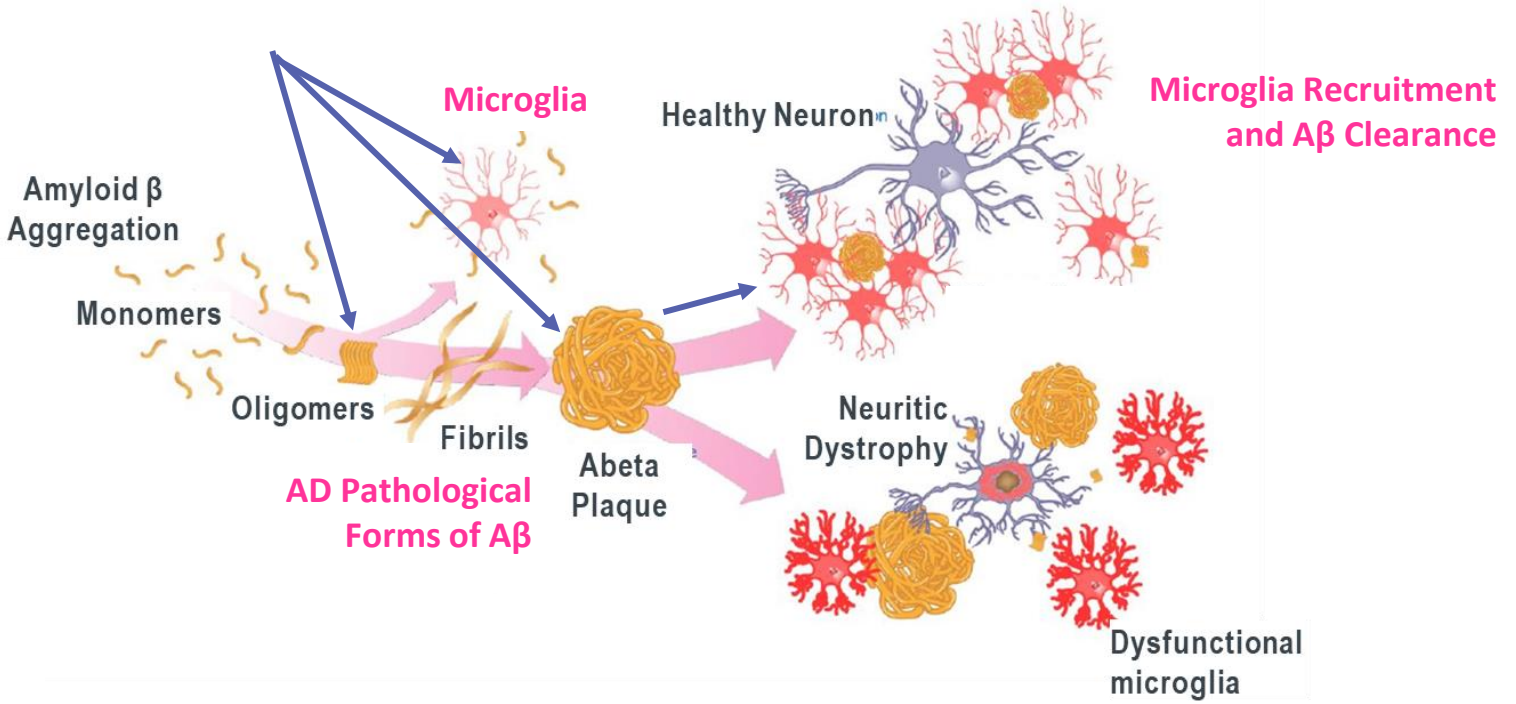
*Wang, S et al. (2020) J Exp Med*

# 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


**Washington Univ.**
Marina Cella
Susan Gilfillan

Jonathan Kipnis
Igor Smirnov

David M. Holtzman
Jason Ulrich

**Weizmann Institute**
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.*

vigil™ NEURO

vigilant for you®

# VG-3927: First & Only Clinical Oral Small Molecule TREM2 Agonist

## We Are Microglia Experts

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

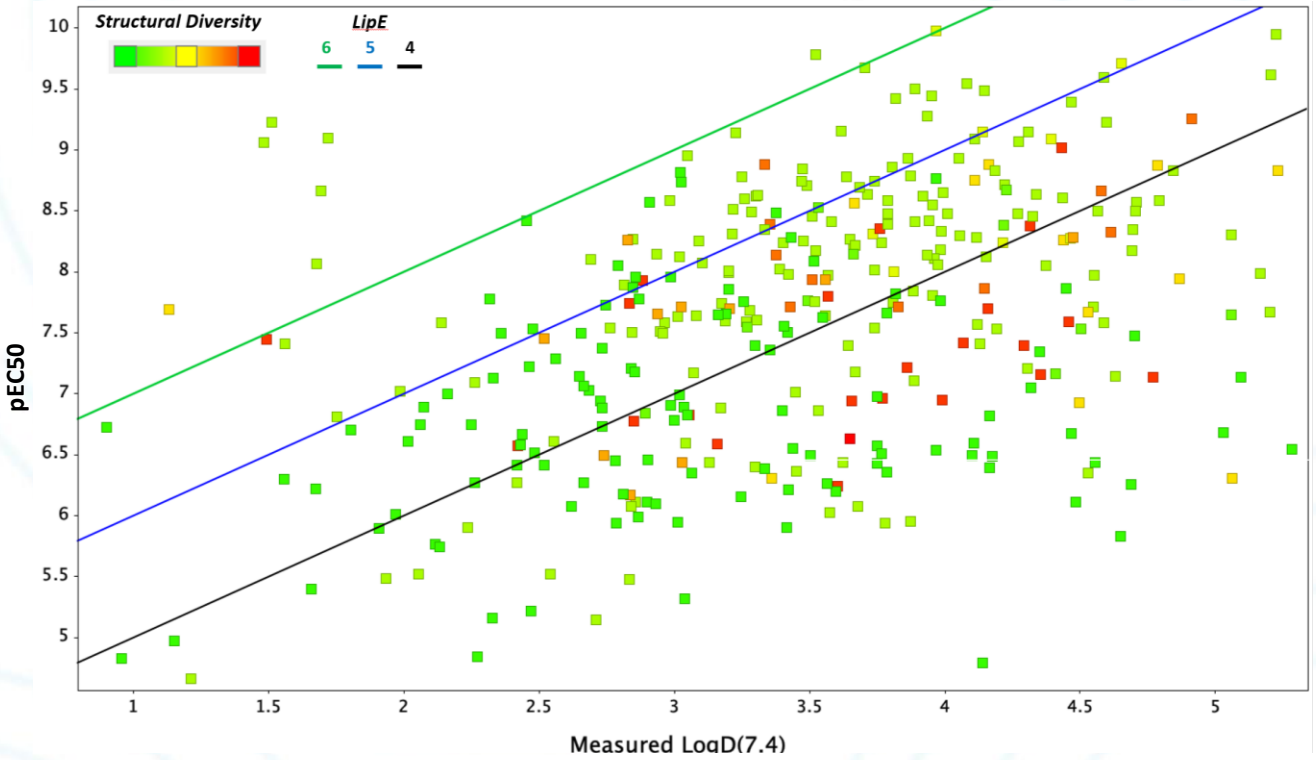
**Potent TREM2 agonism synergizes with natural damage ligands**

**Broad and favorable modulation of neuropathology**

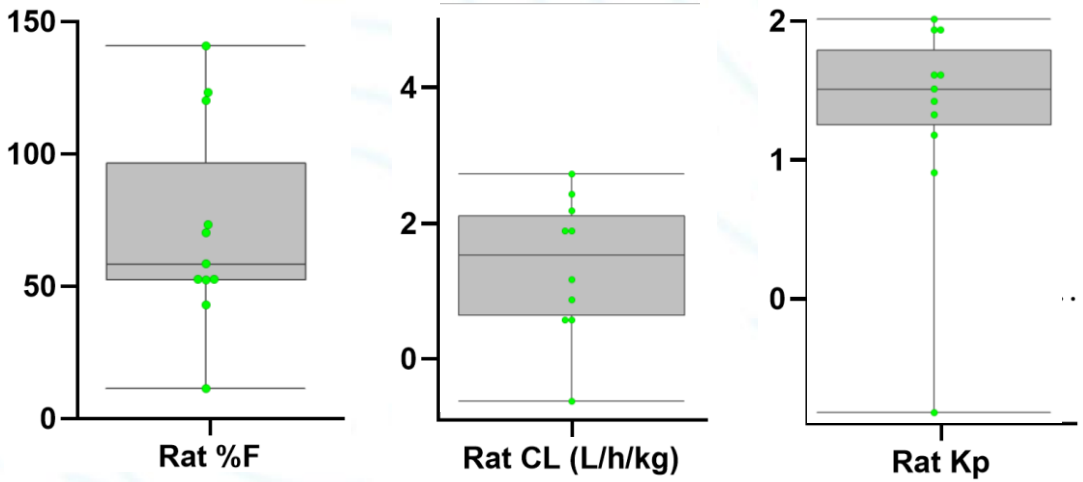
# VG-3927 Selected from High Quality Chemical Matter

## *Deep Understanding of MoA with Multiple Excellent Back-up Compounds*

### Highly Efficient and Structurally Diverse




### Target Coverage in CNS via Oral Dosing



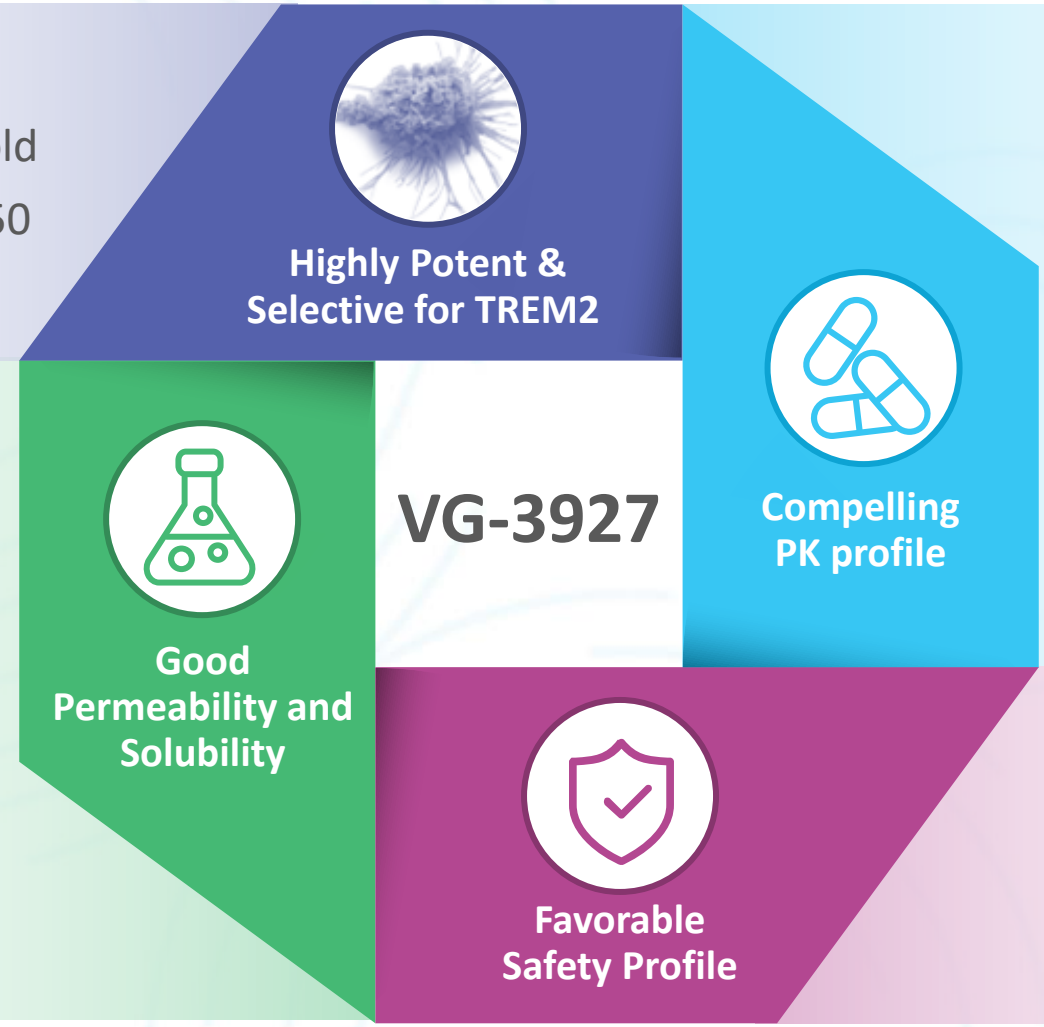

### Strong Development Path

- 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

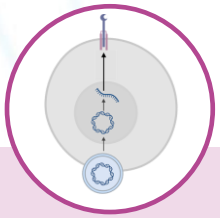


*$EC_{50}$: half maximal effective concentration; PK: pharmacokinetics; QD: once-daily; CSF: cerebrospinal fluid; CYP: cytochrome P450 enzymes; TDI: time-dependent inhibition; hERG: human ether-a-go-go-related gene; SIF: stimulated intestinal fluids; MDCK Papp: Madin-Darby canine kidney apparent permeability;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

# Establishing VG-3927 for Development in AD

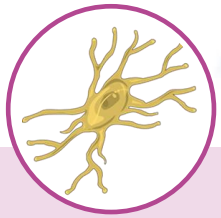
## *Pharmacological & Clinical Translation*

### VG-3927 Pharmacological Profile



**TREM2 engineered systems**

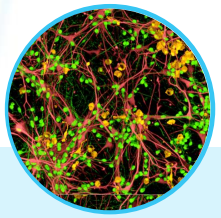
High-throughput profiling



**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**

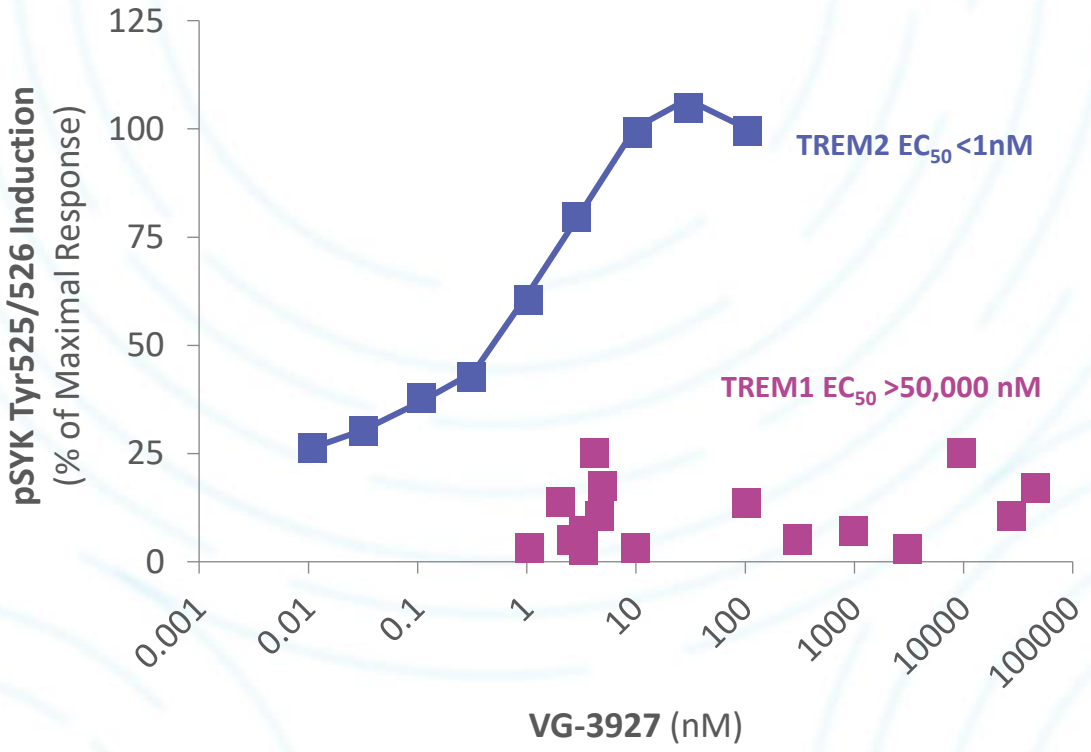
Established preclinical AD transgenic mice

**Nonhuman primate profiling**

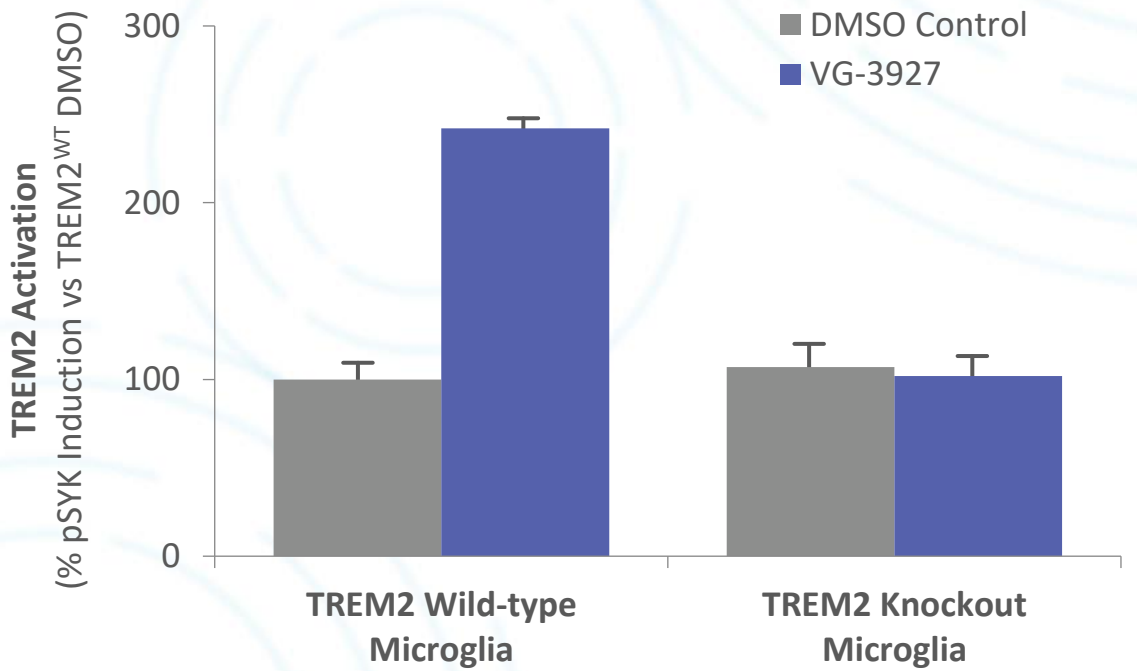
ID and validation of translational biomarkers

# 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

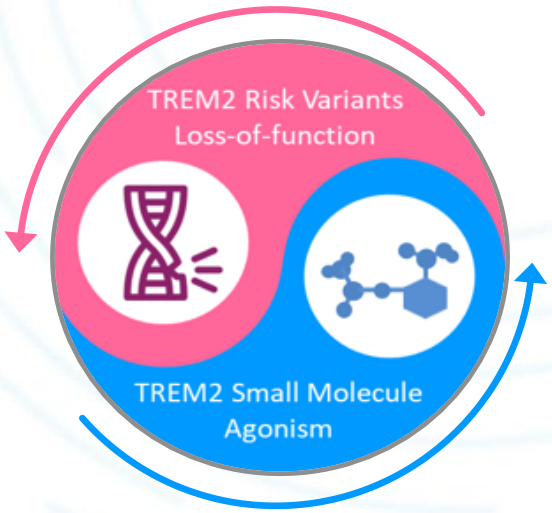



*DMSO: dimethyl sulfoxide*

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

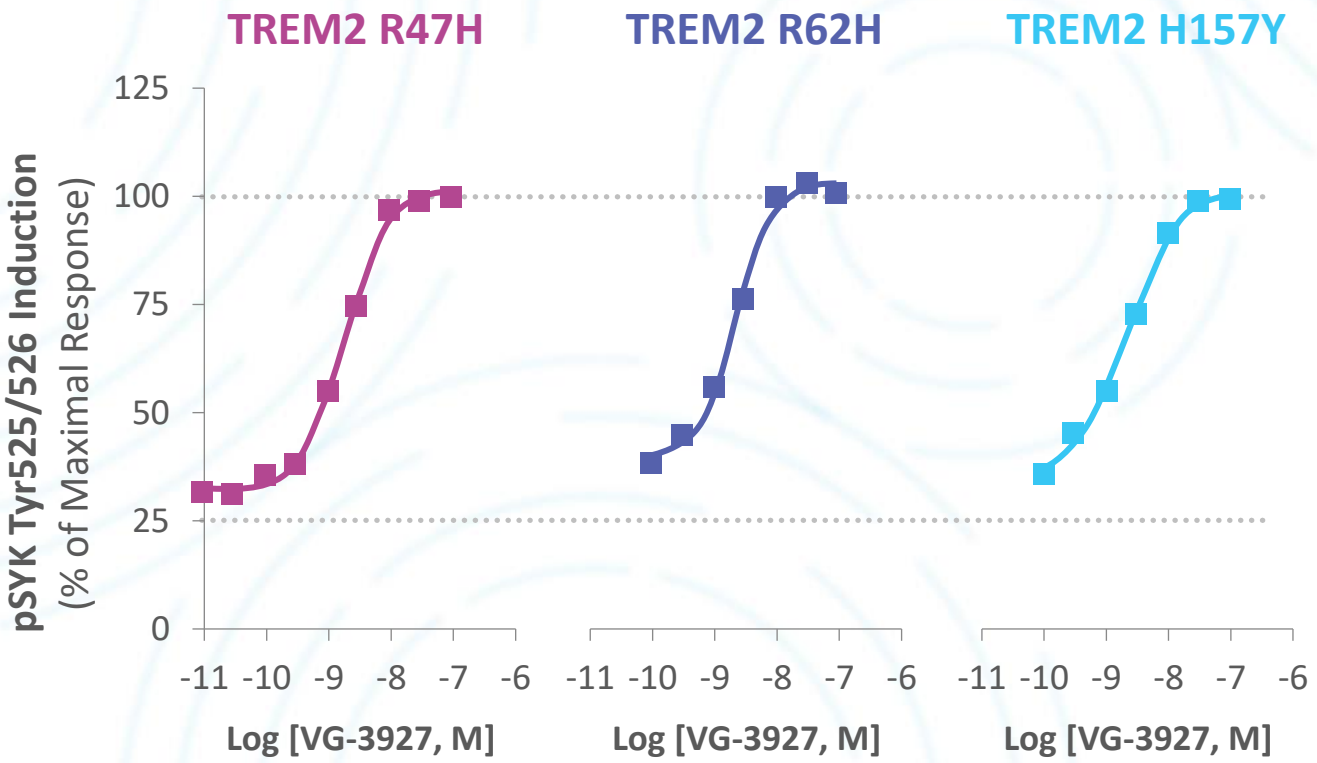
## *Supports Precision-based Clinical Development*

### Vigil Precision AD Strategy




**Accelerated Path to Successful Clinical POC**

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

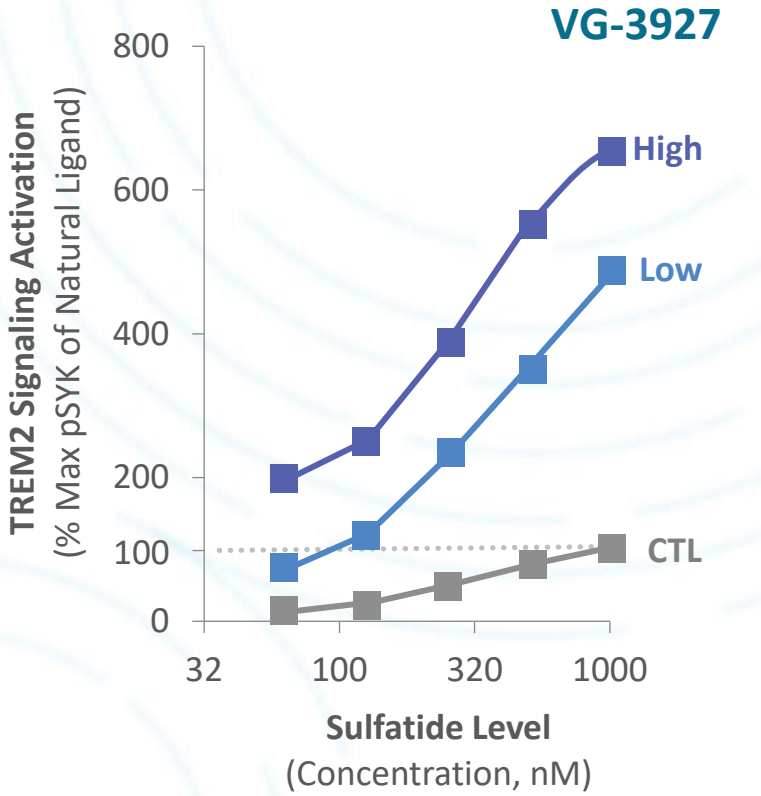



| TREM2 Variant | Highly Potent |
|---|---|
| Common Variant | ✓ |
| R47H | ✓ |
| R62H | ✓ |
| H157Y | ✓ |
| T96K | ✓ |

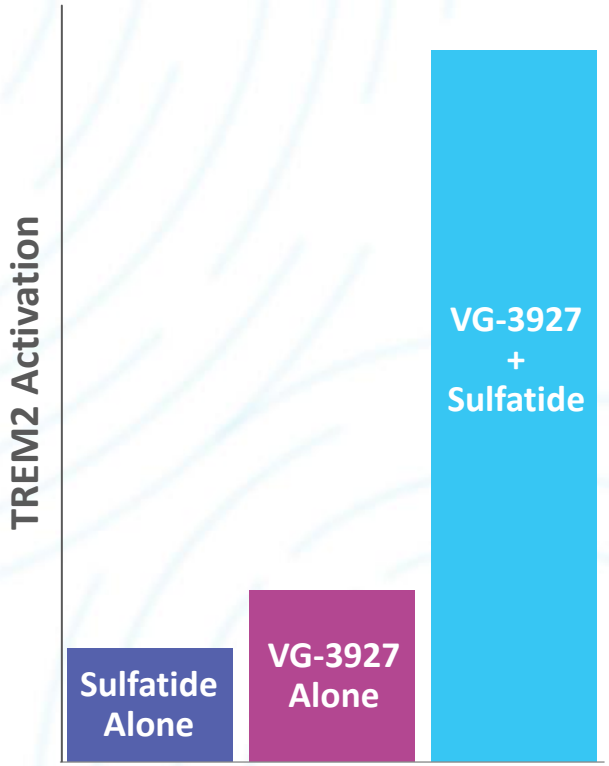
# VG-3927 Potentiates Signaling of Damage-associated Ligands

## *Damage-associated Ligand: Sulfatide*

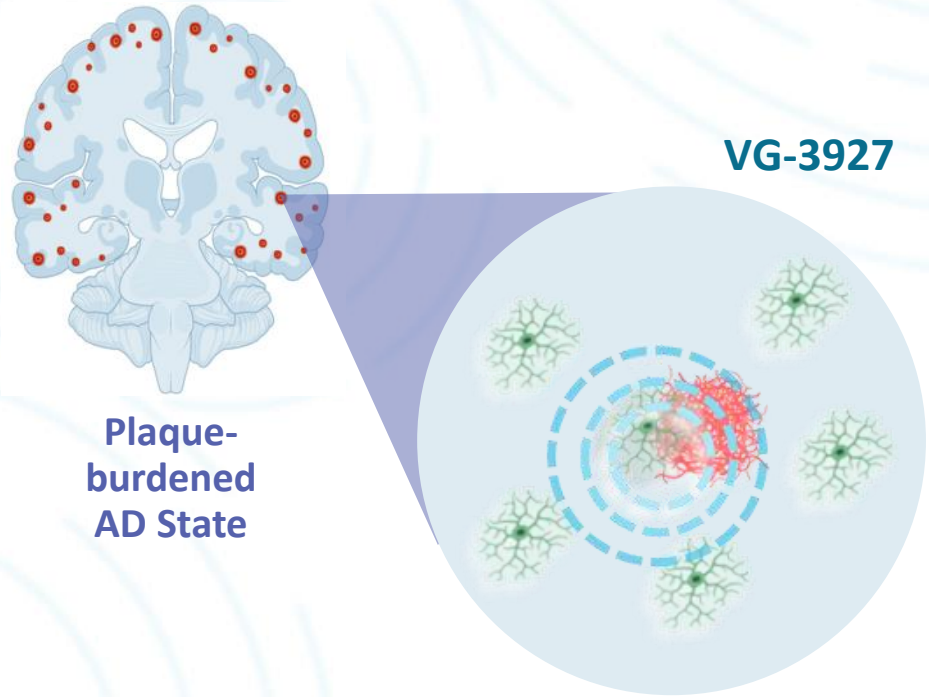
### TREM2 Signaling Activation




### Potentiation of TREM2 Activation




### Focusing Efficacy in Pathological Microenvironments




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

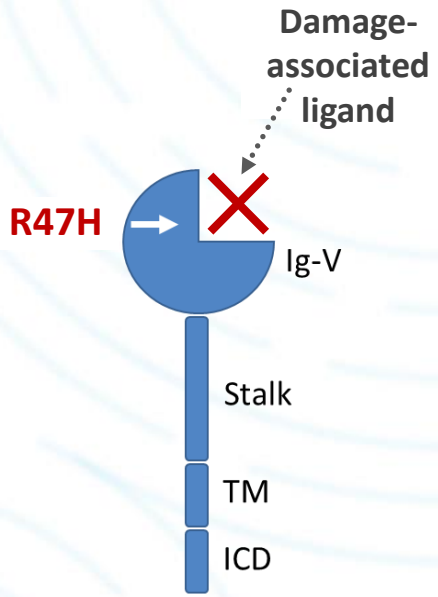
# TREM2 AD-risk Variants Are Loss of Function & Impact Signaling

## *Example: R47H Leads to Defective Sensing of Sulfatide*

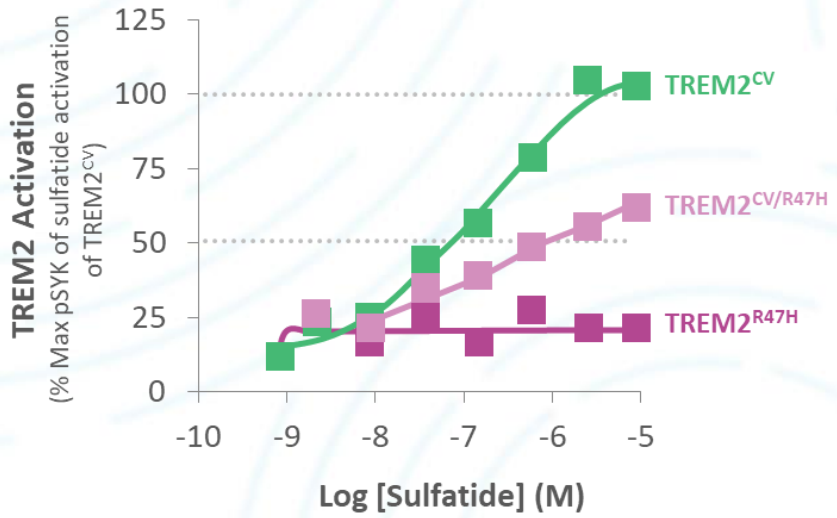
**TREM2$^{R47H}$ Variant**

**Mutation Impact:**

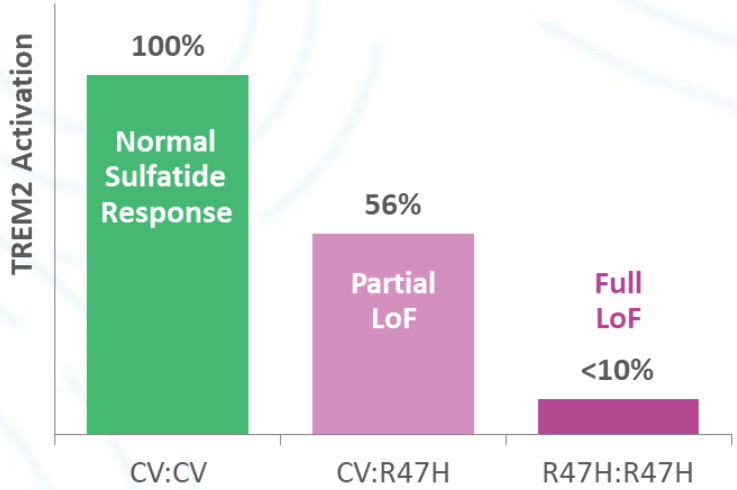
- Missense in ligand binding domain
- Loss of TREM2 response to sulfatide (damage-associated ligand)




**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*

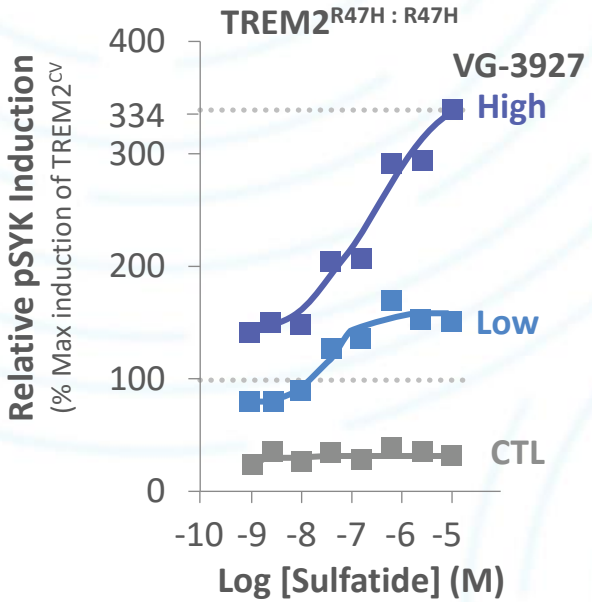
# VG-3927 Restores TREM2 Response to Damage-associated Ligand in R47H

## *Rescues Signaling Impairment in AD-risk Variant*

**VG-3927**
**TREM2 SM for AD**

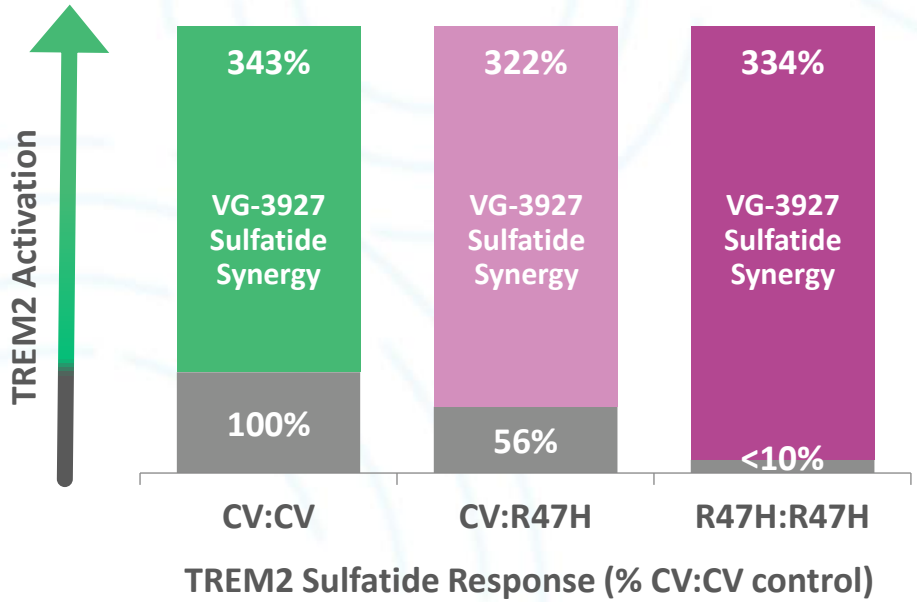
- TREM2-R47H defective response to damage-associated ligand (sulfatide)
- VG-3927 rescues signaling and response to sulfatide
- Similar effects observed in TREM2 R62H AD-risk variant

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



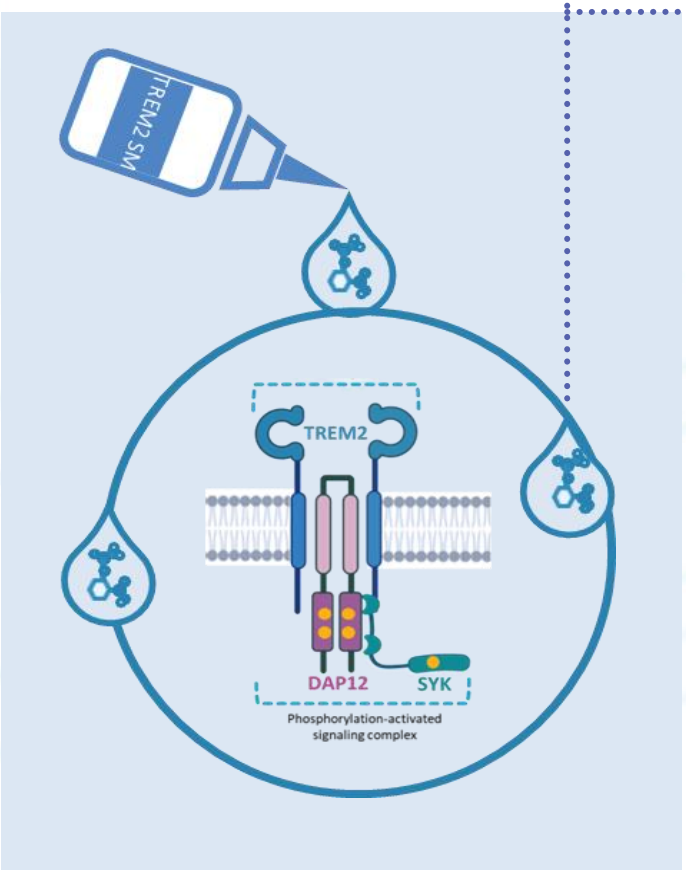

CTL: control; Low: VG-3927 at 1 nM; High: VG-3927 at 100 nM

### VG-3927 Fully Restores TREM2 R47H Defect

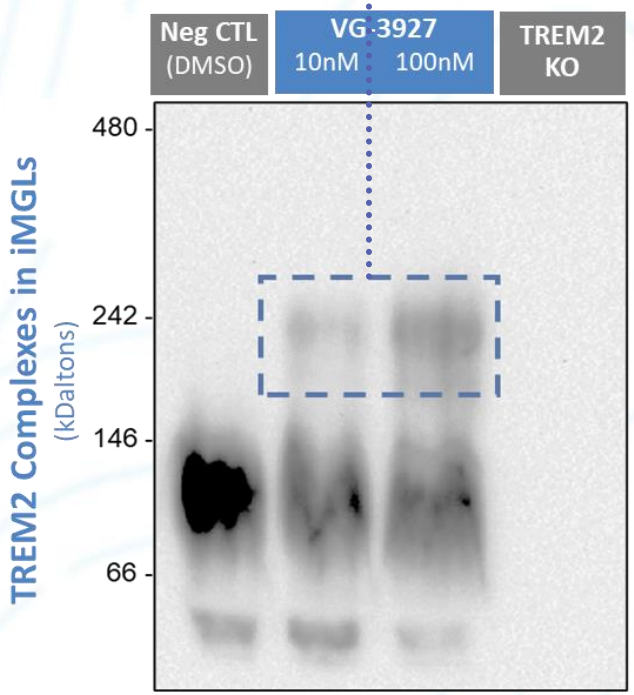


# VG-3927 Acts as a Molecular Glue to Stabilize TREM2 Complex

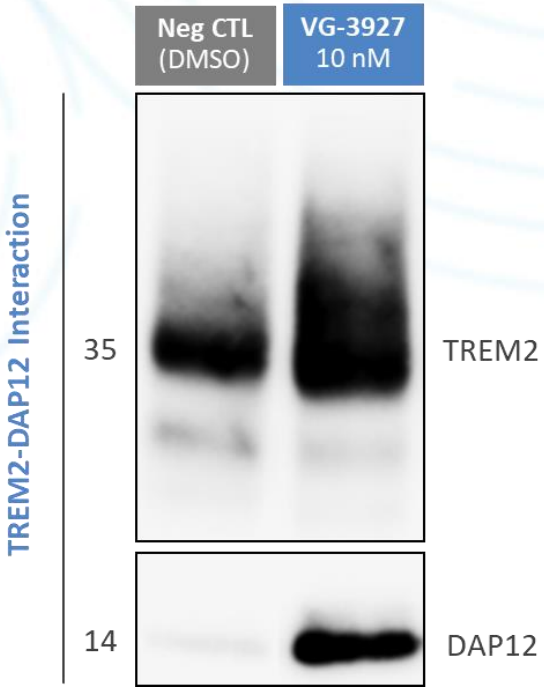
## *Novel Mechanism of Action*




***Higher molecular weight band reveals novel receptor ligand complex***




*Non-denatured states (Native PAGE) in iMGLs*




*TREM2 immunoprecipitation in HEK system*

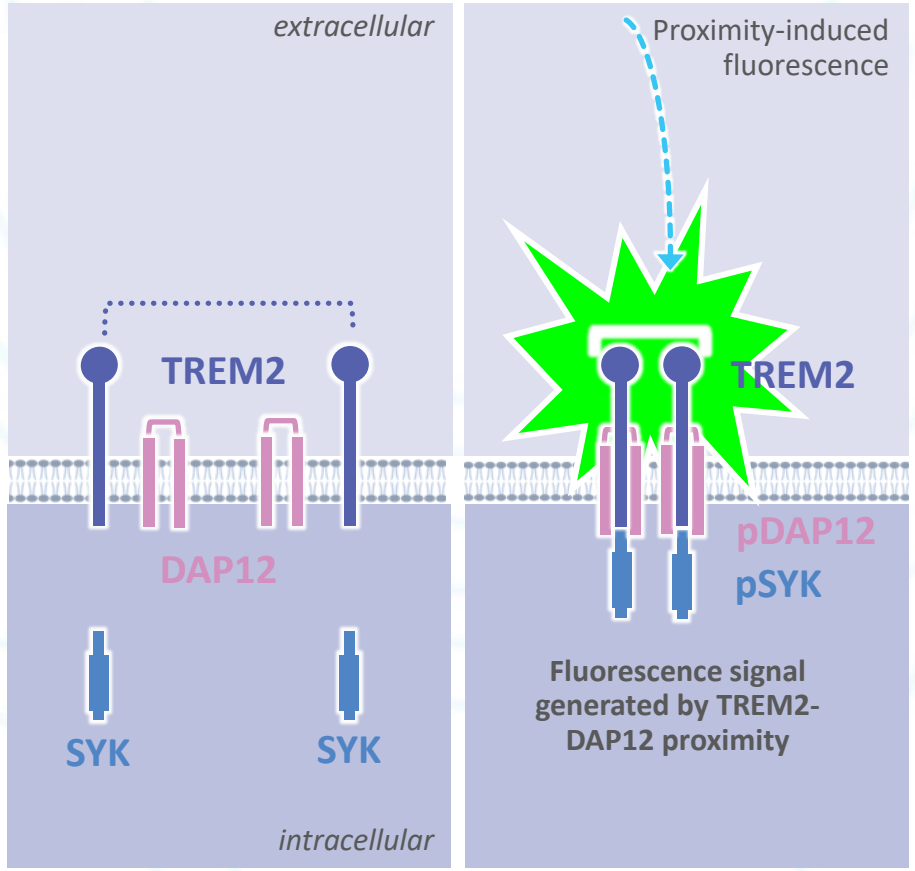


*Neg CTL: negative control; DMSO: dimethyl sulfoxide; KO: knock-out; PAGE: polyacrylamide gel electrophoresis; iMGLs: induced pluripotent stem cell-derived microglia; HEK: human embryonic kidney*

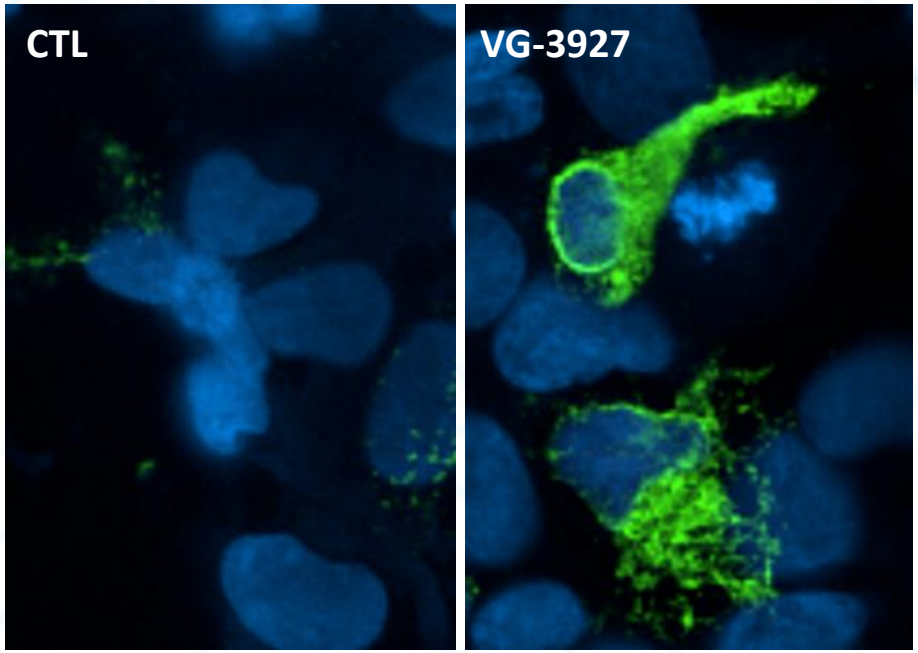
# VG-3927 Orchestrates Multi-Protein Interaction to Trigger Signaling

## *Unique Molecular Glue Mechanism of Action*

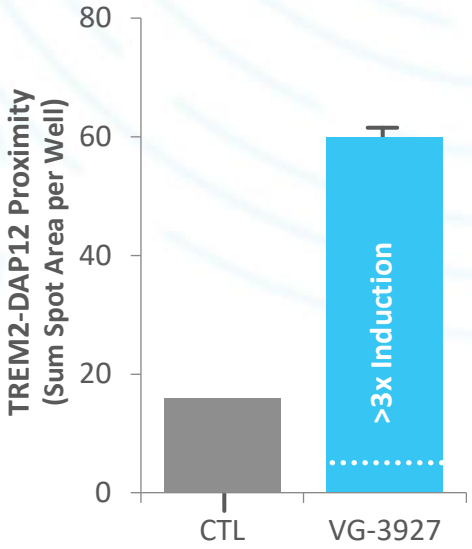
**Unassembled Inactive TREM2 Receptor Complex** → **VG-3927 TREM2 SM for AD**




**Minimal TREM2 and DAP12 Interaction at Baseline** → **VG-3927 Brings Together Both Signaling Partners**




**Quantification of TREM2-DAP12 Interaction**

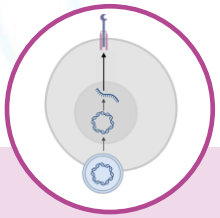



- TREM2 clusters and utilizes DAP12 to initiate downstream signaling
- VG-3927 coordinates these protein-protein interactions

# Establishing VG-3927 for Development in AD

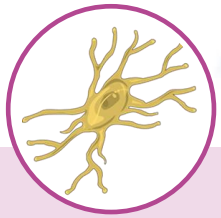
## *Pharmacological & Clinical Translation*

### VG-3927 Pharmacological Profile



**TREM2 engineered systems**

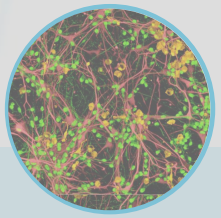
High-throughput profiling



**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.*

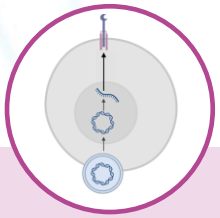
vigil™ NEURO

vigilant for you®

# Establishing VG-3927 for Development in AD

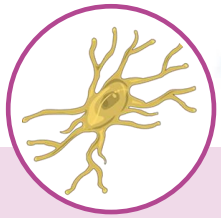
## *Pharmacological & Clinical Translation*

### VG-3927 Pharmacological Profile



**TREM2 engineered systems**

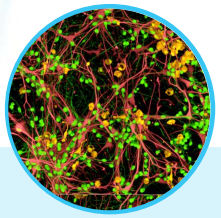
High-throughput profiling



**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**

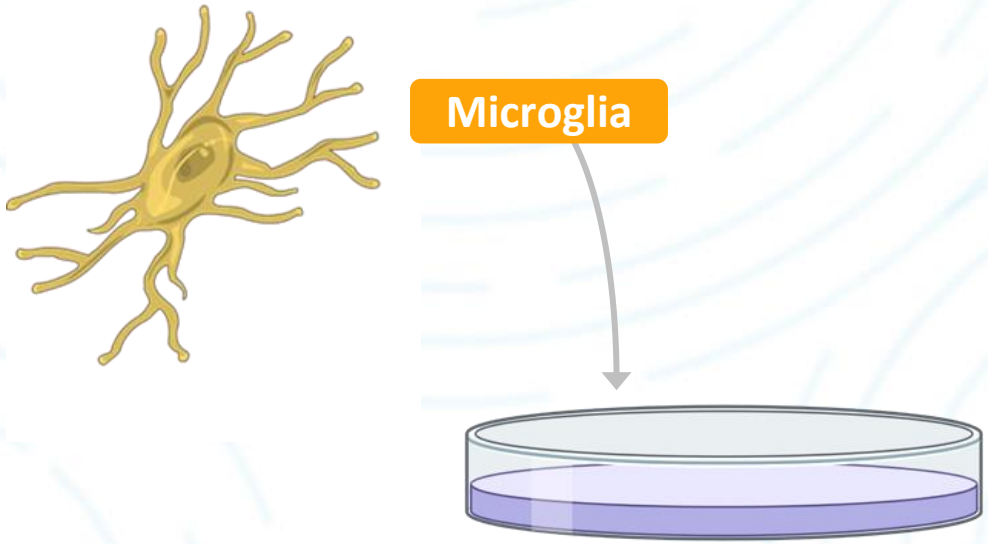
ID and validation of translational biomarkers

# Vigil Human CNS Platform Combines Neurons, Astrocytes & Microglia

## Human iMGL Monoculture Platform

**Pharmacology in disease-relevant human cells**

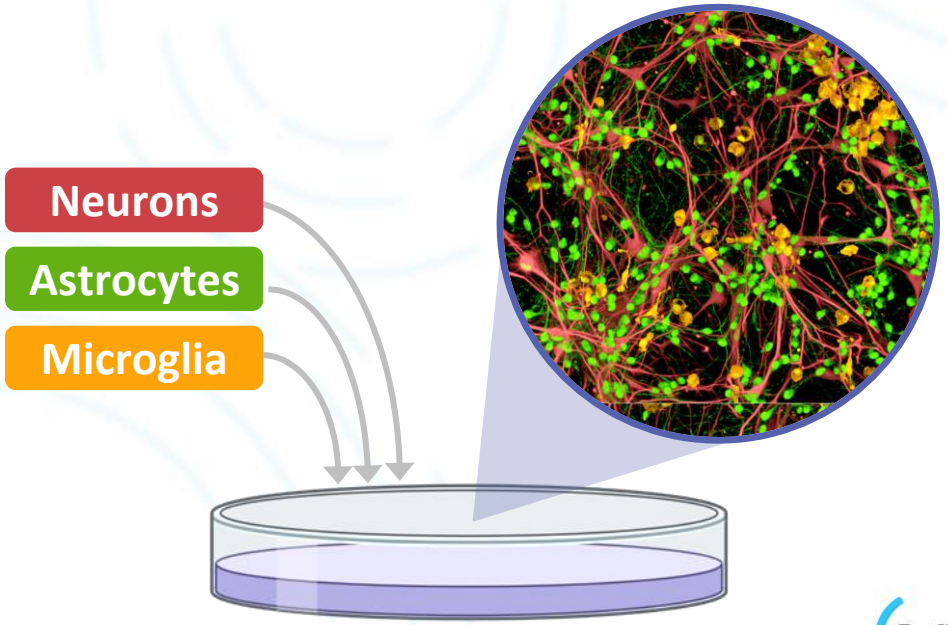
- Microglial pharmacology
- Target selectivity
- Fine mapping agonism




## Human CNS Tri-culture Platform

**Bridge to a predictive human translational system**

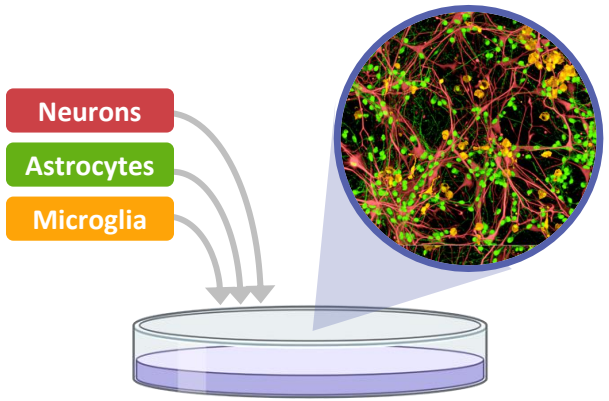
- Vigil's fully human translational cell model
- Understand interactions between diverse CNS cells
- Complementary with mono-culture applications



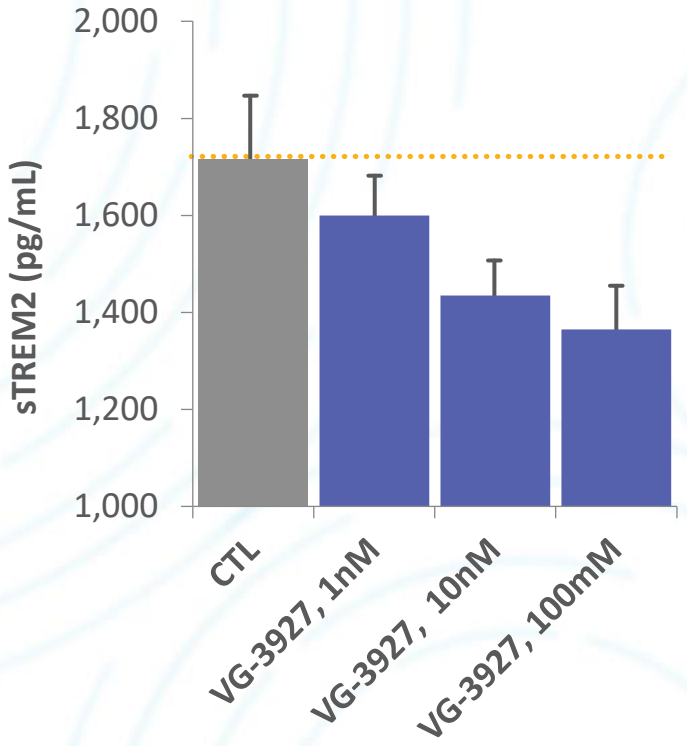

*iMGL: induced pluripotent stem cell (iPSC)-derived microglia*

# 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**

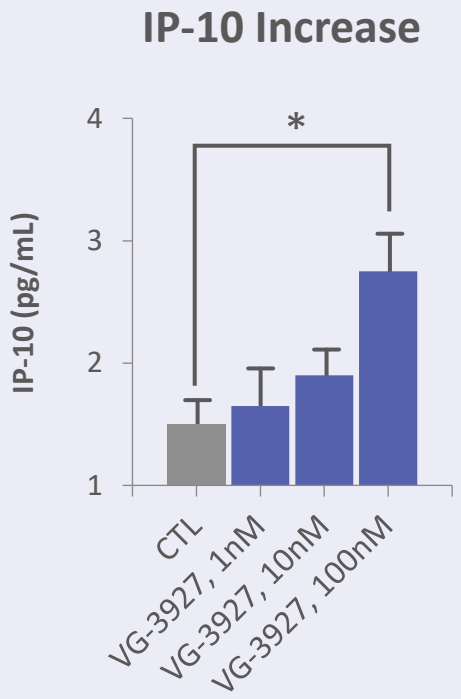
**Mobilizing microglia response with a favorable, non-inflammatory profile**

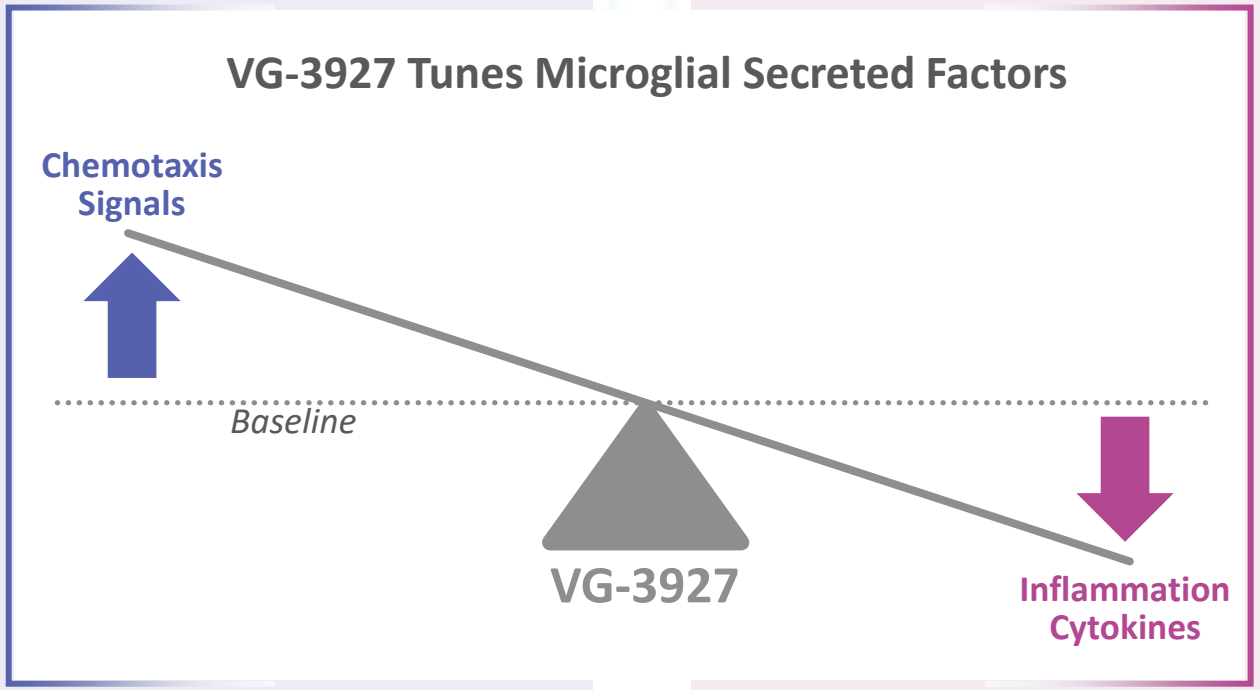
- Boosting of neuroprotective markers
- Plus countering inflammation-induced neurodegeneration

# VG-3927: Enhances Signals of Microglia Mobilization

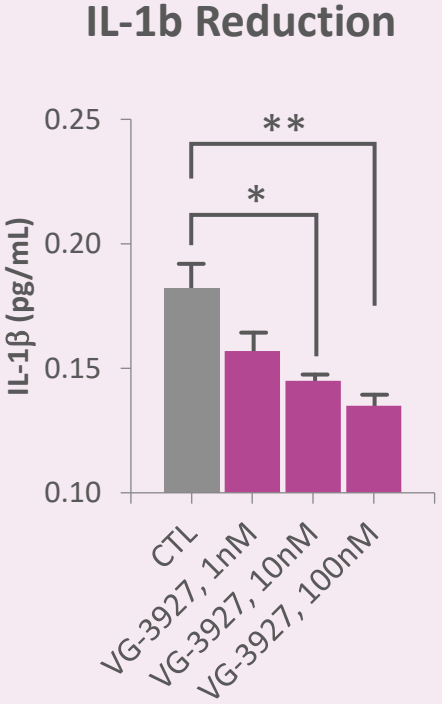
## *Favorable, Non-inflammatory Profile*

### Enhancement of Microglia Migration Signal




### Suppression of Pro-inflammatory Cytokines



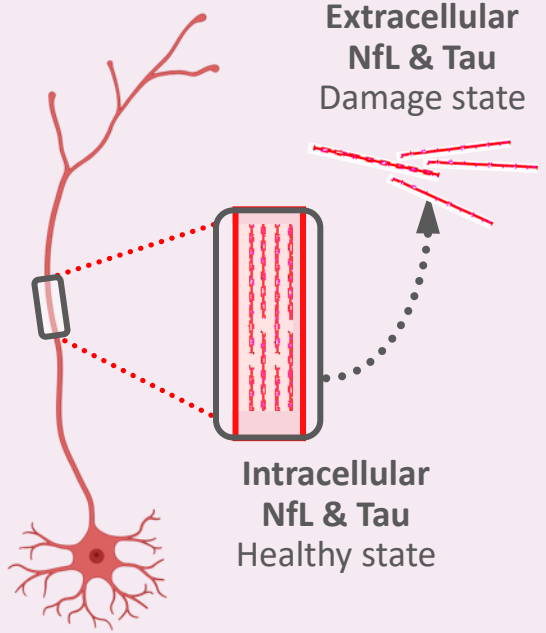

* denotes p<0.05

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

# VG-3927 Reduces Established Neurodegeneration Biomarkers

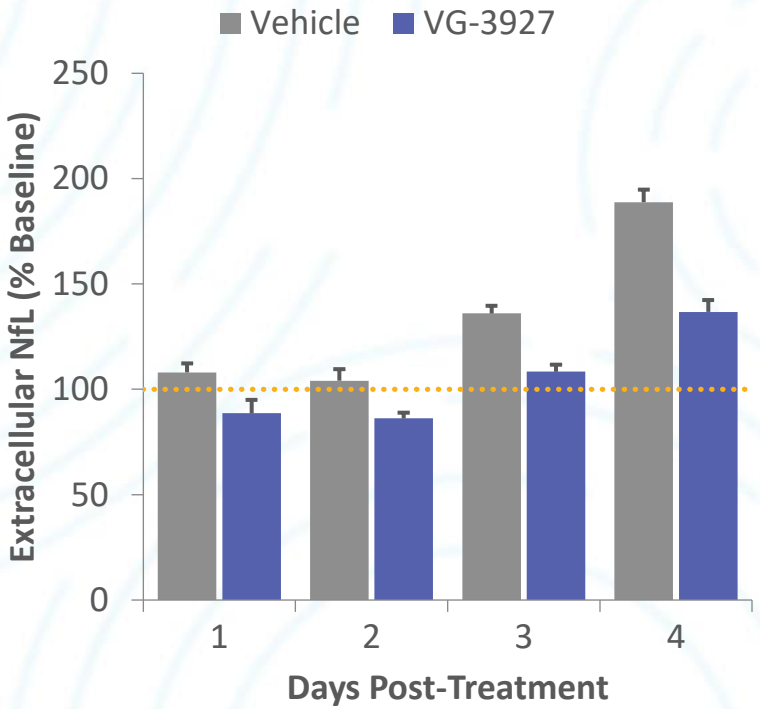
## *Reduction of Extracellular NfL & Tau*

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



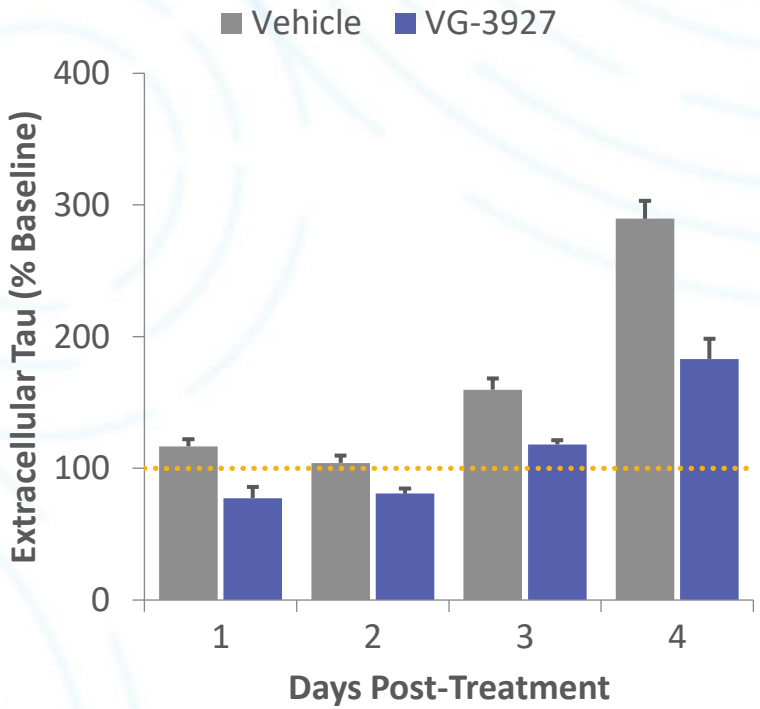

*NfL: neurofilament*

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




$ANOVA_{Treatment}$, $p<0.0001$

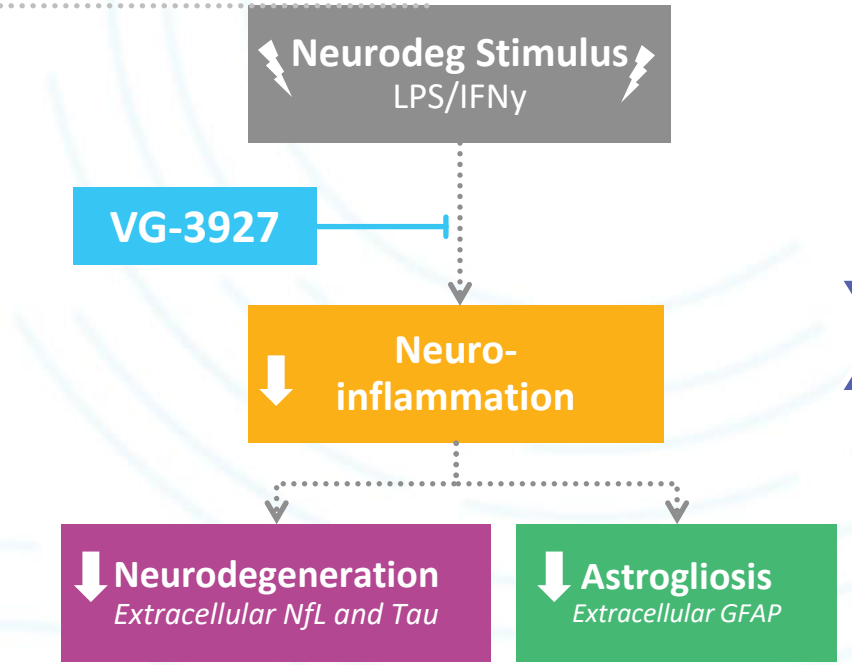
### VG-3927 Reduces Extracellular Tau Accumulation in Human Tri-cultures



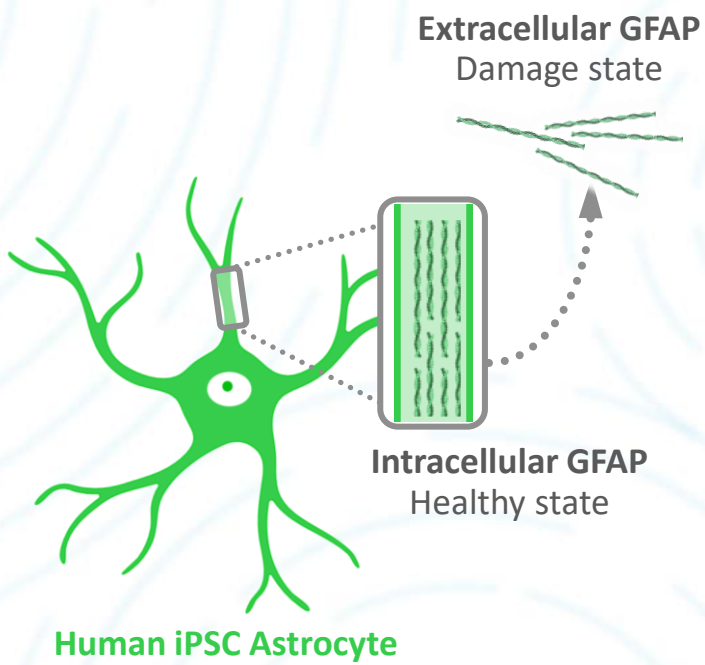

$ANOVA_{Treatment}$, $p<0.0001$

# VG-3927 Protects Against Inflammation-Induced Astrogliosis

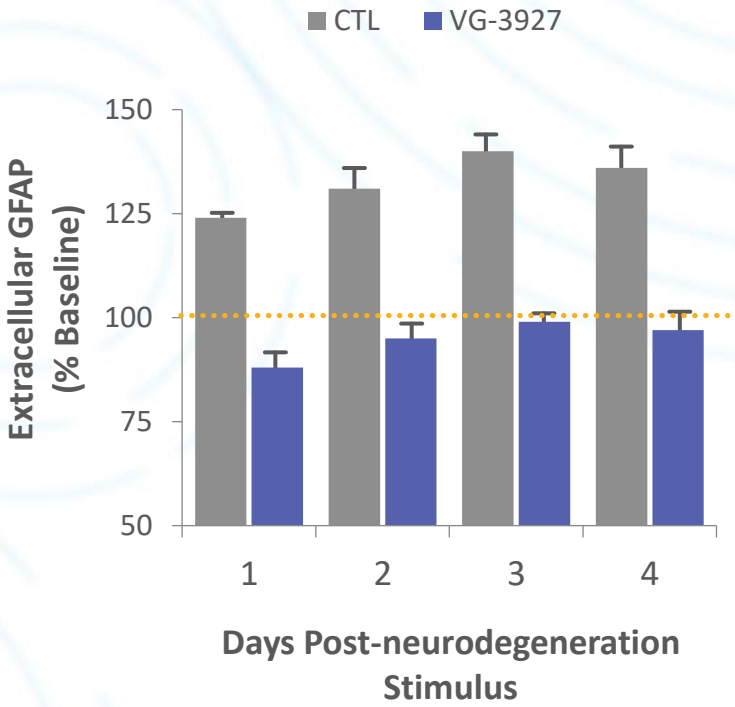
## TREM2 Agonism Activates Anti-inflammatory Benefit




## GFAP: Marker of Astrogliosis



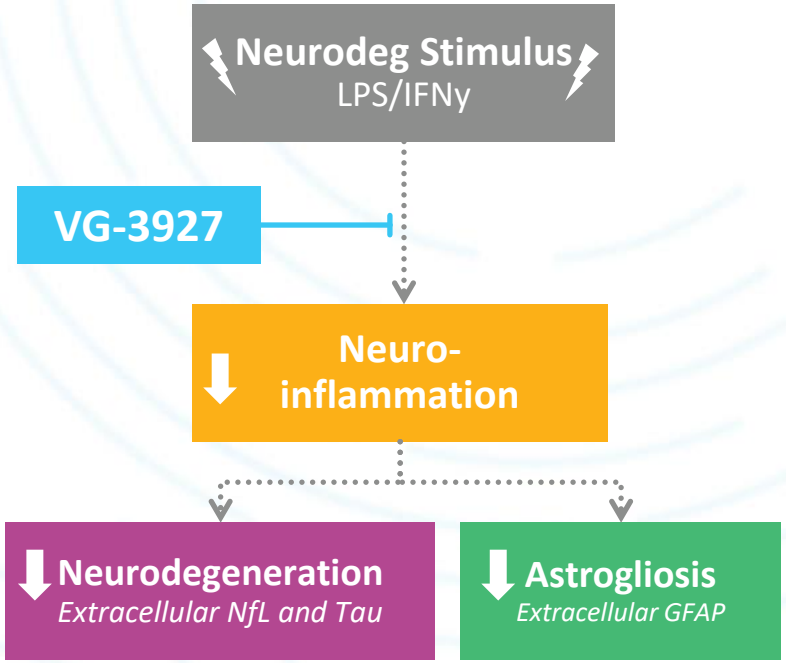

## VG-3927 Reduces Astrogliosis Biomarker (GFAP) in Human CNS Tri-cultures



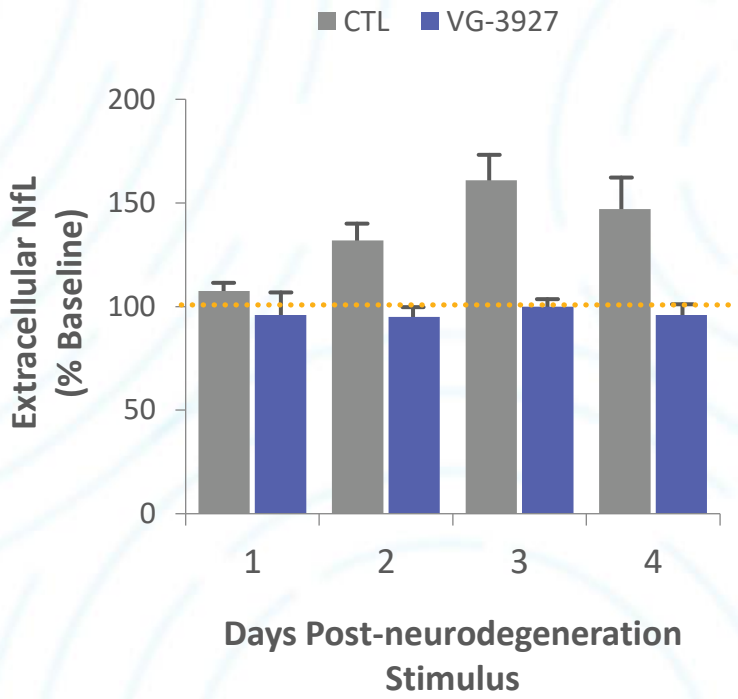

*LPS: lipopolysaccharide; IFNY: interferon-gamma; GFAP: glial fibrillary acidic protein*

# VG-3927 Protects Against Biomarkers of Inflammation-Induced Neurodegeneration

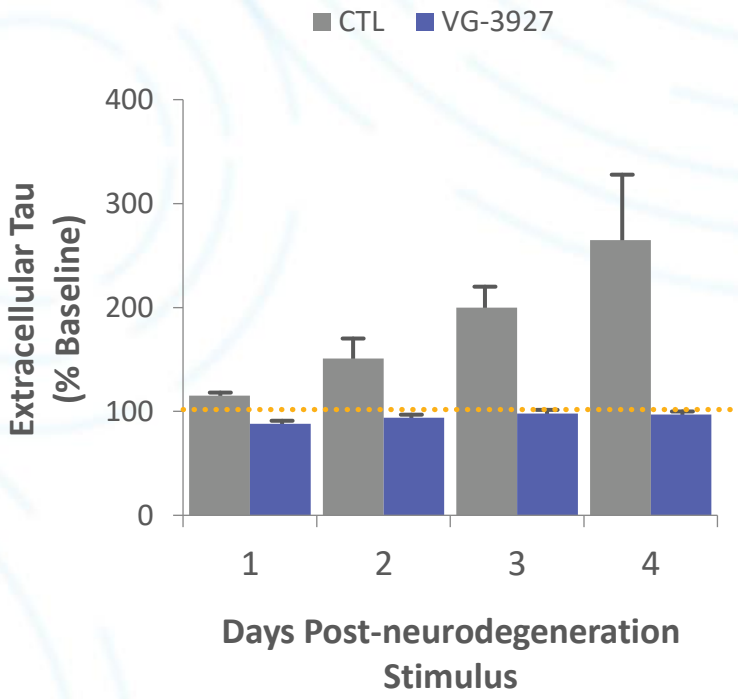
## TREM2 Agonism Activates Anti-inflammatory Benefit




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




$ANOVA_{Treatment}$, $p<0.05$

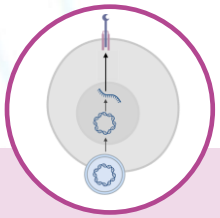



$ANOVA_{Treatment}$, $p<0.05$

# Establishing VG-3927 for Development in AD

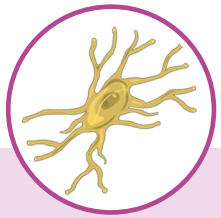
## *Pharmacological & Clinical Translation*

### VG-3927 Pharmacological Profile



**TREM2 engineered systems**

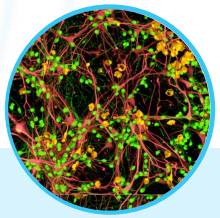
High-throughput profiling



**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

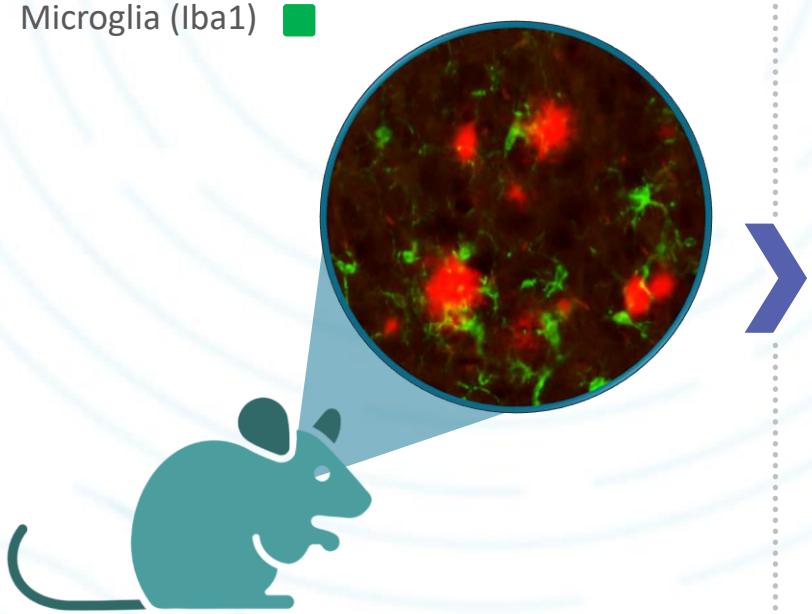
# VG-3927: Functionally Active in AD State

## *VG-3927 & VGL101 mAb Activate Neuroprotective Genes Similarly*

### Mouse Amyloidosis Model VG-3927 Oral Dosing

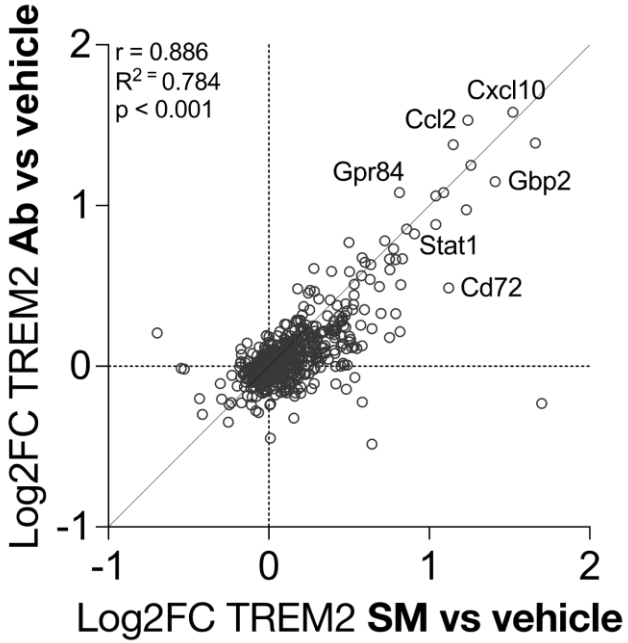
Amyloid-beta (Aβ)

Microglia (Iba1)

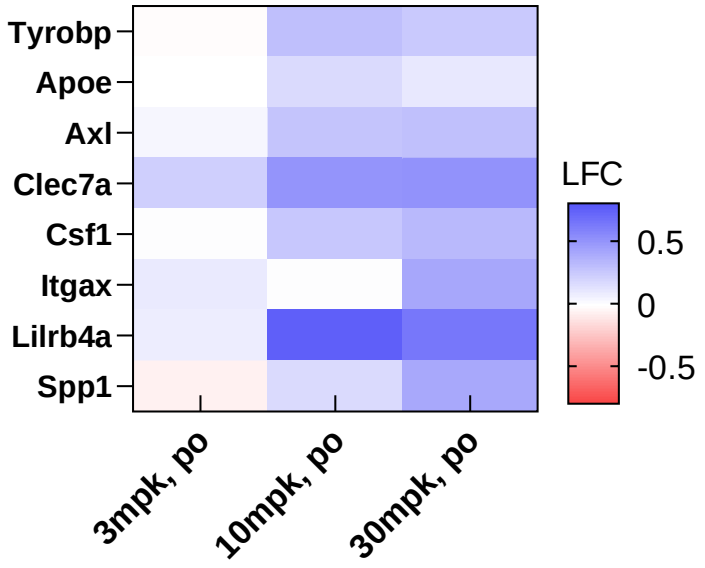


*Model: 5xFAD AD (mut APP/PS1) + hTREM2*

### 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

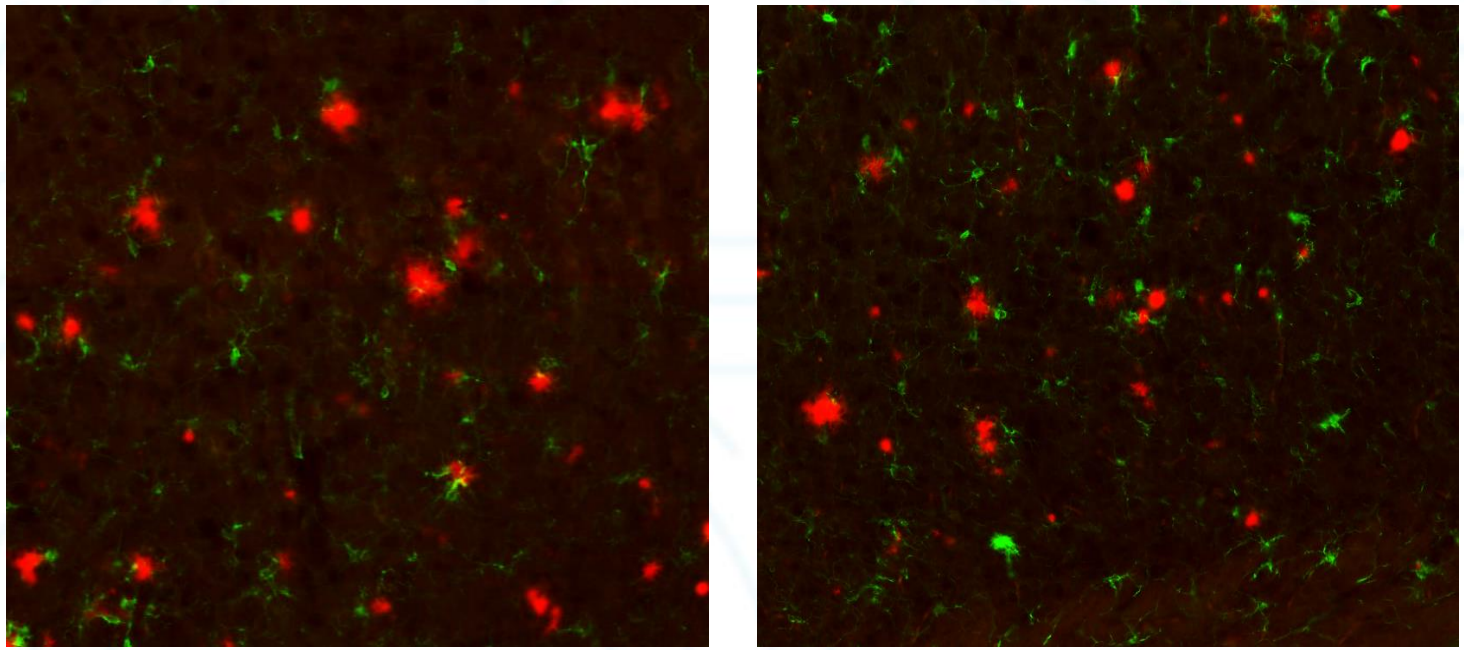
**Initial age:** 4.5 month-old 5xFAD-hTREM2 mice

**Daily Dosing for 6 Weeks**

VG-3927
10mpk
QD

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

Vehicle vs VG-3927



Amyloid plaques

Microglia

# VG-3927 Reduces Aβ Pathology in Plaque-bearing Mice

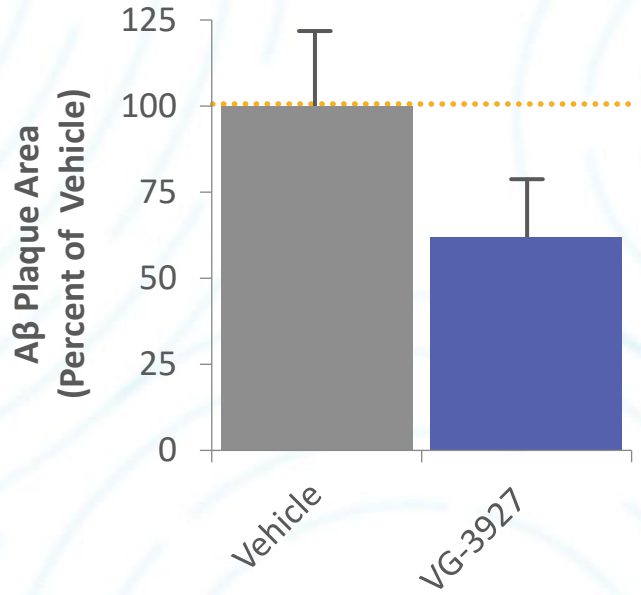
## *Preliminary Effects Following 6 Weeks of Oral Dosing*

### VG-3927

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

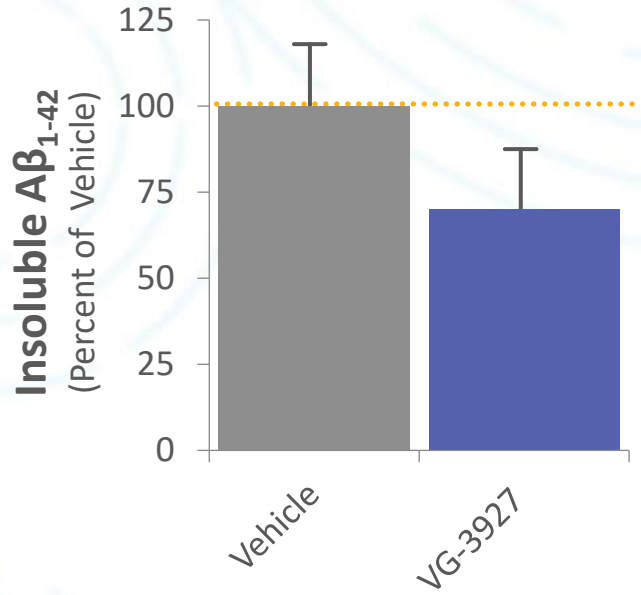
### VG-3927 Effects on Aβ Plaque Area

Immunohistology from Brain Slices




### VG-3927 Effects on Insoluble $Aβ_{1-42}$

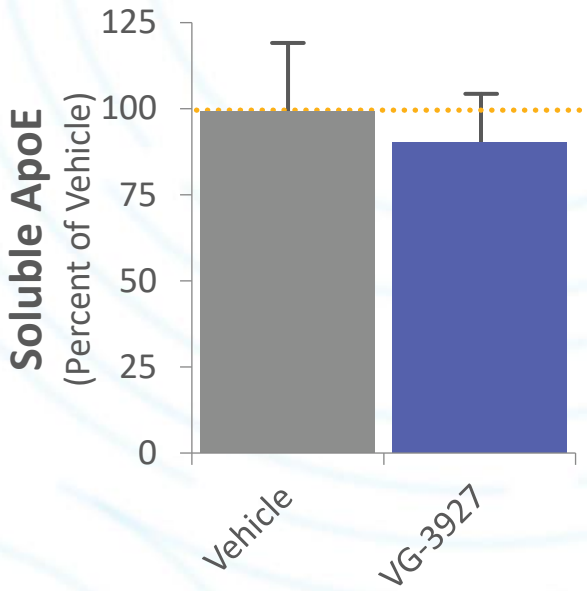
Biochemistry of Brain Homogenates



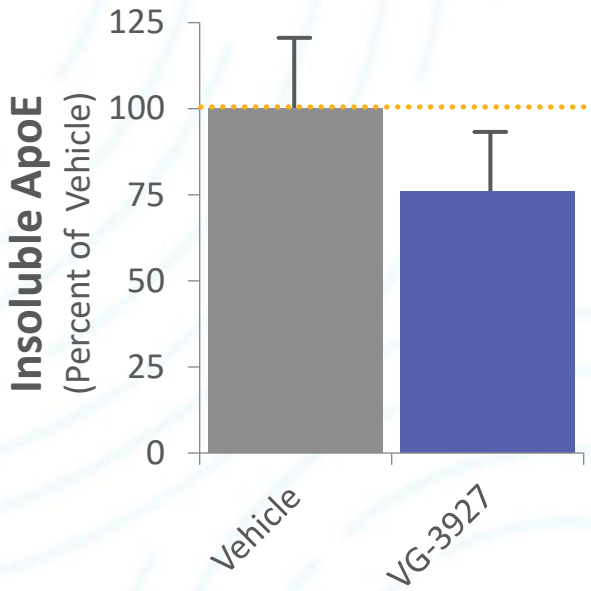
# VG-3927 Reduces Neuropathology-associated Aggregated ApoE

## *Preliminary Effects Following 6 Weeks of Oral Dosing*

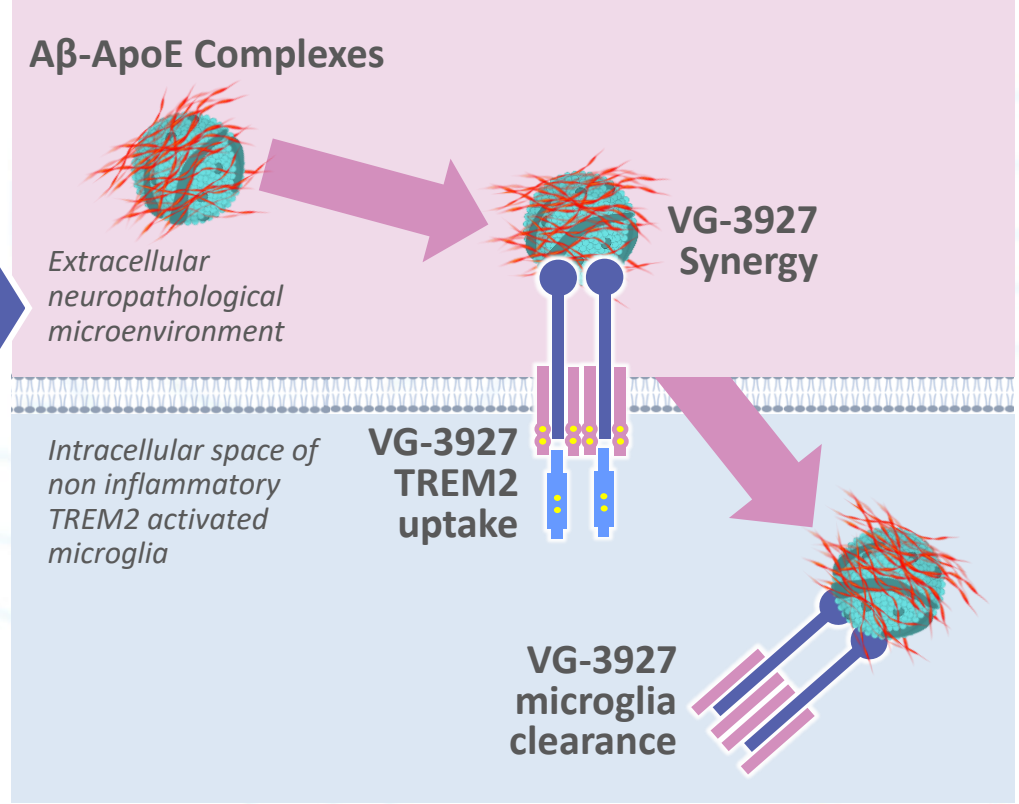
### No Change in Soluble ApoE
**Functional Form**




### Reduced Aggregated ApoE
**Pathological Form**




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



# Confirmation of Oral Bioavailability, Brain Penetrance & CNS Target Engagement

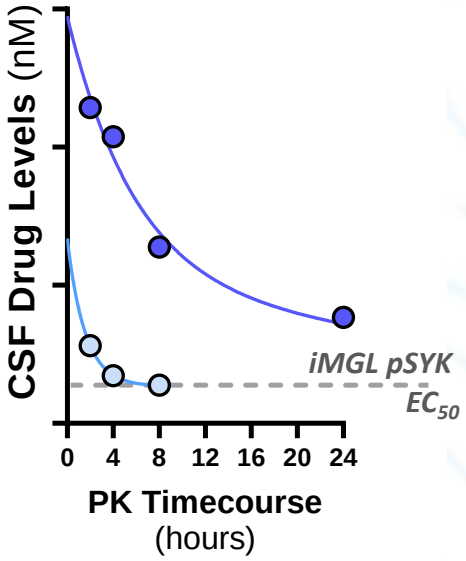
## *Favorable PK & PD Demonstrated in Non-Human Primates (NHPs)*

### Translation Biomarker Path to Clinic

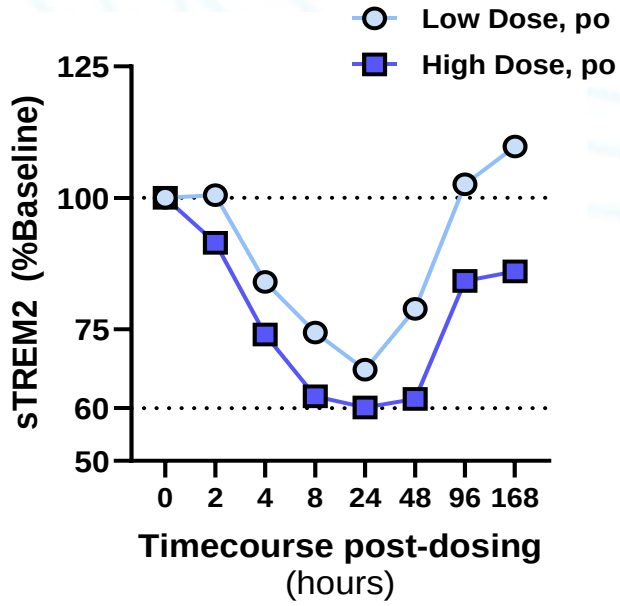

Cynomolgus Monkey

### 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

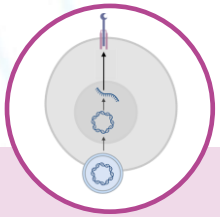



*po: "per os" or oral dosing*

# Establishing VG-3927 for Development in AD

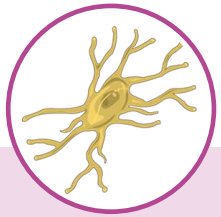
## *Pharmacological & Clinical Translation*

### VG-3927 Pharmacological Profile



**TREM2 engineered systems**

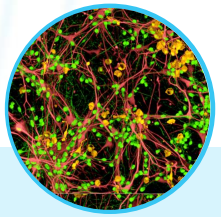
High-throughput profiling



**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: 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,*

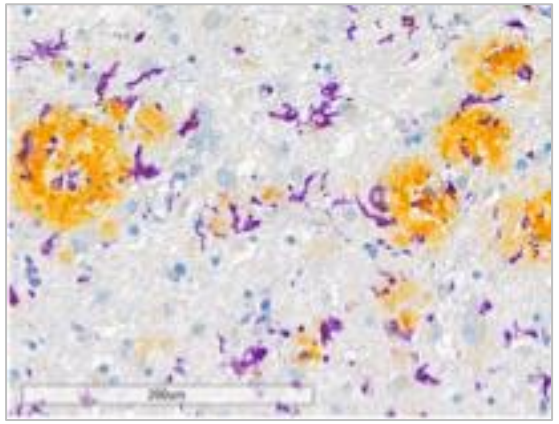
*Professor of Neurology & Psychiatry*

*Associate Director of Mount Sinai Alzheimer's Disease Research Center, NYC*

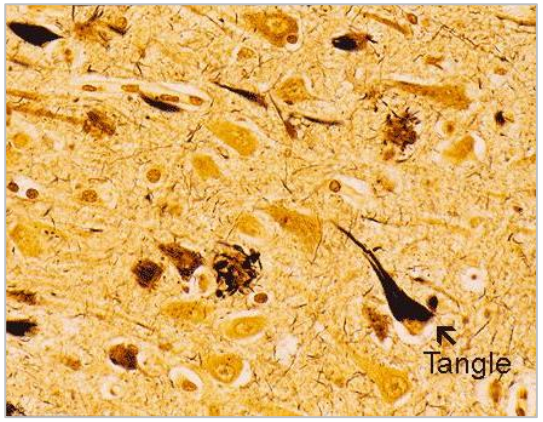
*Past Chairman, National Medical & Scientific Advisory Council of the Alzheimer's Association*

# Alzheimer's Disease (AD)

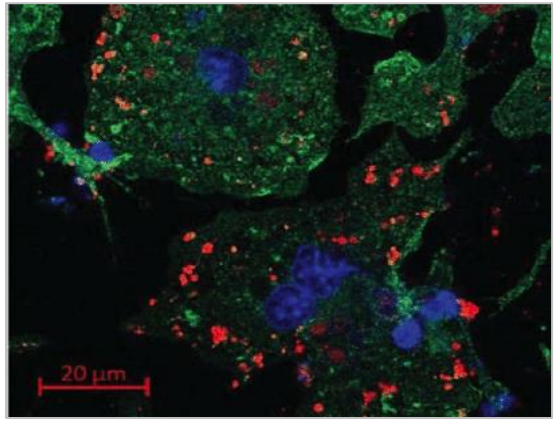
**β-amyloid**



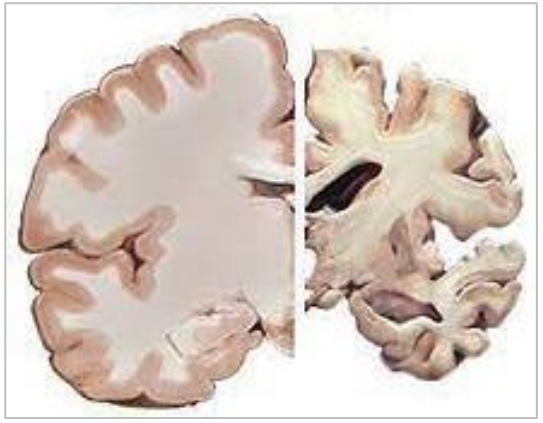
**Tau**




**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

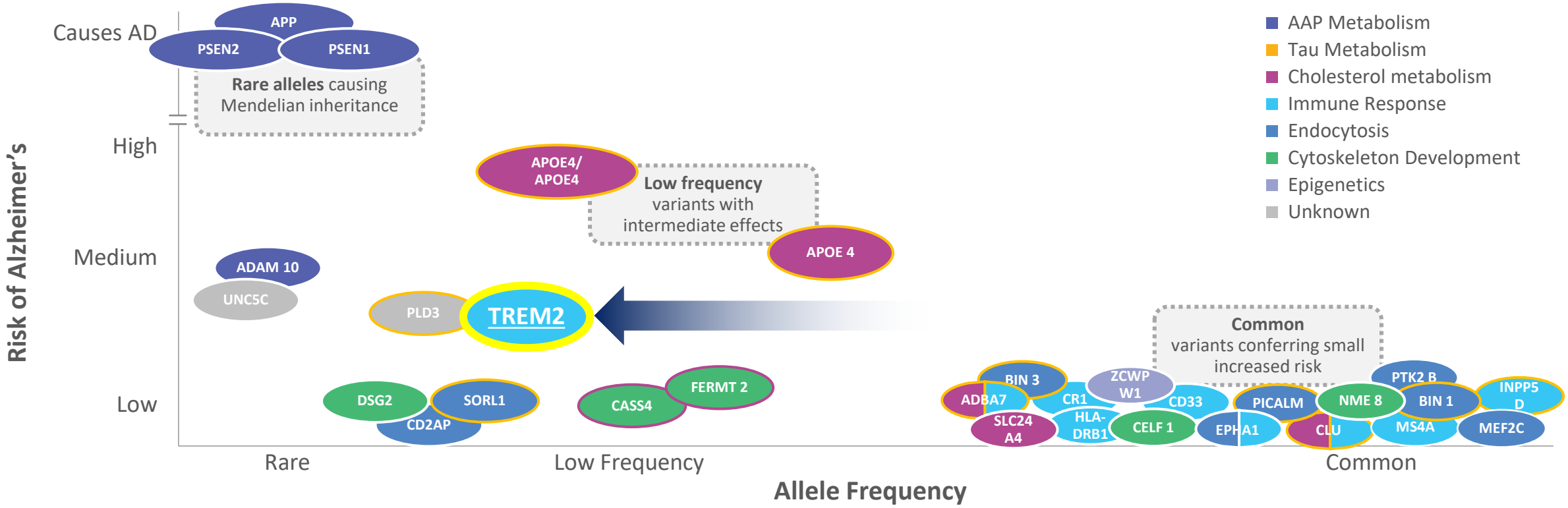

- ARIA a common side effect, requires MRI monitoring
- Immunogenicity

- 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



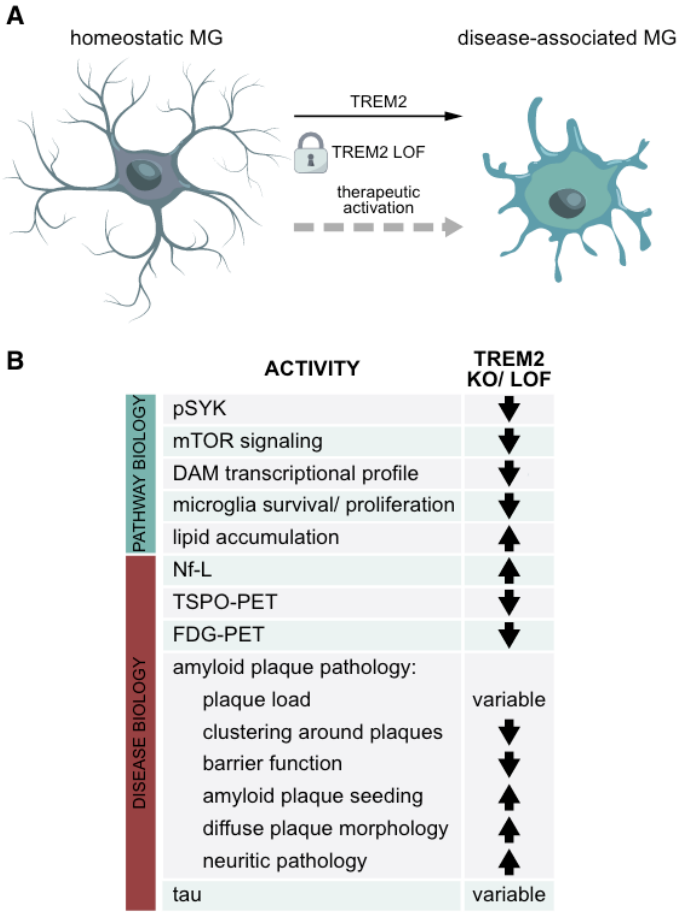

Lane et al *European Journal of Neurology* (2017)

# 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<br>Increase risk for AD |
| **TYROBP/DAP12** | NHD/PLOSL |
| **CSF1R** | ALSP |

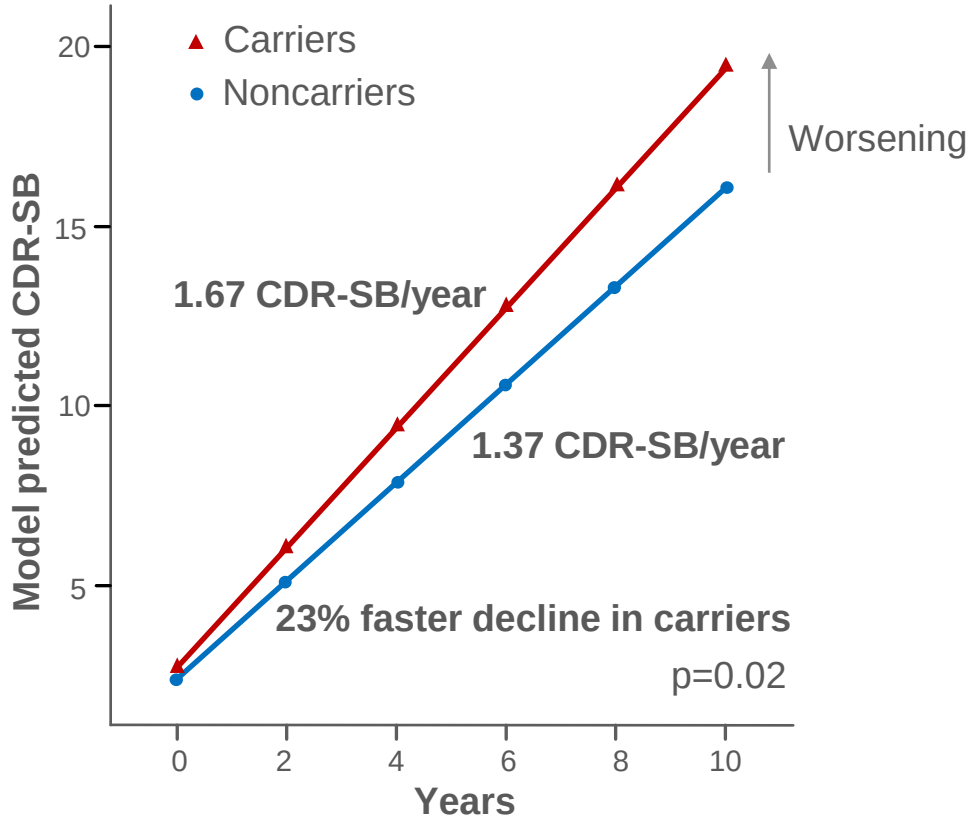
**TREM2 Agonism Enhanced Barrier Function and Phagocytosis Resulting in Reduced Neuronal Loss in *in vitro* and Animal Models of AD**



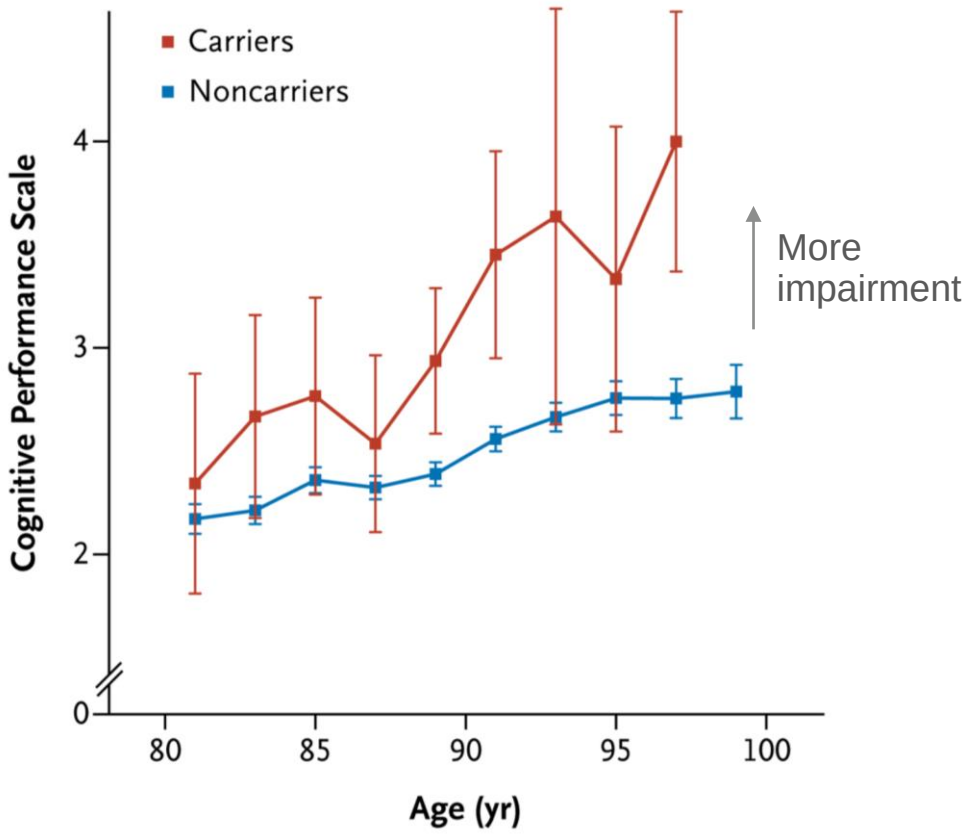

NHD – Nasu Hakola; PLOSL - Polycystic Lipomembranous Osteodysplasia; FTD – Frontotemporal Dementia; ALSP - Adult-onset Leukoencephalopathy with Axonal Spheroids Pigmented Glia
Golde T. *Neuron* (2019); Lewcock JW et al. *Neuron* (2020); Wang S et al *JEM* 2020

# 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

# Clinical Development of VG-3297, Vigil's Small Molecule TREM2 Agonist

**David Gray, PhD**
*Chief Science Officer*
*Vigil Neuroscience, Inc.*



vigilant for you®

# VG-3927 Phase 1 Trial in Healthy Volunteers

| | |
|---|---|
| **Trial Population** | ▪ Healthy volunteers (HVs) including an elderly cohort |
| **Trial Design** | ▪ Double-blind, placebo-controlled<br>▪ Single (SAD) & multiple (MAD) ascending dose cohorts |
| **Treatment Duration** | ▪ VG-3927 or placebo (oral dosing)<br>▪ SAD – single dose<br>▪ MAD – once daily for 14 days |
| **Treatment Duration** | ▪ Safety and tolerability<br>▪ Pharmacokinetics (PK)<br>▪ 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


# Closing Remarks

**Ivana Magovčević-Liebisch, PhD, JD**
*Chief Executive Officer*
*Vigil Neuroscience, Inc.*

# 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

# Q&A



vigilant for you®