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Industry Report

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NeuroNavigator:
To TREM or Not to TREM? Digging Into Modulating Neuroinflammation

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Quick Hits

- Aberrant neuroinflammation and microglial dysfunction is increasingly linked to neurodegenerative diseases through genetic, mechanistic, and clinical observations.
- We conservatively estimate a base-case market opportunity of more than $17 billion for neuroimmune-mediated therapies across Alzheimer's disease, frontotemporal dementia, Parkinson's disease, Lewy body dementia, and ALS.
- Neurology remains a significant area of investment, accounting for a quarter of total disclosed deal value ($502 billion) across all of biotech in the last few years, potentially a result of increased disease understanding and delivery methods.
- We estimate there are at least 50 companies (public and private) with assets in development (preclinical to Phase III) against targets related to neuroinflammation including TREM2, progranulin, NLRP3, Tyk2 inhibition, and others.
- TREM2 has become increasingly validated as a target through identification of multiple loss-of-function and partial loss-of-function mutations leading to increased risk of developing Alzheimer's and other dementias. Conversely, protective mutations linked to microglial activation can support increasing microglial activity as a disease-modifying strategy.
- While translation to the human condition is limited, preclinical models overall support a role of TREM2-mediated microglial activation in amyloid-β clearance response, although direct impact on tau is less clear.
- Key event for the field will be fourth-quarter data from Alector's INVOKE-2 study of AL002, a TREM2-agonizing antibody, which has shown signals of target engagement in Phase I and blinded Phase II studies. While not without significant risk, the setup leading into data for Alector is skewed heavily positive, in our view, as the company is currently trading around cash levels. We also see significant read-through to Vigil, which is developing its own TREM2-targeting programs with additional data expected in 2025.

Executive Summary

Genetics in Neurology Are Helping De-risk Clinical Programs With Neuroinflammation—The Next Therapeutic Frontier

Neurology drug development has enjoyed a recent resurgence, including recent landmark regulatory approvals for disease-modifying treatments for devastating conditions. These include amyotrophic lateral sclerosis (ALS) with the approval of the targeted SOD1 treatment Qalsody from Biogen and Ionis; Alzheimer's disease (AD) with the approval of Biogen and Eisai's Leqembi and Eli Lilly's Kisunla; Reata's (now Biogen's) Skyclarys for Friedreich's ataxia (FA); along with numerous others in late-stage development. While Qalsody is a genetically restricted treatment, others have more broad applicability resulting in expectations of blockbuster sales performance given the prevalence of these diseases. Currently 11% of adults over the age of 65 are estimated to have AD (per the Alzheimer's Association) with more than 6 million people living with the disorder in the U.S. alone, 1 in 40,000 people in the U.S. are estimated to be diagnosed with FA (per the National Organization for Rare Diseases), and millions of others suffer from diseases like Parkinson's disease (PD), ALS, Huntington's disease (HD), and other progressive neurodegenerative conditions.

However, these recent successes have not come without several high-profile setbacks expected given the difficulty in developing therapies for neurodegenerative disease specifically. These include the failed PHOENIX confirmatory trial of Amylyx's Relyvrio for ALS and multiple trials in PD failing to advance to Phase III studies (McFarthing, et al., 2024). Despite well-defined genetic targets, developing HD treatments have also hit snags as evidenced by the GENERATION-HD trial of Roche and Ionis's tominersen. The dosing in the Phase III GENERATION-HD1 trial was halted after the unblinded independent data monitoring committee (iDMC) determined that the risk/benefit profile no longer supported further dosing after transient increases in CSF NfL levels and no apparent clinical benefit on the cUHDRS score. However, a post-hoc analysis suggested potential benefit in a subset of patients, and the companies are now conducting a Phase II study with modified dosing in a younger patient population with lower disease burden (see: CHDI Data Highlight That Lower Tominersen Exposures Might Be an Answer for Early HD; Will Phase II Doses Lower HTT Enough?). Important questions remain about overall risk/benefit for some of these emerging treatments, particularly the anti-amyloid antibodies, and in many cases the standard of care remains symptom management. In our view, these antibodies demonstrate a clear but modest benefit over time, and while there is emerging evidence that earlier intervention can improve outcomes (see: Second-Quarter Earnings: Continued Momentum as Biogen Seeks Return to Growth; AAIC Update Builds on Leqembi Benefit Potential), ultimately AD and other neurodegenerative diseases remain fatal conditions, leaving patients desperately in need of additional treatment options.

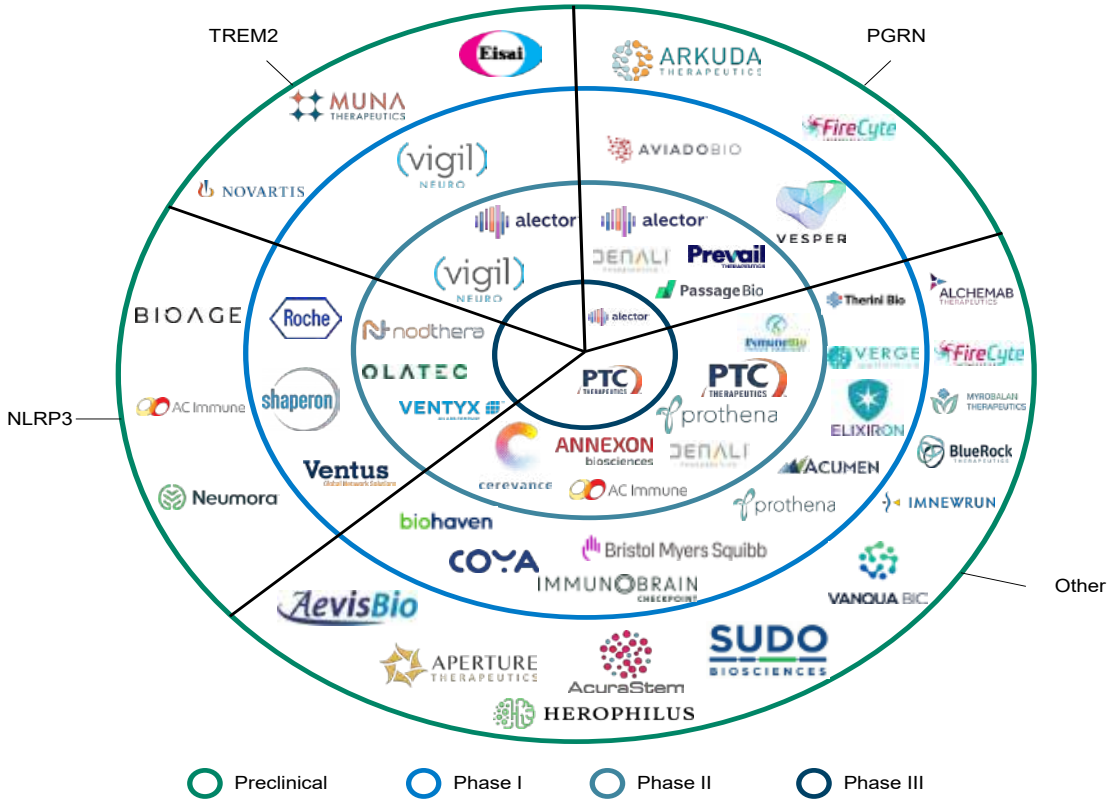
Neuroinflammatory dysfunction has become increasingly accepted as a contributor to neurodegenerative disease pathology and an active area of drug development (reviewed in Mortada, 2021, Giri, 2024, Zhang, 2023, and previously discussed in our deep dive NeuroNavigator: Advancing Targeted Neurology With Genetic Insights Into Neuroinflammation; see exhibit 1 and appendix A of this report). Microglia act as the immune cells of the nervous system and play roles in responding to infection, phagocytosing cellular debris, and harmful protein aggregates (for example, amyloid-β) secreting neurotrophic or pro-inflammatory cytokines, recruitment of additional microglia, and other regulatory functions. This support function appears to be dysregulated across neurodegenerative diseases, leading to lysosomal dysfunction, accumulation of toxic proteins, maladaptive inflammation, and neuronal death (exhibit 2). Critically, this neuroinflammatory component of disease, when dysregulated, is different from directly targeting the initial proteinopathy (e.g., amyloid/tau in AD, α-synuclein in PD, HTT in HD, SOD1/others in ALS) or injury signal (e.g., obstructive clots in stroke or vascular damage in traumatic brain injury) in CNS tissue and could carry complementary benefits to clearance of protein aggregates alone. Thus, targeting neuroinflammation represents a truly novel way in which to potentially treat neurodegenerative disease, and in theory this therapeutic strategy could be used in combination with several approved therapies targeting underlying proteinopathies across neurodegenerative disease.

Advancements in genotyping methods, transcriptomics, and machine learning capabilities have enabled identification of at least 322 genes with altered expression in patients with neurodegenerative diseases versus controls, and these genes were largely involved in immune response, synaptic signaling, and cellular metabolism (Arneson, et al., 2018; Li, et al., 2014; see exhibit 3). Intervening early in disease states prior to excessive protein aggregation and neuronal loss to prevent these pathological processes remains a highly attractive strategy, although optimizing timing of intervention, target selection, and therapeutic delivery to the CNS are significant challenges.

We note that excessive inflammation is established as a key pathology in multiple sclerosis (MS), a chronic autoimmune disorder characterized by progressive destruction of the myelin sheath surrounding neuronal axons resulting in muscle spasms and weakness, potential paralysis, and cognitive dysfunction, among other symptoms. While there are multiple subtypes of MS depending on the disease course (i.e., relapsing-remitting, primary-progressive, secondary-progressive), anti-inflammatory treatments such as corticosteroids are typically used first-line to reduce symptom

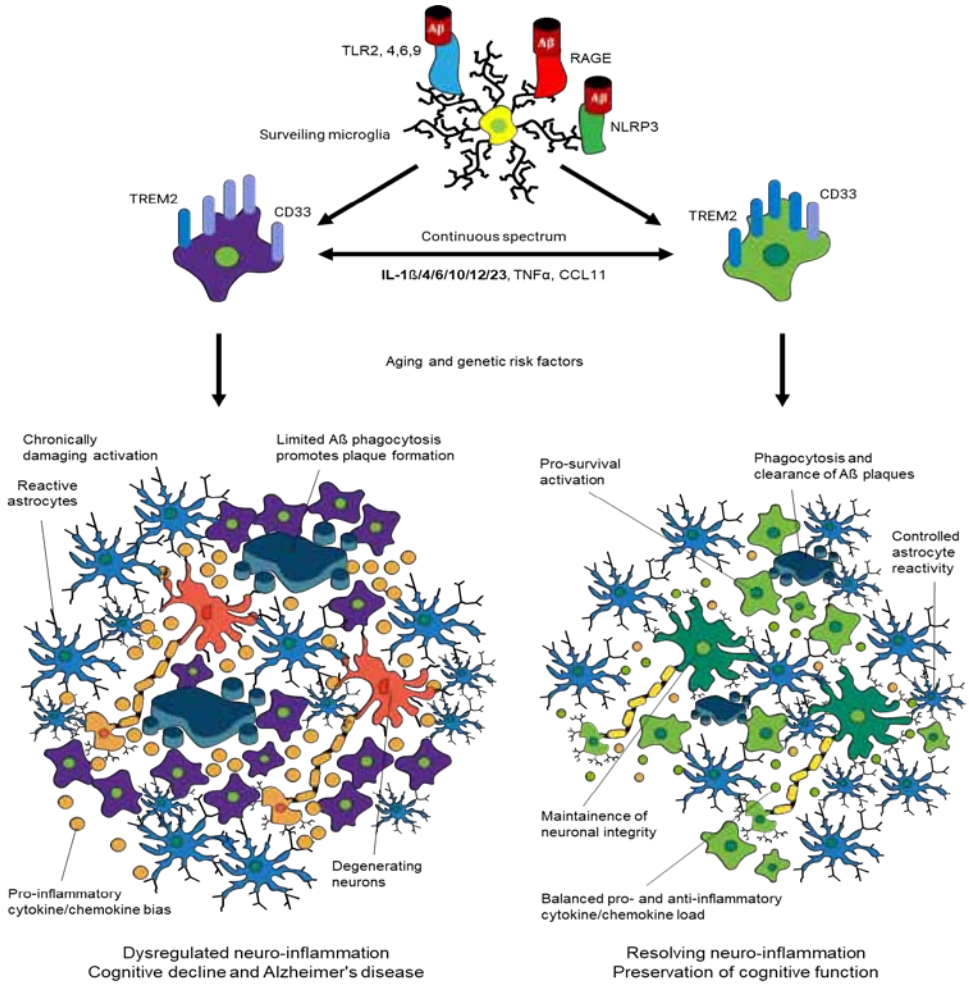
flare-ups. In addition, several disease-modifying treatments have been developed that alter immune activation including interferon therapies (e.g., Biogen's Plegridy), anti-CD20 therapies (e.g., Roche's Ocrevus and Novartis's Kesimpta), and others including anti-CD40L antibodies in clinical development. Given the established success of immune modulatory treatments in MS, the following report is focused on more developing indications, particularly AD. However, we note that animal models have suggested potential for TREM2-targeted therapies in MS, and we see this as a potential area for future development and parallel for development of these therapies between chronic neurogenerative (AD, PD, etc.) and chronic autoimmune demyelinating disease (MS; Cignarella, et al., 2020).

Exhibit 1
Landscape of Select Companies With Neuroinflammatory Target Pipelines



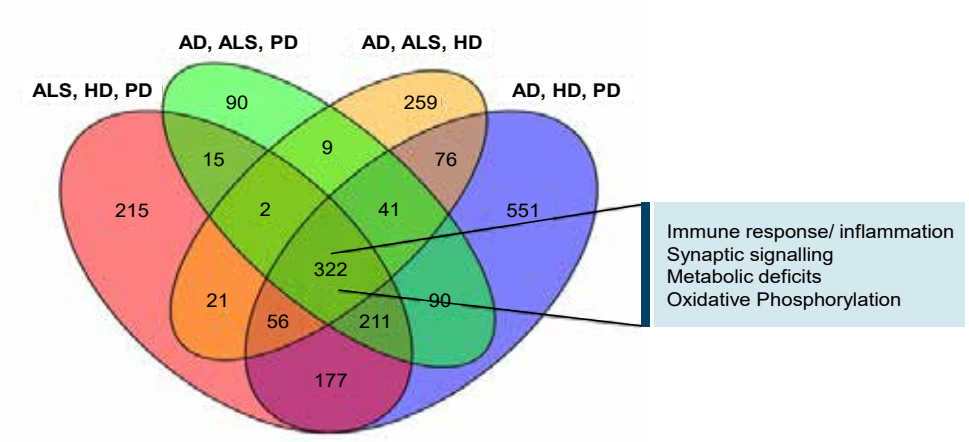
Source: William Blair Equity Research

Exhibit 2
Microglial Activation States in Response to Disease-Related Environmental Stimuli



Source: Minter, et al., 2015; modified by William Blair Equity Research

Exhibit 3
Overlap of Differentially Expressed Genes in Neurodegenerative Diseases



Source: Arneson, et al., 2018; adapted by William Blair Equity Research

Key Neurology Markets Represent Greater Than $17 Billion TAM

We estimated market metrics and peak sales estimates for neuroinflammatory treatments for neurodegenerative diseases in a prior edition of NeuroNavigator (NeuroNavigator: Advancing Targeted Neurology With Genetic Insights Into Neuroinflammation) and have updated this data in the current report. In short, considering conditions in which microglia appear to play a key role in disease progression (AD, frontotemporal dementia [FTD], PD, ALS, and Lewy body dementia), we estimate a base-case market opportunity of more than $17 billion for disease-modifying neuroinflammation-mediated therapies (exhibit 4). This is a non-exhaustive list of all CNS disorders where neuroinflammation could play a role, but we believe these are the major indications to date where this process has been clearly described and has strong therapeutic rationale for intervention.

Our analysis assumes an estimated 6.2 million Americans have AD currently, although the number is expected to grow to 12.7 million by 2050 as the population ages. While exact estimates vary, the NIH's National Institute on Aging indicates that 50% of patients have mild disease, 30% have moderate disease, and 20% have severe disease. Assuming neuroinflammatory-modulating drugs are restricted to only patients with mild cognitive impairment and early disease stages before significant amyloid-β deposition, this could still result in an eligible patient population of at least 3 million in dementia due to AD alone, although this number could be closer to 5.5 million or more (Langa & Levine, 2015). This also assumes a list price of $30,000 based on current costs for anti-amyloid therapies Leqembi and Kisunla. Similarly for FTD, which is estimated to occur in 4-15 per 100,000 people per the Association for FTD, we would expect a similar use-case of earlier in disease onset, although with a potentially higher list price given rarity of the disease. As it relates to Parkinson's and Lewy body dementia, we estimate 1 million patients each are living with these diseases in the U.S., per the Parkinson's Foundation and Hogan, et al., 2016. We would again expect use predominantly in early disease stages to prevent accumulation and spread of α-synuclein. Lastly, ALS is the rarest of these conditions with an estimated prevalence of between 4.1 and 8.4 per 100,000 persons, or 15,000-30,000 people in the United States. While there have been exciting developments for genetically targeted treatments such as Qalsody, the majority of ALS cases are sporadic with 90% of patients having no familial history and therefore unlikely to benefit from targeted therapy. However, ALS progresses much more rapidly than AD, with average survival of only two to five years from diagnosis. Therefore, we assume only one-third of patients regardless of genotype would be early enough in the disease course to be amenable to neuroinflammatory intervention. However, we expect rare disease pricing and model a maintenance list price of about $350,000 annually (given the price of Spinraza for spinal muscular atrophy [SMA] and superior risk/benefit to Relyvrio, which was priced at $158,000 per year when marketed).

As discussed further in this report, there are several additional indications in which neuroinflammation has been implicated and where these therapeutic strategies could be implemented. Therefore, this remains a non-exhaustive list of the market opportunity for this class of potential therapies.

Exhibit 4
Market Metrics and Peak Sales Estimates—Neuroinflammatory/Non-genetically Restricted Treatments

						Market penetration			Market size (millions)		
Indication	Total pts	% eligible for immune therapy	Total pts eligible	Annual list price $	TAM (millions)	Bear	Base	Bull	Bear	Base	Bull
Alzheimer's	6,200,000	50%	3,100,000	30,000	93,000	1%	5%	10%	930	4,650	9,300
FTD	50,000	50%	25,000	50,000	1,250	15%	35%	60%	188	438	750
ALS	30,000	33%	9,900	350,000	3,465	40%	60%	80%	1,386	2,079	2,772
PD	1,000,000	50%	500,000	50,000	25,000	10%	20%	30%	2,500	5,000	7,500
Lewy Body Dementia	1,000,000	50%	500,000	50,000	25,000	10%	20%	30%	2,500	5,000	7,500
Total	***8,280,000***		***4,134,900***	***106,000***	***147,715***				***7,504***	***17,167***	***27,822***

Source: William Blair Equity Research

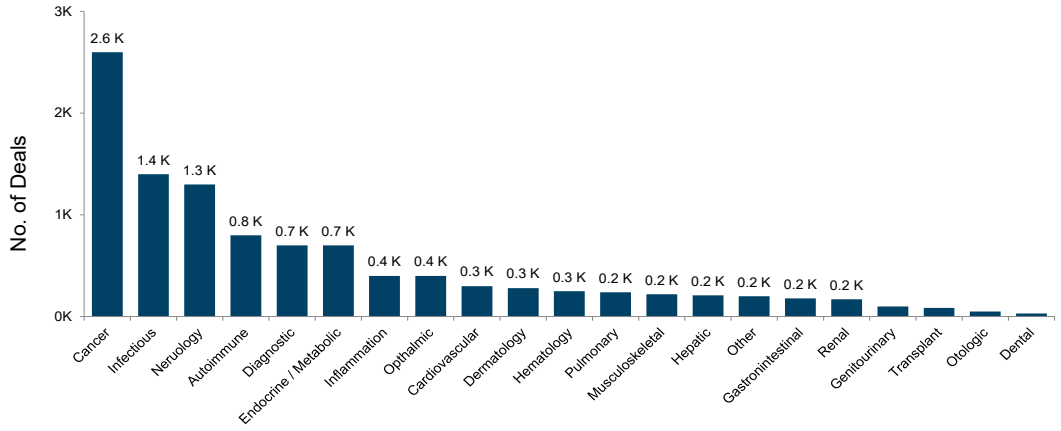
Deal Metrics in Neurology Are Healthy and Venture Funding Trails Only That of Oncology—Driven by Innovation

Given the significant unmet need and tremendous market opportunity, neurology remains a major area for invested capital. According to data available from BioCentury IQ, between 2019 and August 2024, there were approximately 1,300 deals (merger and acquisition agreements, partnership agreements, or asset purchases) in the neurology space, trailing only oncology and infectious diseases areas for total deal volume (exhibit 5). Over this time frame, total deal value in neurology (for transactions with disclosed amounts) of $502 billion accounted for a quarter of the $2.01 trillion recorded for all of biotech (exhibit 6). Nearly half of this, or $235 billion, was related to adult-onset neurodegenerative diseases (AD, FTD, PD, HD, ALS, cognitive dysfunction), with the average M&A deal value of $5.3 billion exceeding that of the broader neurology space and all of biotech.

We also note that $5.0 billion in disclosed deal value was related to transactions of targets of interest (TREM2, NLRP3, and PGRN), although these were not exclusive to neurology with additional applications in immuno-oncology (TREM2) and obesity (NLRP3), which are beyond the scope of this report. Similar trends were seen in recent venture capital financing rounds, with $3.97 billion raised by private biotech year-to-date for neurology applications (second only to oncology), according to a recent report published in *Nature Biotechnology* (exhibit 7).

Collectively, we view the significant deal-making in the space as reflective of both the significant unmet need and recent progress in genetic validation of therapeutic targets. Along with improvements in delivery to the CNS, these may help de-risk these opportunities where probability of success has been an issue. We expect neurology to remain an area of increased investment focus in coming years, despite the space carrying significant clinical development risk, as these technologies accrue proof-of-concept datasets supporting novel approaches to treating illnesses with little to no disease-modifying options. We continue to believe neurology innovation is being driven by advances in genetics and precision therapeutics and that the field is likely 10 to 15 years behind oncology, which has significantly benefited from the advent of PD-1 checkpoint inhibitors. These approaches have ushered in an era of precision oncology that is tailored to an individual patient and significantly de-risked from a clinical development standpoint, and we see neurology benefiting from similar strategies.

Exhibit 5
Neurology Is Third-Largest Indication for M&A, Partnerships, and Asset Purchase Deals From 2019 to 2024



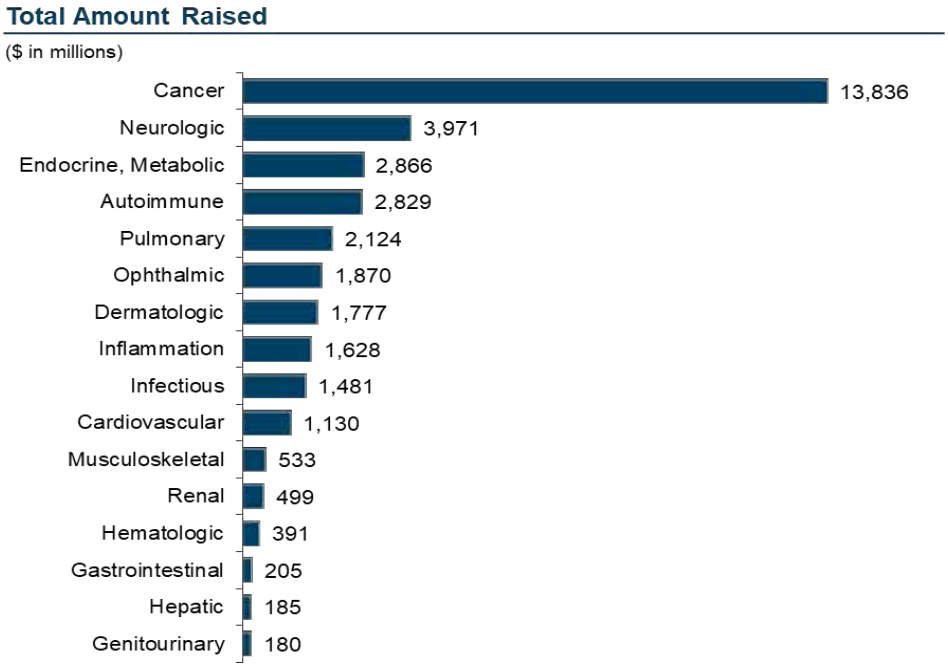
Source: BioCentury IQ

Exhibit 6
Summary of M&A, Partnership, and Asset Purchase Agreement Deal Activity Focused on Select Neuroinflammation Targets and Indications—2019-2024

		# of Deals	# of Deals with Disclosed $	Total Deal Value	Avg. Deal Value
All Biotech	M&A:	1231	564	$961.1B	$1.7B
	P&AP:	7823	1962	$1.05T	$535M
	Total:	**9054**	**2526**	**$2.01T**	
Neurology	M&A:	225	105	$365B	$3.5B
	P&AP:	1057	340	$137B	$401M
	Total:	**1282**	**445**	**$502B**	
Adult-onset Neurodegener-ative	M&A:	79	36	$190B	$5.3B
	P&AP:	310	96	$45B	$473M
	Total:	**389**	**132**	**$235B**	
TREM2, PGRN, NLRP3	M&A:	5	3	$2.5B	$834M
	P&AP:	9	5	$2.5B	$492M
	Total:	**14**	**8**	**$5.0B**	

Source: BioCenturyIQ, William Blair Equity Research

Exhibit 7
Venture Capital Dollars Raised for Neurology-Focused Companies Second Only to Oncology YTD Through August 2024



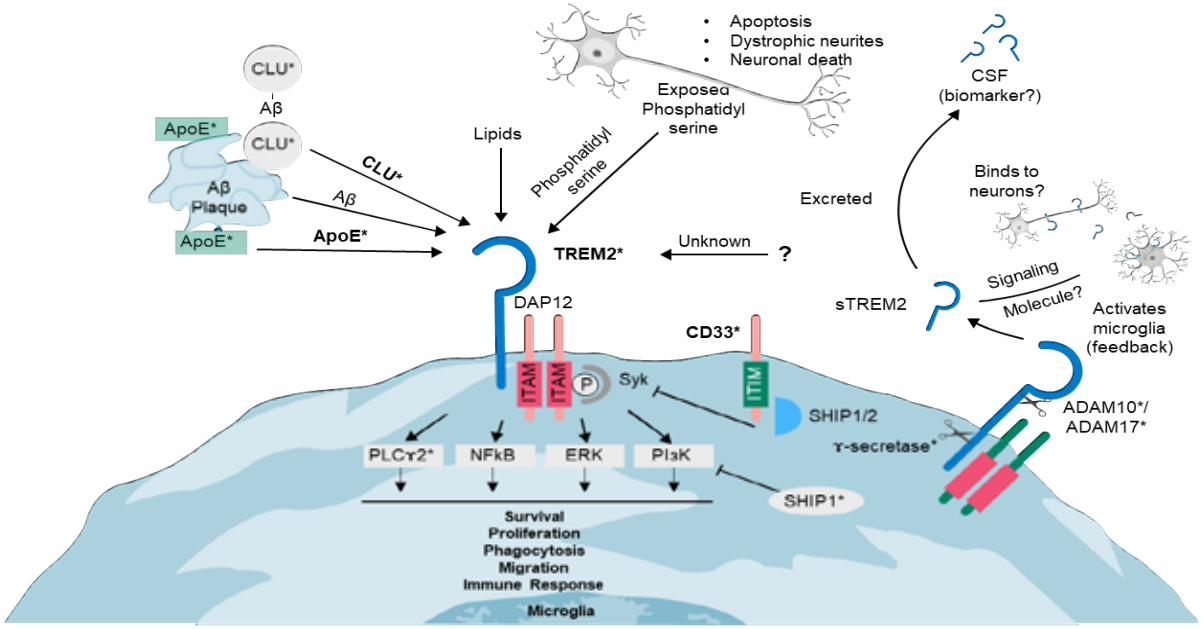
Source: Senior, *Nature Biotechnology* 2024

Key Genetic Evidence Points to TREM2 as an Exciting Target to Impact Neuroinflammation Currently Unaddressed by Approved Agents

Neuroinflammation is a complex, multicellular-mediated process and thus there are numerous outstanding questions about how best to target this process therapeutically and when to intervene in the disease course for optimal risk/benefit. One increasingly attractive and genetically supported neuroinflammatory target is TREM2, a microglial cell-surface receptor that can be expressed as a soluble fraction or as a membrane-bound receptor that is cleaved or activated via ligand binding to promote SYK phosphorylation, activating downstream cascades leading to multiple key microglial responses (exhibit 8; Hammond, et al., 2019; Colonna, 2023).

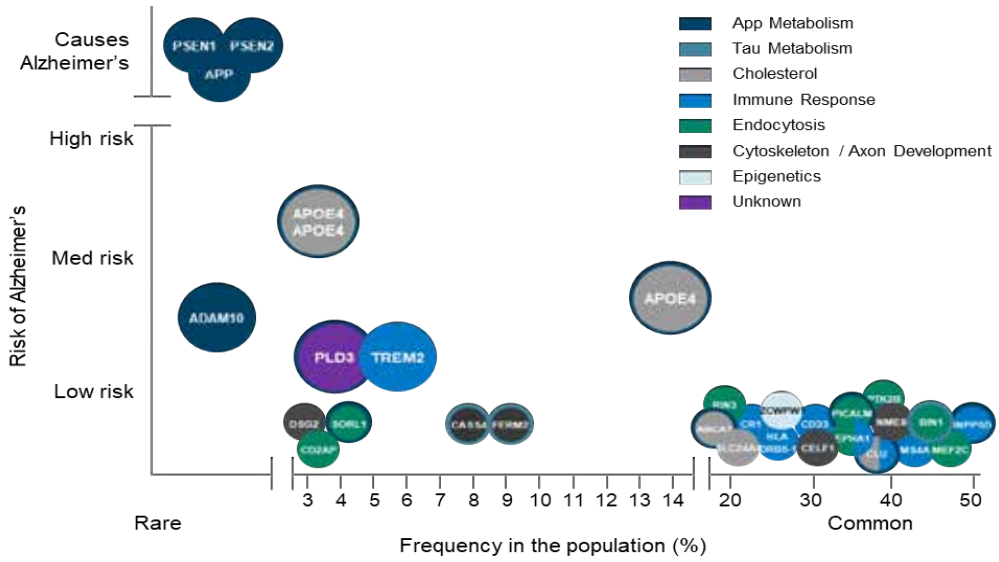
Large genome-wide association studies (GWAS) have identified mutations in TREM2 and other related immune response genes as some of the greatest risk factors for developing AD (exhibit 9). Multiple TREM2 mutations leading to increased risks have now been identified including the R47H and R62H mutations, which are believed to be partial loss-of-function mutations resulting in decreased receptor affinity for important AD pathology-related ligands such as amyloid beta (Kober, et al., 2016; Song, et al., 2017). Other mutations associated with increased risk of developing AD include the H157Y SNP, which is a mutation in the ADAM cleavage region that results in increased shedding and therefore high levels of soluble TREM2 (sTREM2) (Jiang, et al., 2016; Schlepckow, et al., 2017). While there is some debate about the role of sTREM2, we believe the human genetics and rising sTREM2 levels in disease states suggest increasing sTREM2 alone is not sufficient to be protective and therefore reducing sTREM2 is unlikely to be detrimental, particularly in the context of increased TREM2 signaling. In addition, protective gain-of-function mutations associated with proteins downstream of TREM2 (specifically PLCγ2; Sims, et al., 2017) or increased microglial response to environmental stimuli (APOEch; Chen, et al., 2024) support potential benefits with TREM2 agonist approaches. Lastly, rare loss-of-function mutations in the *TYROBP* gene, which encodes for DAP12, a membrane-bound protein that co-localizes with TREM2 and is essential for activation of downstream TREM2-mediated signaling, are associated with increased AD and dementia risk (Pottier, et al., 2016; Paloneva, et al., 2000). Collectively, we believe the human genetics results point to reduction in membrane-bound TREM2 activation as deleterious in AD, while promoting microglial activity associated with TREM2 activation could be protective.

Exhibit 8
Schematic of TREM2 Receptor Signaling in Microglia



Source: Hammond, et al., 2019, adapted by William Blair Equity Research

Exhibit 9
Known Variants Contributing to Alzheimer's Disease, by Function



Source: Karch & Goate, 2015 *Biol. Psych;* adapted by William Blair Equity Research

These mutations as well as TREM2 knockout and overexpression systems have been incorporated into numerous in vitro and animal models. Overall, the preclinical model systems illustrate binding of amyloid beta to TREM2 receptors to activate microglial motility, survival, and amyloid compaction and/or clearance appears to be a key factor in promoting a protective impact of microglia. These processes are disrupted in systems lacking TREM2 or with loss-of-function mutations expressed, discussed at length below. Less clear is the role of TREM2-mediated signaling

in tau clearance or aggregation, with various studies reporting conflicting results. These studies may indicate that the timing of intervention is key, with amyloid accumulation thought to precede fibrillary tau seeding and spreading. We also note emerging evidence from the anti-amyloid antibody therapeutic class that clearing amyloid burden is correlated with improvements in tau status in early-stage AD patients. Ultimately, animal models of AD face significant limitations and generally are not easily translated to humans, probably due to both differences in immune systems (Zhou, et al., 2020) and the lack of a naturally occurring AD-like phenotype in mice, thus requiring models of disease to harbor extensive genetic and other manipulations not necessarily reflective of the AD patient journey (Walker & Jucker, et al., 2017).

Alector's INVOKE-2 Data in AD Expected in Fourth Quarter 2024 Will Be Informative for Both TREM2 Players and the Broader Neuroinflammation Space

We believe collectively the body of evidence from human genetics and preclinical mechanistic studies supports a TREM2-focused approach to treating AD. This therapeutic strategy will need to be evaluated in the clinic, and the first key data point is expected later this year from Alector's placebo-controlled Phase II INVOKE-2 study of AL002, a TREM2 receptor stabilizing/agonizing antibody. This asset has shown signals of target engagement in a Phase I study and similar patterns of amyloid-related imaging abnormalities (ARIA) as have been seen with approved anti-amyloid therapies (see: Leveraging Neurogenetics to Usher in a New Era of Chronically Dosed, Targeted CNS Therapy; Initiating at Outperform and AAIC Update: INVOKE-2 Update Shows Similar ARIA Incidence to Amyloid Antibodies; Top-Line AL002 Data on Track for Late 2024). INVOKE-2 is a placebo-controlled common close study (48-96 weeks) enrolling 381 participants (approximately 250 study completers; see Second-Quarter Earnings: All Eyes Remain on INVOKE-2 Data on Track for Fourth Quarter After Baseline Update at AAIC and AAIC Update: INVOKE-2 Baseline Characteristics Largely Similar to Peer Programs; Catalytic Data Expected in Fourth Quarter) with early AD testing three doses of AL002. The study completed enrollment in third quarter 2023 and will close data collection in third quarter 2024, with data expected in the fourth quarter. The primary endpoint is CDR-SB (a widely accepted regulatory endpoint) with a number of secondary endpoints of cognitive measures and biomarker investigations.

We believe INVOKE-2 will provide a wealth of information on both cognitive and pharmacodynamic outcomes at various doses and should provide key proof-of-concept data if positive. We note the pivotal trials of lecanemab (CLARITY-AD) and donanemab (TRAILBLAZER-ALZ-2) showed separation on cognitive measures versus placebo as early as 6 months and maintained through at least 3 years of treatment, with potentially widening benefit when considering an external control. While these studies were much larger than INVOKE-2, they demonstrate potential for measurable decline and biomarker changes within the time frame being evaluated in the study (48-96 weeks). Key questions heading into the data include whether timing of a TREM2-based intervention in patients with mild AD will be beneficial, whether sufficient antibody levels cross the blood-brain-barrier and disperse throughout the cortex to have a therapeutic effect, and whether targeting microglia directly has a different risk/benefit profile from approved anti-amyloid therapies, among others. While not INVOKE-2 is without significant risk as the first study of its kind in AD, we remain optimistic heading into the data based on the collective genetic and preclinical data and numerous efficacy assessments. Further, we believe Alector, currently trading near cash levels, is significantly undervalued with its risk/reward skewed heavily positive leading into the fourth-quarter update. In addition, this update will have significant read-through to Vigil Neuroscience, developing its own TREM2 programs (discussed further below). Vigil will have its own significant readouts in first half 2025 when it will report full data from the IGNITE study of its TREM2 agonist antibody iluzanebart in development for adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP). The company has indicated the potential to file for accelerated approval, depending on the data. Additional data from the company's small molecule TREM2 agonist including in an AD patient cohort is also expected in first quarter 2025.

Targets to Modulate Neuroinflammation

Neuronal damage is a key pathological hallmark of degenerative CNS diseases including AD, PD, ALS, HD, spinocerebellar ataxia (SCA), and MS, among others. Despite differences regarding underlying genetic risk factors, timing of disease onset, and presence of aggregate proteins, neuronal damage is frequently associated with chronic activation of the central nervous system's innate immune response. There is increasing understanding that this system is not only critically involved in shaping the brain during development, but also key to mediating damage response and supporting regeneration and repair throughout the life span. However, when dysregulated, neuroinflammation can impart a self-perpetuating deleterious cycle that contributes to progression of a vast range of CNS neurodegenerative disease processes as noted above. These observations have stimulated therapeutic approaches to modulate the immune system in neurodegenerative diseases. Some of the more commonly explored therapeutic targets are summarized below, although we emphasize this is not an exhaustive list in a rapidly evolving space that is one to watch in the coming months and years.

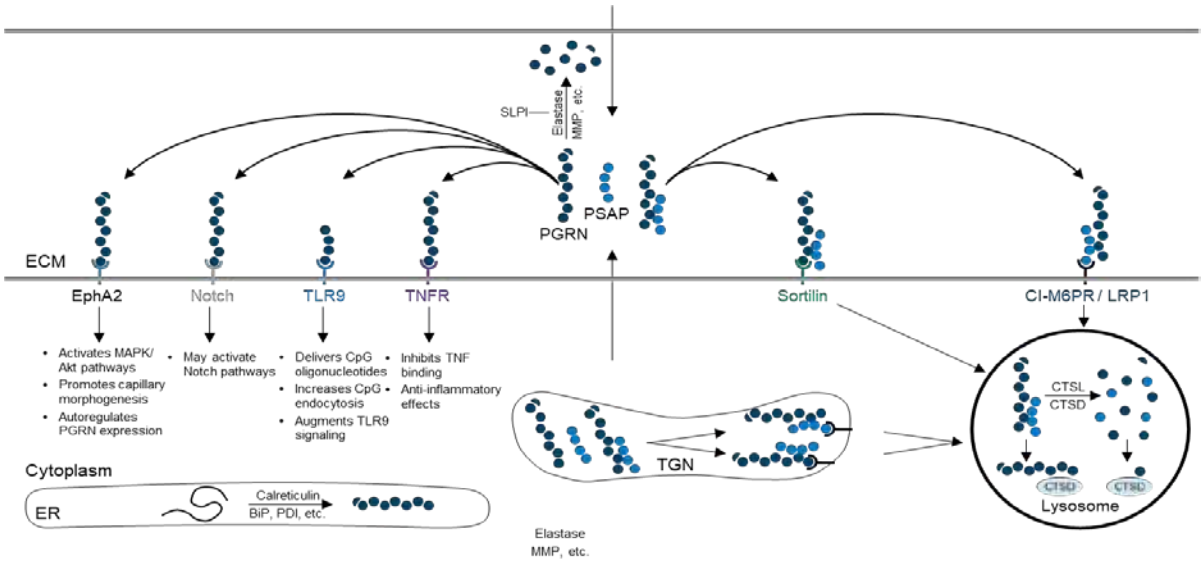
TREM2

Triggering receptor expressed on myeloid cells 2 (TREM2) is the focus of this report and is discussed in greater detail below. At a high level, TREM2 signaling in the CNS acts to regulate microglial activation states, with variations in microglial activity involved in phagocytosis, cytokine secretion, neurotrophic factor release, synaptic pruning, induction of apoptosis, and activation of other cell types through paracrine and juxtacrine signaling mechanisms (Colonna, 2023). Genetic variants of TREM2 resulting in decreased function have been linked to numerous neurodegenerative diseases including AD, FTD, PD, Nasu-Hakola disease, and ALS (Jay, et al., 2017). Attempting to increase TREM2-mediated activity has become an attractive approach to treat neurodegenerative disease, with key clinical proof-of-concept data expected in late 2024 from Alector's Phase II study of AL002 in patients with Alzheimer's disease and Vigil's Phase II study of iluzanebart in ALSP in the first half of 2025, among other peer programs.

PGRN

Progranulin (PGRN), encoded by the *GRN* gene, is a protein with diverse function including roles in neuronal and microglial development, survival, function, and maintenance. More specifically, progranulin is key for regulating lysosomal biogenesis, inflammation, repair, and the cellular stress response (exhibit 10). Loss-of-function mutations in the *GRN* gene have a causal relationship with the development of FTD, and mutations that reduce PGRN levels are associated with an increased risk of developing AD and PD and may exacerbate the progression of ALS and FTD cases associated with a hexanucleotide repeat expansion in the C9orf72 gene (Rhinn, et al., 2022). PGRN overexpression has been shown to be protective in various animal models of neurodegeneration, and as such, has emerged as an attractive therapeutic target. Alector and partner GSK are currently testing AL101, a SORT1 antibody designed to increase circulating levels of PGRN, in a Phase II study in AD, and latozinemab, another SORT1 antibody designed to increase circulating levels of PGRN, currently in the Phase III INFRONT-3 pivotal trial in patients with FTD. Other approaches include gene therapies like those in development by Passage Bio, AviadoBio, and Prevail Therapeutics (acquired by Eli Lilly in 2020); peptide conjugates including those from Takeda/Denali; and small molecule potentiators including those developed by Arkuda and Muna, among others.

Exhibit 10
Schematic of Progranulin Receptor Signaling

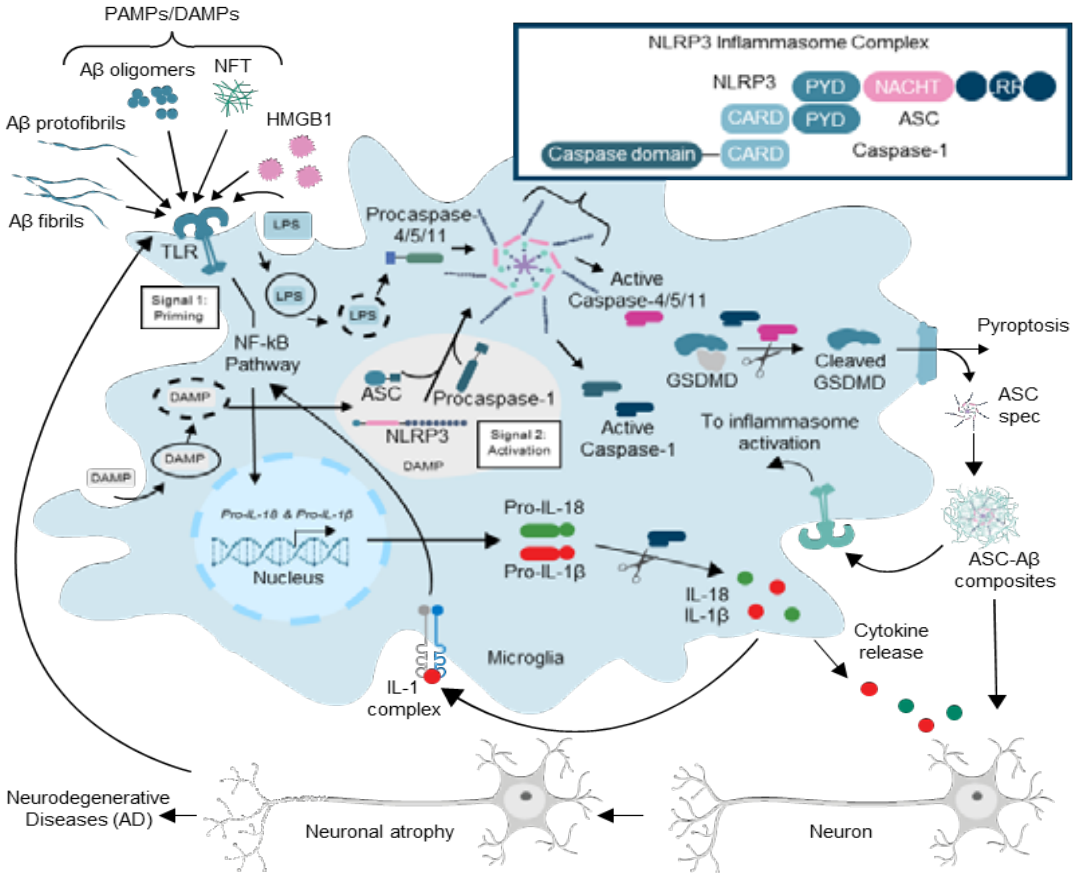


Source: Paushter, et al., 2018 *Acta Neuropathologica;* adapted by William Blair Equity Research

NLRP3

Inflammasomes are multiprotein complexes that are formed in response to inflammatory stimuli and are responsible for activation of innate immunity cascades. NLRP3 is one of the most well-characterized inflammasome systems, and canonical activation involves NF-κB-dependent transcriptional upregulation of NLRP3 and pro-IL-1β followed by oligomerization and activation of the NLRP3 inflammasome and pro-caspase-1. Active caspase-1 then cleaves pro-IL-1β and pro-IL-18 to their mature forms, IL-1β and IL-18, which get secreted. In addition, caspase-1 can cleave gasdermin D, releasing its N-terminal fragment, which translocates to the plasma membrane inducing pore formation and pyroptotic cell death and releasing ASC proteins, which can potentially exacerbate amyloid-β deposition (Stephenson, et al., 2018, Hanslik & Ulland, 2020; exhibit 11). IL-1β and IL-18 are important activators of pro-inflammatory signaling in the CNS in the context of infection, but chronic activation can lead to excessive phagocytosis, neuronal damage, and cell death. Increased IL-1β and IL-18 are often seen in patients with a variety of neurodegenerative diseases, with IL-1β specifically thought of as a hallmark pro-inflammatory cytokine, and therefore prevention of upstream NLRP3-mediated inflammasome activity could be a mechanism to prevent harmful chronic inflammation. Examples of companies pursuing this strategy include Ventus, which is testing VENT-02 in a Phase I study; Ventyx with its CNS penetrant NLRP3 inhibitor VTX3232 currently in a Phase II study in PD patients (NCT06556173); and NodThera, which recently presented biomarker data from a Phase Ib/IIa study of NT-0796 showing reductions in CSF levels of multiple key pro-inflammatory markers in healthy elderly controls. Targets like RIPK1/RIPK3 are also upstream of NLRP3 but eventually signal through this inflammasome, and companies like Sanofi and Denali are developing assets against these targets.

Exhibit 11
Schematic of Microglial Response Through Inflammasome Activation



Source: Hanslik & Ulland, 2020; adapted by William Blair Equity Research

Others

Given the complexity of the immune system and variation in pathology between disease states and even patients who have the same disease at different stages, there is a multitude of potentially viable neuroimmune therapeutic targets, with even more emerging as understanding of underlying pathology improves. The next wave of innovation could feature Tyk2 inhibitors like Biohaven's BHV-800, currently in a Phase I study and with a Phase II study in PD expected to initiate by year-end; modulators of the complement cascade such as those in development from Annexon and Vanqua Bio; or PIKfyve inhibitors such as those in development by Verge Genomics. We have provided a (certainly non-exhaustive) summary of known programs involving neuroinflammatory targets in preclinical and clinical development stages in exhibit 1 and appendix A. We look forward to following this space in the coming months.

TREM2 Biology and Signaling Overview

Origin and Function of Microglial Cells

Microglia, the resident myeloid cells of the CNS, are derived from yolk sac progenitor cells that populate the brain early in development. Microglia account for 5%-20% of all glial cells in the adult brain, depending on the brain region (Gosselin, et al., 2017). Microglia are distinct from other myeloid-lineage cells such as monocytes, which include CNS-infiltrating macrophages. Both microglia and monocytes are members of the phagocytic system and carry out essential tissue-specific functions that are critical for homeostasis, tissue repair, and pathogenic response (Spiteri, et al., 2022).

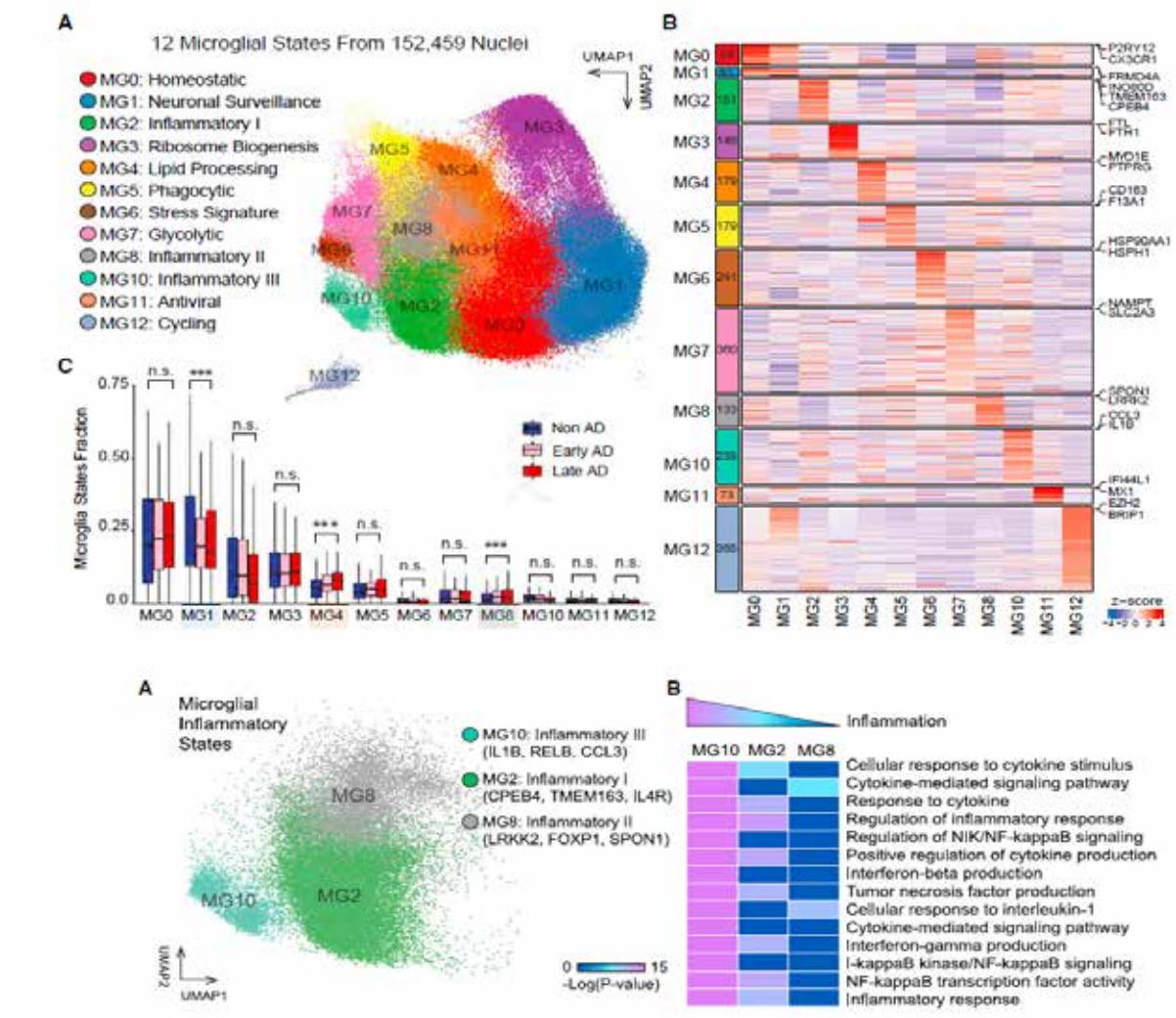
Excellent reviews on the role of microglia in various health states have been published, including Cai, et al., 2022; Keren-Shaul, et al., 2017; Deczkowska, et al., 2018, and Gratuze, et al., 2018. We refer readers to these for additional detail, but briefly, microglia play diverse roles across the lifespan and in the context of insult response and disease. During development, microglia play a key role in proper synaptic pruning and neuronal survival. As the key innate immune cells of the CNS, microglia respond to infection and promote tissue repair and clearance of apoptotic cells and cellular debris. Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) act as activation triggers to induce microglial state changes and include misfolded and aggregated proteins as in, for example, amyloid and tau aggregates in AD; SOD1, TDP-43, and other aggregates in ALS; and alpha-synuclein (α-syn) deposits in PD. Cellular receptors that recognize PAMPS and DAMPs such as heat-shock proteins (HSPs), protein aggregates, viral and bacterial antigens, and oxidized lipids, include the Toll-like receptors (TLRs), C-type lectins and oxidized lipoprotein detectors, and nuclear oligomerization domain-like receptors (NLRs) that play a key role in the assembly of the NOD, LRR, and pyrin-domain containing 3 (NLR3) inflammasome. This inflammasome activation can then lead to cytokine release such as IL-1β and IL-18, which can induce inflammatory states in microglia and recruit additional cells to areas of damage. However, excessive IL-1β and IL-18 exposure can be neurotoxic (Hanslik & Ulland, 2020). Alternatively, TREM2 also binds and responds to cellular debris and other ligands, leading to changes in activation state to promote phagocytosis, microglial motility and survival, and other functions discussed in detail below.

At a high level, microglial activation had been described in terms of pro- or anti-inflammatory phenotypes based on morphology, changes in cell-surface markers, and cytokine release profiles (Cherry, et al., 2014). However, advances in nuclear transcriptomics have greatly increased the complexity of classifying microglial activation states, with recent studies suggesting as many as 12 unique microglial transcriptional states involved in various processes and stimuli responses when assessing human iPSC microglia-like cells (exhibit 12; Sun, et al., 2023). These transcriptional states map to various functions such as homeostasis, surveillance, phagocytosis, and multiple inflammatory responses, among others.

Interestingly, the study by Sun and colleagues showed that proposed lipid-processing MG4-type microglia and proposed inflammatory MG8-type microglia showed significantly increased levels in AD, while proposed neuronal surveillance MG1-type showed significantly decreased levels in AD relative to levels in non-AD controls. In addition, correlation analysis between the microglial state proportions and multiple pathological variables seen in prefrontal cortex tissue samples showed that lipid-processing MG4 microglia had the most significantly positive correlation with tau neurofibrillary tangles, amyloid, Braak score, and cognitive decline, while inflammatory MG8 was more positively correlated with amyloid plaque burden. Phagocytic MG5 microglia were more positively correlated with tangles, suggesting a potential role in elimination of tau as well, depending on the activation state. Lastly, functional categorization of activation pathways significantly enriched the three "inflammatory" clusters and pointed to a pattern of decreasing microglial inflammatory status (MG10>MG2>MG8), suggesting that these clusters may represent states during the progression of inflammation. This progression through inflammation processes may be impaired in aging

and neurodegenerative diseases, thereby preventing proper stimuli clearance and subsequent inflammation resolution leading to chronic inflammation, lack of protein aggregate clearance, and microglial exhaustion (Millet, et al., 2024).

Exhibit 12
Transcriptomic Analysis of iMG Profiles



Source: Sun, et al., 2023

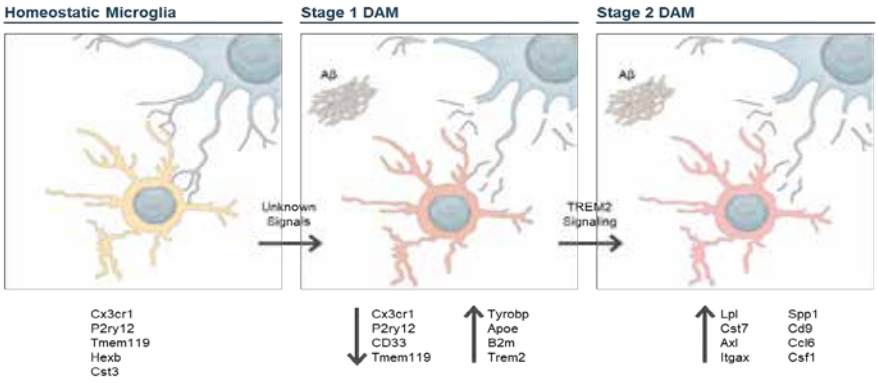
TREM2 Signaling and Normal Function

As discussed above, microglia can adopt a range of phenotypic states in the presence of various disease- and damage-associated ligands within the cellular microenvironment. These microglia display unique transcriptional and functional signatures and are sometimes broadly referred to as disease-associated microglia (DAM; Deczkowska, et al., 2018). DAM are characterized as immune cells expressing typical microglial markers such as *Iba1, Cst3,* and *Hexb,* along with downregulation of microglial genes indicative of homeostatic states, including *P2ry12, P2ry13, Cx3cr1, CD33,* and *Tmem119.* DAM further display upregulation of genes involved in lysosomal, phagocytic, and lipid metabolism pathways, including several known AD risk factors, such as *Apoe, Ctsd, Lpl, Tyrobp,* and

Trem2. Importantly, single-cell RNA-seq studies indicate the DAM phenotype is conserved in multiple rodent models as well as humans (Keren-Shaul, et al., 2019; Deczkowska, et al., 2018), which could help improve translatability of the microglial biology in drug development across species.

Multiple signaling cascades are associated with the DAM phenotype and may therefore represent additional therapeutic targets. However, TREM2 signaling appears to be critical to induce and sustain the transition into an activation state characterized by upregulation of the lysosomal, phagocytic, and lipid metabolism pathways (such as *Lpl, Cst7, and Axl*) required to clear cellular debris and respond fully to damage signals in the disease microenvironment (exhibit 13).

Exhibit 13
Schematic of Disease Associated Microglial Activation and Key Regulators



Source: Deczkowska, et al., 2018; adapted by William Blair Equity Research

TREMs are a family of cell-surface receptors expressed broadly on myeloid cells, discussed in an excellent review by Dr. Marco Colonna published in 2023. Briefly, TREM1 was first identified and shown to be an amplifier of immune response to pathogens such as microbial products, and TREM receptors are generally thought to function as modulators that define the threshold and duration of myeloid cell responses. The TREM2 receptor includes a short cytoplasmic domain that lacks obvious signaling motifs but forms a complex with other signaling players, most commonly DNAX-activating protein of 12 kDa (DAP12), encoded by *TYROBP*, which contains a cytoplasmic immunoreceptor tyrosine-based activation motif (ITAM). In response to TREM receptor binding of known ligands such as amyloid-β, apolipoproteins, lipoproteins, and anionic lipids (with additional characterization of other ligands needed), SRC kinases phosphorylate ITAM tyrosines within the DAP12 intracellular region. This results in activation of scaffolding proteins and downstream signaling molecules such as phosphatidylinositol 3-kinase (PI3K), linker for activation of T-cell family member 2 (LAT2), phospholipase Cγ2 (PLC γ2), guanine exchange factor VAV family members, and the E3 ubiquitin ligase CBL. DAP12 signaling via SYK can also induce ERK signaling pathways, although ties to TREM2 activation are somewhat less clear. PI3K triggers the kinase AKT, which activates mTOR to support the pathway responsible for protein synthesis and energy metabolism and inactivates glycogen synthase kinase 3β (GSK3β). Inactivation of GSK3β stabilizes β-catenin, which acts to promote cell survival and proliferation. Phospholipase Cγ2 degrades phosphatidylinositol 4,5-biphosphate into inositol 1,4,5-triphosphate and diacylglycerol, which induce intracellular Ca2+ mobilization and NF-κB activation, respectively (exhibit 8, above; Hammond, et al. 2019; Colonna, et al., 2023). NF-κB induces the expression of various pro-inflammatory genes, including those encoding cytokines and chemokines, and participates in inflammasome regulation.

TREMs can form complexes with other receptors beyond DAP12, including DAP10. DAP10 lacks an ITAM region for signal transduction but does contain a cytoplasmic YXNM motif similar to that identified in the T-cell co-stimulatory molecules CD28 and ICOS. This motif can directly recruit the

p85 subunit of PI3K11 and GRB2, with GRB2 playing a role in promoting cellular motility. Overall, DAP12 and DAP10 activation in conjunction with other signal transduction pathways creates a network that facilitates regulation of cellular responses to extracellular stimuli.

TREM2 Dysfunction in Disease States

TREM2 is specifically expressed by tissue macrophages, both on the cell surface and in intracellular pools, and can be found on/in microglia in the central nervous system, osteoclasts in the bone, and macrophage subsets in the liver, adipose tissue, skin, gut, and tumors. Key roles of TREM2 signaling were identified through the study of a rare disease known as Nasu-Hakola disease (NHD). NHD is an autosomal recessive disorder that causes joint swelling and recurring bone fractures during adolescence, followed by an early-onset frontal-type dementia that begins to manifest by age 30 and often leads to death by age 40 (Paloneva, et al., 2001). NHD is caused by homozygous loss-of-function mutations in either *TYROBP* (encoding DAP12) or *TREM2* genes, although similar TREM2 mutations can also cause frontotemporal dementia with no bone pathology. Relatedly, heterozygous loss-of-function variants of *TREM2* are known risk factors for the development of Alzheimer's disease, frontotemporal dementia, Parkinson's disease, and ALS, pointing to microglia as key players in dementia progression (Guerreiro, et al., 2013; Borroni, et al., 2014; Rayaprolu, et al., 2013; Cady, et al., 2014).

Additional genetic studies and preclinical models implicating TREM2 as a therapeutic target are discussed further below, but briefly, given the role of microglia in proper neuronal health and function, researchers have sought to understand microglial activity in neurodegenerative disease settings. Certain TREM2 mutations have been linked to ineffective ligand binding, such as reduced response to extracellular phospholipids, while characterization of the microglial transcriptome in TREM2-deficient mice during accumulation of amyloid-β plaques demonstrated that TREM2 is required to sustain the microglial response to amyloid-β required for effective clearance. This response includes expression and coordination of TREM2, integrins (Cd11c), pro-inflammatory chemokines (Ccl4), extracellular matrix proteins (Spp1), and genes directing lipid metabolism (Lpl), cholesterol efflux (ApoE), and lysosomal function (Ctsb, Ctsd, and Cts7) (Colonna, et al., 2023; Nugent, et al., 2020). Additional TREM2-mediated microglial responses to amyloid-β include an interferon-response profile, MHC class II expression, and proliferation induction, indicative of a CNS innate immune response.

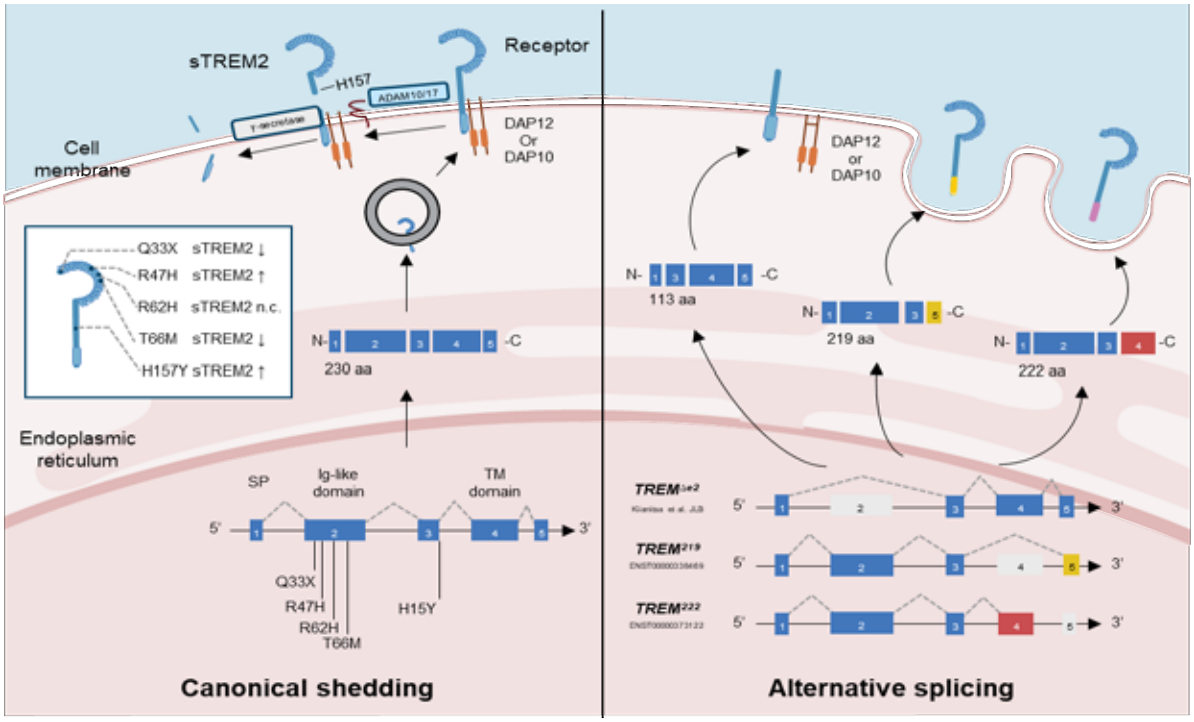
In light of this TREM2 functionality, it is unsurprising that hypofunctional TREM2 impairs the ability of microglia to encase amyloid-β plaques, resulting in enhanced spreading and neurotoxicity of amyloid-β plaques, which leads to progression of AD in mouse models. Similar results were observed in AD mouse models that lacked TREM2 or that were grafted with human microglia lacking TREM2 (Colonna, et al., 2023). Conversely, overexpression of TREM2 was protective against toxic amyloid-β pathology in the 5xFAD mouse model. However, the role of TREM2 in regulating intracellular tau pathology, particularly in mouse models of AD, is less clear, with different models showing TREM2 deficiency related to less severe pathology in some and aggravated pathology in others. Varying evidence from these models is discussed further in the following sections.

While the focus of this *NeuroNavigator* is TREM2-mediated microglial activity and therapeutic intervention, it is worth noting that TREM2 signaling has been linked to other physiological processes, including metabolic syndrome. A study in mice with insulin resistance induced by a high-fat diet revealed an accumulation of TREM2+ lipid-associated macrophages (LAMs) encircling hypertrophic adipocytes. Genetic ablation of *Trem2* in these mice inhibited the LAM response and aggravated adipocyte hypertrophy, leading to body fat accumulation, hypercholesterolaemia, and insulin resistance (Jaitin, et al., 2019). We view this as further support for TREM2-mediated signaling as a key response to potentially damaging environmental stimuli.

Soluble TREM—A Player or Bystander?

The extracellular domain of the TREM2 receptor includes a cleavable region, referred to as soluble TREM2 or sTREM2, once shed from the cell surface via ADAM10 and ADAM17 proteases with additional processing by γ-secretase (exhibit 14; Filipello, et al., 2022; Wunderlich, et al., 2013). In addition, an alternative TREM2 transcript lacking the transmembrane domain has been characterized and may contribute approximately 25% of total sTREM2 levels, providing an alternative source of sTREM2 signaling, a potentially important factor to consider in the case of therapeutics that stabilize and prevent TREM2 cleavage (Del-Aguila, et al., 2019).

Exhibit 14
Schematic of TREM2 Isoforms and Location of Select AD-Risk Mutations



Source: Filipello, et al., 2022; adapted by William Blair Equity Research

The exact function of sTREM2 remains unclear. Some hypotheses suggest sTREM2 shedding, which may occur following ligand binding, acts as a decoy receptor to bind endogenous ligands and negatively regulate downstream TREM2 signaling to prevent excessive activity (negative feedback loop). To maintain membrane-bound TREM2 levels sufficient for continued activity following cleavage, upregulation of TREM2 translation and trafficking to the cell surface would be needed. Sustained sTREM2 elevations would then be reflective of continuous cell-surface receptor replenishment. Indeed, there is evidence for both upregulation of TREM2 protein expression and sTREM2 levels in cerebrospinal fluid (CSF) under conditions of increased microglial activation in inflammatory neurologic diseases (Diaz-Lucena, et al., 2021; Piccio, et al., 2008). In addition, the intracellular cleavage product of TREM2 initially generated by ADAM proteases was reported to inhibit TREM2 signaling through interaction with the DAP12 co-activator, suggesting that both the sTREM2 and the resulting intracellular fragment are involved in preventing premature signaling, which we believe argues against beneficial effects of TREM2 cleavage given negative signal regulation.

Interestingly, the intracellular fragment of TREM1 is further cleaved by γ-secretase to alleviate this inhibition (Wunderlich, et al., 2013). Initially, γ-secretase inhibitors were developed as potential treatments for AD given the role of γ-secretases in the cleavage of amyloid precursor protein (APP), generating various amyloid-β isoforms, which can become aggregated and linked to cognitive decline. However, trials of γ-secretase inhibitors resulted in toxicity concerns and cognitive worsening (see: Potential for Game-Changing APPlications: Previewing ALN-APP Readout to Enable CNS Delivery of siRNA). This may be related to excessive reduction in APP processing and/or inhibition of other signaling systems including Notch signaling, another cleavage-depending cascade, which is implicated in neuronal survival. Another possibility is that these poor outcomes were a consequence of preventing γ-secretase-mediated restoration of TREM2 signaling through inhibition of intracellular fraction cleavage. Indeed, loss-of-function mutations in presenilin, the catalytic components of γ-secretases, have been linked to early-onset AD. While these are broadly believed to be related to alterations in amyloid processing, excessive inhibition of TREM2 signaling due to reduced intracellular fragment processing could also contribute to this process (Wunderlich, et al., 2013; Hur, 2022).

A further contributing possibility is that sTREM2 acts as a signaling ligand itself. Recent work from Zhang, et al., 2023 using HEK293 and SH-SY5Y cell lines suggests that transgelin-2 (TG2) acts as a receptor for sTREM2, inducing RhoA phosphorylation at S188 to deactivate the RhoA-ROCK-GSK3β pathway, thereby ameliorating tau phosphorylation and presumably neurofibrillary tangles. This was translated into an animal model, with overexpression of sTREM2 or administration of the active peptide rescuing tau pathology and behavioral defects in tau P301S transgenic mice, which overexpress an FTD-causing mutant tau. This may be related to work published by Zhong, et al., 2017 showing that sTREM2 promotes microglial survival in a PI3K/Akt-dependent manner, which stimulates the production of inflammatory cytokines via NF-κB, and suppresses apoptosis. Triggering of certain inflammatory responses was also blunted with sTREM2 variants associated with increased risk of AD. The study also showed sTREM2 delivered to the hippocampi of both wild-type and *Trem2*-knockout mice elevated the expression of inflammatory cytokines and induced morphological changes of microglia. However, it remains unclear how TG2 acts as a receptor as the protein is believed to lack a membrane-spanning domain, which raises the question if TG2 can actually act as a receptor for sTREM2 and how well the P301S tau mouse model translates to humans given differences in pathology (lack of amyloid accumulation). More generally, questions remain on what level of sTREM2 reduction would potentially lead to deleterious effects in humans; when in disease course, what sTREM2 reductions would be most impactful; and if sTREM2-induced microglial activation is necessary or sufficient to reduce disease pathology or whether similar beneficial effects can be seen with membrane-bound TREM2 agonism.

Genetic studies in humans have identified a TREM2 variant (H157Y) with a mutation in the ADAM cleavage region, which results in increased shedding, elevated sTREM2 levels, and a considerable increase in risk of developing AD (*P* corrected=0.02, odds ratio=11.01 in Han Chinese population, 4.7 in Caucasian; Jiang, et al., 2016; Schlepckow, et al., 2017; Song, et al., 2016). This increased risk may be due to reduced membrane-bound TREM2 and associated downstream signaling cascades. However, this is somewhat contradicted by findings from a study using the 5xFAD mouse (a murine model of fast amyloid deposition) engineered with CRISPR/Cas9 to express the *Trem2* H157Y mutation (Qiao, et al., 2023). In this study, homozygous expression of the *Trem2* H157Y mutation led to increased sTREM2 shedding, which was correlated with a reduction in amyloid-β42 in cortical lysates, including reductions in neurotoxic oligomeric amyloid-β42 and reduction in plaque coverage and density in both cortex and hippocampus at 8.5 months, suggesting potentially beneficial effects of increased sTREM2. However, there were no differences in plaque size or fibrillar amyloid-β levels. Further, there was no significant change in neuronal/synaptic loss markers in animal models with the *Trem2* H157Y mutation, but there were significant reductions in TREM2-positive areas, potentially related to the reduced number of microglia overall as indicated by reduced Iba1 and CD68 signal at the 8.5-month late-disease-stage time point. There was also

reduced TREM2 signaling as indicated by reductions of pSYK levels and pSYK/SYK ratios despite no difference in the total SYK levels, indicating that *Trem2* H157Y suppressed TREM2 signaling in the presence of amyloid-β. Interestingly, there was no effect on amyloid plaque area, densities, or sizes in the cortex or hippocampus at earlier disease stages (4 months).

While one possibility is beneficial effects of increased sTREM2 given reductions in certain amyloid-β measures, this in confounded by lack of benefit early in disease stage, lack of reduced fibrillary amyloid-β, and lack of benefit on neuronal/synaptic loss. Importantly, this study does show *Trem2* H157Y leads to reduced TREM2 signaling in the presence of amyloid-β, particularly at high levels. This somewhat contradictory mouse model data may indicate that increased risk of disease in humans is due to the non-amyloid effects of the mutation (for example on tau accumulation, especially in more advanced disease) or highlight the lack of translation between animal models and humans in complex AD pathology, which is a known caveat of the preclinical models.

In humans, numerous studies have linked increasing sTREM2 (particularly in CSF) with multiple disease states including AD, MS, FTD, and CNS infections, suggesting it is unlikely to be protective against disease development on its own in humans, although its impact may change with disease stage (Filipello, et al., 2022). For example, longitudinal studies of patients with AD showed that a higher ratio of sTREM2 versus phosphorylated tau in the CSF predicts slower cognitive decline; in addition, high CSF concentrations of sTREM2 were associated with attenuated amyloid and tau positron-emission tomography (Colonna, et al., 2023). Ultimately, the putative protective effects of TREM2 and sTREM2 may be complementary rather than antagonistic, and potentially both may be protective against AD, or sTREM2 increases may be largely a byproduct of increased TREM2 signaling in general (reviewed in Brown & St. George-Hyslop, 2021; Filipello, et al., 2022). Additional interventional studies in humans will be important to confirm potential benefits of TREM2 and/or sTREM2 signaling in humans.

While the exact signaling function of sTREM2 in the context of neurodegenerative disease remains unclear, emerging roles for sTREM2 include a biomarker of target engagement for therapeutics targeting TREM2 and a potential indicator of disease progression. The current view by drug developers is that increasing CSF sTREM2 is a function of increased TREM2 signaling. CSF sTREM2 positively correlates with CSF tau and phosphorylated tau (ptau), but not with CSF amyloid-β_{42}, suggesting that sTREM2 may be associated with pathological processes occurring after the accumulation of amyloid-β and beginning approximately five years before clinical symptom onset in autosomal dominant forms of AD (Suarez-Calvet, et al., 2016; Deming, et al., 2019). In the absence of data suggesting a clear beneficial impact of certain sTREM2 levels in humans along with the knowledge that soluble TREM isoforms are generated without requiring membrane-bound cleavage, we accept that leaders in the TREM2 clinical development field currently point to sTREM2 as a useful pharmacodynamic marker and look forward to future clinical data to better understand any relationship between sTREM2 and disease progression. From a regulatory perspective, the use of sTREM2 as a biomarker of any sort has not yet been validated in a prospectively designed and well-controlled clinical trial, to our knowledge.

TREM2 in Aging—Considerations for Timing of Intervention in Neurodegenerative Disease
TREM2 expression and signaling, and microglial states in general, have been shown to change with age. For example, independent studies have shown that CSF sTREM2 levels positively correlate with human age and rise from about 2 ng/ml at 43 years to 6 ng/ml at 80 years of age (Henjum et al., 2016; Filipello, et al., 2022). Sleep disturbances associated with age and/or prodromal neurodegenerative disease may also impact microglial cell activity and sTREM2 levels (Hu, 2021). Aging is associated with alterations in microglial health and function in general, as discussed in Yoo & Kwon, et al., 2021. For example, studies of aged mice suggest reduced functional recovery after spinal cord injury (SCI) associated with impaired induction of IL-4

receptor α (IL-4Rα) on microglia (Fenn, et al., 2014). Further, ex vivo cultured microglia isolated from the brain of aged mice secreted greater amounts of pro-inflammatory cytokines, such as TNF-α and IL-6, and exhibited less amyloid-β phagocytosis, leading to higher amyloid burden (Njie et al., 2012). Other animal studies have suggested that proteomic analysis of aged microglia (CD11b+ve) show disruption in chromatin remodeling, loss of nuclear architecture, and impairment in RNA processing, suggesting functional and survival deficits (Flowers, et al., 2017). In the Flowers study, aged microglia showed a bioenergetic shift from glucose to fatty acid utilization, linking with the results of Baik, et al., 2019, which showed that chronic exposure to amyloid-β led to metabolic reprogramming of microglia associated with a tolerant state characterized by diminished immune responses. This microglial exhaustion and tolerance to disease stimuli was rescued with recombinant interferon-γ treatment, and we hypothesize that similar rescue could be induced with TREM2-mediated activation.

With aging, microglia can overexpress pro-inflammatory cytokines such as tumor necrosis factor (TNF)α, TNFβ, interleukin (IL)-1α, IL-1β, and IL-6, and continuous activation of cytokine receptors are thought to contribute to a mild chronic inflammatory condition that develops over time (reviewed in Harry, 2014). This pro-inflammatory signature coincides with a decrease in anti-inflammatory cytokines, such as IL-10 (Ye and Johnson, 2001). It has been hypothesized that the active monitoring functions of microglia become compromised due to an onset of cell senescence with age that hinders the cell's ability to sense changes in its environment, limiting its ability to detect and respond to aggregate prone or neurotoxic proteins. For example, a loss of phagocytic ability of the cells would result in the accumulation of aberrant proteins, such as amyloid beta, α syn, and apolipoprotein E (ApoE), that are known to be associated with neurodegenerative diseases. In addition, with aging, microglia may shift their functional phenotype such that they either express a higher level of proinflammatory factors, creating an environment facilitating oxidative stress and becoming toxic to the neuronal or glial population. Such a shift could also occur in microglia that would inhibit the regulatory aspects or repair capabilities of microglia to downregulate inflammation and promote recovery and tissue remodeling (Harry, 2014).

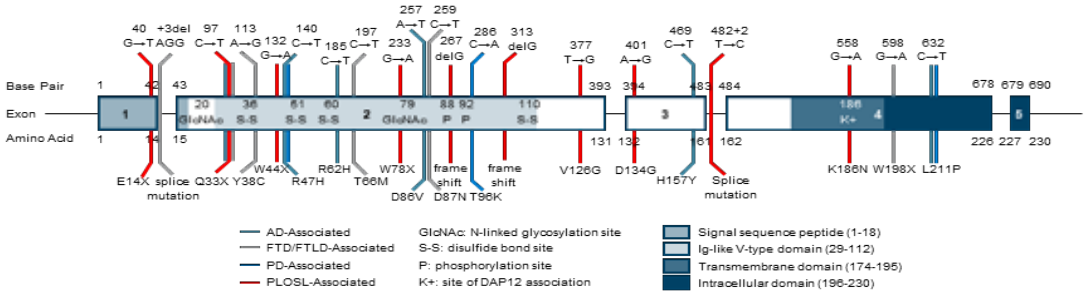
In fact, studies from postmortem human tissue show that degenerating neuronal structures positive for tau (neuropil threads, neurofibrillary tangles, neuritic plaques) were invariably colocalized with severely dystrophic (fragmented) microglia rather than with activated microglial cells. Based on Braak staging of AD neuropathology, the researchers determined that microglial dystrophy preceded the spread of tau pathology and that deposits of amyloid-β protein devoid of tau-positive structures were found to be colocalized with nonactivated, ramified microglia (Streit, et al., 2009). Collectively, the authors concluded that progressive, aging-related microglial dysfunction and degeneration contribute to the onset of sporadic AD. The potential role of TREM in permitting or preventing this age-related dysfunction in humans remains a key question when considering the therapeutic potential for TREM2-activating approaches and when to intervene in a specific neurodegenerative disease setting.

Genetics of TREM2 Mutations and Neurodegenerative Disease Risk—Focus on AD

Numerous TREM2 mutations in humans have been identified and are associated with varying risk of neurodegenerative diseases (exhibit 15; Jay, et al., 2017; Jin, et al., 2014; Guerreiro, et al., 2013). As explained previously, homozygous TREM2 mutations were first identified as the genetic cause of Nasu-Hakola disease, which is characterized clinically by bone cysts and fractures, neuropsychiatric symptoms, and dementia. Subsequent studies in families with hereditary FTD found these same TREM2 variants, among others, in either homozygosity or heterozygosity in these patients. Other TREM2 mutations were linked to AD with certain variants increasing risk of late-onset disease by 2- to 4-fold, or similar to the risk associated with APOE4 heterozygosity. In particular, the R67H variant has been linked to significantly increased risk of AD onset, ranging from 2.6 to 4.5 times increased risk, depending on the source and population studied (exhibit 16; Jin, et al., 2014; Guerreiro, et al., 2013). While the exact mechanism by which TREM2 mutations increase the risk of disease remains unknown, consequences of some more well-studied mutations on cell-surface expression, ligand binding, phagocytosis, and other microglial functions as observed in various models are discussed elsewhere in this report.

Exhibit 15

SNP Mutations Associated With Variable Risk for Neurodegenerative Diseases



Gene Variant	Protein Change	Associated Pathologies
40G→T	E14X	PLOSL
42+3 delAGG	Splice mutation (partial skipping of exon 2)	FTD/FTLD
97C→A	Q33X	AD FTD/FTLD PLOSL
113A→G	Y38C	FTD/FTLD
132G→A	W44X	PLOSL
140→T	R47H	AD FTD/FTLD PD ALS Essential Tremor
185→T	R62H	AD
197→T	T66M	FTD/FTLD
233G→A	W78X	PLOSL

Gene Variant	Protein Change	Associated Pathologies
257A→T	D86V	FTD/FTLD
259C→T	D87N	AD
267→delG	Frameshift (premature stop)	PLOSL
286C→A	T96K	FTD/FTLD
313delG	Frameshift (premature stop)	PLOSL
377T→G	V126G	PLOSL
401A→G	D134G	PLOSL
469C→T	H157Y	AD
482+2T→C	Splice mutation (predicted skipping of exon 3)	PLOSL
598G→A	K186N	PLOSL
598G→A	W198X	FTD/FTLD
632C→T	L211P	AD FTD/FTLD

Source: Jay, et al., 2019

Exhibit 16
Coding Variants in TREM2 Gene and Associated Risk of AD

Coding Variants Found in TREM2 through DNA Sequencing in Patients with Alzheimer's Disease and in Controls.*

Variant	SNP Number	Position†	Minor Alleles	Patients with Alzheimer's Disease		Controls		Reference Allele	P Value‡	Odds Ratio (95% CI)	Polyphen-2ʃ
				No. of Nonreference Alleles	No. of Cases	No. of Nonreference Alleles	No. of Controls				
All variants				60		38			0.02■		
L211P	Rs2234256	41126655	G	0	281	3	503	A	0.56	0	Benign (0.001)
HI5Y	Rs2234255	41127543	A	1	281	0	504	G	0.36	NA	Possibly damaging (0.7)
R136Q	Rs149622783	41127605	T	1	281	1	501	C	1.00	1.8 (0.1-28.6)	Benign (0.0)
R98W	Rs147564421	41129100	A	1	1091	0	1107	G	0.50	NA	Probably damaging (1.0)
T96K	Rs2234253	41129105	T	4	1091	3	1105	G	0.72	1.4 (0.3-6.0)	Probably damaging (1.0)
D87N	Rs142232675	41129133	T	6	1091	0	1105	C	0.02	NA	Probably damaging (1.0)
N68K	NA	41129188	C	0	1090	1	1105	G	1.00	0	Benign (0.05)
T66M	rs201258663	41129195	A	1	1091	0	1107	G	0.50	NA	Probably damaging (1.0)
R62H	Rs143332484	41129207	T	25	1090	31	1104	C	0.50	0.8 (0.5-1.4)	Benign (0.02)
R47H	rs75932628	41129252	T	22	1091	5	1105	C	<0.001	4.5 (1.7-11.9)	Probably damaging (1.0)
Y38C	NA	41129279	G	3	1091	0	1107	A	0.12	NA	Probably damaging (1.0)
Q33X	Rs104894002	41129295	A	2	1084	0	1103	G	0.25	NA	NA
Nasu-Hakola mutations	Q33X, Y38C, T66M			6		0			0.01	NA	Known damaging

* NA denotes not applicable.
† Position refers to the location of the variant in base pairs in chromosome 6 (hg19)
‡ P values were calculated by means of Fisher's exact test with the use of PLINK software, version 1.07, except as noted. P <0.05 indicates statistical significance
ʃ PolyPhen-2 refers to the pathogenicity prediction on Polymorphism Phenotyping, version 2 (PolyPhen-2). The numbers in parentheses are prediction scores in which 0 indicates benign and 1 damaging.
■This P value was calculated with the use of a burden test in PLINK/SEQ, version 0.08. A comparison of frequencies with those in the Exome Variant Server (EVS) database is provided in Table S5 in the Supplementary Appendix.

Source: Guerreiro, et al., 2013; adapted by William Blair Equity Research

While TREM2 variants discovered thus far appear to be damaging partial or complete loss-of-function mutations, protective variants in related signaling systems have been identified. For example, a rare coding variant, *P522R,* in the phospholipase C gamma 2 (*PLCG2*) gene has been identified as protective against late-onset AD, and recent studies have identified PLCγ2 (the protein product of the *PLCG2* gene) to be downstream of TREM2 signaling *(*Sims, et al., 2017). This was explored further in Solomon, et al., 2022 using healthy control hiPSCs that were CRISPR edited to generate cells heterozygous and homozygous for the PLCG2^{P522R} variant. Results showed heterozygous variant expression was associated with increased microglial clearance of amyloid-β, synapse preservation, upregulation of the anti-inflammatory cytokine Il-10 and the synapse-linked CX3CR1, and alterations in mitochondrial function and increased cellular motility. Interestingly, homozygous expression resulted in different outcomes on synapse preservation and a differential gene expression profile relative to heterozygous cells. Relatedly, van Lengerich and colleagues showed PLCγ2 is required for proliferation and metabolic pathways downstream of TREM2 in hiPSC-derived microglia as *PLCG2* knockout phenocopies *TREM2* knockout, showing deficient proliferation and mitochondrial respiration.

Another protective genetic factor was identified in a case report from an individual who was a homozygous carrier of the APOE3 Christchurch (APOE3ch) mutation and resistant to autosomal dominant AD, usually caused by an underlying rare PSEN1-E280A mutation. This subject showed only mild cognitive delay in her 70s in contrast to family members who developed early-onset dementia in their 40s (Arboleda-Velasquez, et al., 2019). While the exact mechanism by which the mutation confers protection remains unclear, a presentation at the 2024 AAIC meeting discussed a recently published paper from Chen and colleagues that used a humanized *APOE3ch* knock-in mouse crossed with an APP/PS1 mouse characterized by amyloid-β plaque-deposition. The mice were then injected with AD-tau brain extract to investigate tau seeding and spreading in the presence or absence of amyloid plaque. Results showed that APOE3ch reduced overall amyloid-β plaque deposition and markedly reduced peri-amyloid plaque tau seeding and spreading. The researchers found an enhanced peri-plaque microglial response and increased myeloid cell phagocytosis and degradation of human tau fibrils in the presence of APOE3ch, driven in part by reduced binding affinity for APOE in favor of hTau and enhanced lysosomal activity and phagocytosis of hTau. This suggests that promoting microglial activity, including enhanced phagocytosis, could result in reduced tau seeding and accumulation. However, the role of TREM2 in the process remains unclear, with mixed results from animal models, as discussed further below.

Overall, we believe that these protective genetic variants are largely restricted to signaling systems downstream or adjacent to TREM2 and not directly tied to mutations in TREM2 itself. Therefore, it is our view that the genetic evidence supporting TREM2 partial or complete loss-of-function mutations as drivers of dysregulated neuroinflammation in the context of several neurodegenerative diseases warrants exploration of TREM2 stabilizers and/or agonist molecules as a therapeutic strategy.

Preclinical Data Indicates Key Role of TREM2 Modulation in Neurodegenerative Disease Outcomes

In Vitro Characterization of Mutant TREM2

Considering the aforementioned TREM2 genetic observations, many studies have focused on the impact to cellular health and function of the various mutations. For example, using microglia generated from patient-derived stem cells, Brownjohn, et al., 2018 demonstrated that mutations in TREM2 associated with frontotemporal dementia-like syndrome and Nasu-Hakola disease result in improper protein processing and failed trafficking to the plasma membrane, resulting in reduced cell-surface receptor expression. These cells were still shown to differentiate normally, responded to stimulation with lipopolysaccharide (LPS endotoxin), and were phagocytically competent, suggesting context-specific defects consistent with later-onset diseases. Recent work from Penney, et al. used genetically edited iPSC-derived microglia expressing the R47H mutation linked to increased AD risk, and showed alterations in transcription signatures resulting in impairments in microglial movement, uptake of multiple substrates, hyperresponsiveness to inflammatory stimuli, and impaired injury response in a microglia-neuron co-culture system. These are similar to results from McQuade, et al., 2020, which showed TREM2 loss resulted in reduced microglial survival, phagocytic impairment, and reduced chemotaxis.

From a structural biology perspective, in 2016 Kober and colleagues published studies of various TREM2 mutations versus wild-type proteins and determined that Nasu-Hakola mutations impact protein stability and decrease folded TREM2 surface expression, whereas AD-risk TREM2 variants impact binding to a TREM2 ligand. Risk factors with greater risk association to AD (R47H and to a lesser extent R62H) show greater deficits in ligand binding, further supporting a key role of TREM2 in proper microglial response. This was consistent with observations from Song, et al. 2018, which showed impairments to binding multiple ligands across TREM2 mutations. Another variant of interest, the H157Y mutation, which is linked to increased shedding of TREM2 and increased risk of AD, has been similarly linked to abnormal inflammatory activation and reduced phagocytosis of amyloid-β using genetically edited BV2 microglia (Fu, et al., 2023; Schlepckow, et al., 2017; Jiang, et al., 2016).

Overall, this may be related to reduced expression of functional receptors on the cell surface, and collectively we view these in vitro studies as indicating functional TREM2 receptor-mediated activation as important for microglial survival, motility, and phagocytic activation in response to pathological ligands. Hence, restoring these microglial cellular processes via TREM2 corrective intervention (stabilization or agonism) could be an important factor in the development of effective therapies that modulate neuroinflammation in a variety of neurodegenerative diseases.

Animal Models of TREM2 Modulation in Neurodegeneration

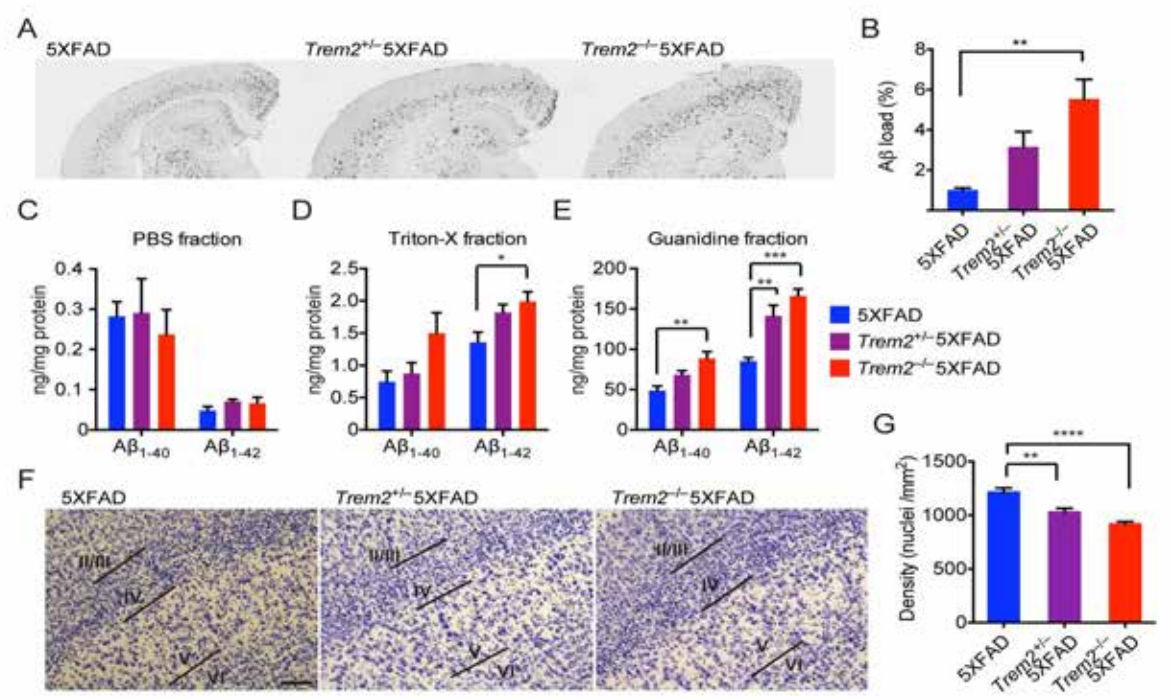
Building on the strong genetic and in vitro mechanistic rationale, the role of TREM2 in neurodegeneration has been widely explored using various animal models of neurodegenerative disease. This section provides an overview of these individual studies that together support the rationale of TREM2 modulation as a therapeutic target in the context of neurodegenerative disease, in our view.

A seminal study by C.Y. D. Lee, et al., published in 2018 explored whether increasing TREM2 gene dosage could modify the disease pathogenesis in a mouse model of AD. Using the common 5xFAD mouse crossed with BAC transgenic mice expressing human TREM2 (BAC-TREM2) in microglia, it was shown that elevated human TREM2 expression reduced amyloid burden (particularly filamentous amyloid-β) in the mouse, rescued disease-associated microglial gene expression, and led to improved memory using a contextual fear condition paradigm. Similar results were shown using APPswe/PS1dE9 mice where TREM2 expression was upregulated via lentiviral delivery and AD-related neuropathology was ameliorated, including amyloid-β deposition, neuroinflammation, and neuronal

and synaptic losses. The TREM2 upregulation intervention was accompanied by an improvement in spatial cognitive functions as assessed by the Morris water maze compared to sham control AP-Pswe/PS1de9 mice (Jiang, et al., 2014). Further, overexpression of TREM2 in a model of intracerebral hemorrhage (stroke) confirmed protective effects, demonstrating reduced neurological dysfunction, inhibited neuroinflammation, and attenuated apoptosis and brain edema (Liu, et al., 2022).

Conversely, TREM2 knockout in a 5xFAD mouse showed significantly increased amyloid-β accumulation in the hippocampus, including increases in insoluble, guanidine-extracted amyloid-β40 and amyloid-β42 species, with the greatest effect in homozygous TREM2 knockouts (exhibit 17; Wang, et al., 2015). This was associated with a failure of TREM2-deficient microglial to co-localize with amyloid-β deposits and reduced microglial survival in the presence of amyloid pathology seen in the 5xFAD mouse, similar to additional observations in the 5xFAD mouse published by Griciuc, et al., 2019. Similar results were seen in TREM2- or DAP12-haplodeficient mice and in humans with R47H TREM2 mutations, which showed impaired ability to interact with individual amyloid fibrils in early noncompact filamentous plaques. These interactions are seemingly required to form specialized protrusions rich in TREM2 and DAP12 that tightly wrap around the surface of compact plaques (Yuan, et al., 2016). This suggests a critical role of proper TREM2-mediated microglial response is to encircle and compact filamentous amyloid-β plaques, providing a physical barrier between plaques and neurons. This was consistent with observations of increased filamentous plaque in a PS2APP-TREM2 knockout mouse (Meilandt, et al., 2020), although some differences by sex in terms of plaque accumulation early in disease were also seen. In addition, TREM2 deficiency reduces myeloid cell internalization of amyloid throughout pathology and exacerbates disease progression in an APPPS1-21 mouse model (Jay, et al., 2017).

Exhibit 17
TREM2 Knockout Shows Gene-Dose Dependent Effects on Amyloid Species and Load



Source: Wang, et al., 2016

Tying these observations to specific genetic risk factors in humans, Song, et al., 2018 generated transgenic mice expressing human control variant or R47H TREM2 and lacking endogenous wild-type TREM2 in the 5xFAD model. Results showed that control variant TREM2 but not R47H can

augment plaque-associated microgliosis and enhance microglial activation. These findings demonstrate that R47H mutations act in vivo as partial loss-of-function variants that affect microglia activation and proliferation in response to amyloid-β plaques. Further, using CRISPR/Cas9 to introduce the R47H variant into the endogenous mouse *Trem2* gene in an APPPS1-21 AD mouse model, Chen-Hathaway and colleagues showed the risk variant demonstrated impaired myeloid response and enhanced neuritic dystrophy around plaques.

More recent work from Tran, et al. published in 2023 addresses whether the effects seen in these and other preclinical model studies incorporating R47H mutations are related to reduced TREM2 protein levels resulting from unintended cryptic splicing products from the mutant *Trem2* allele, which results in dramatically reduced level of TREM2 protein not observed in human R47H carriers. Using a *Trem2*^{R47H} mouse model without cryptic splicing and with normal transcription levels of the *Trem2*^{R47H} allele, the authors confirmed that plaque density along with both soluble and insoluble amyloid-β levels were increased at 12 months, and presence of *Trem2*^{R47H} allele was associated with increases in NfL (marker of neuronal damage) in 5xFAD mice. However, we note that the paper reported sex differences at earlier time points, with female *Trem2*^{R47H} mice producing more plaques compared to their male counterparts at 4 months (an observation seen in other AD mice, including the APP/PS1 mouse [Wang, et al., 2003]), and initial impairments in microglial-plaque interactions, which appeared to subside by 12 months, highlighting that much remains unknown about disease pathology and translation of animal models.

One way in which TREM2 activation may stimulate microglial responses in disease states is through binding lipids such as those known to associate with fibrillar amyloid-β in lipid membranes and to be exposed on the surface of damaged/dystrophic neurons.

This was demonstrated in the paper by Wang and colleagues discussed above, with impaired binding of relevant lipids in TREM2 R47H mutant 5xFAD mice potentially leading to the observations of increased amyloid-β load and other deleterious effects. This was further validated with the work of Kober and colleagues published in 2016 and discussed above, which confirmed the R47H mutation altered ligand binding due to the surface presentation of the mutated residues. Single-nucleus RNA sequencing studies from Zhou, et al., 2020 confirmed TREM2 activity is required to shift microglia to a disease-associated activation state, and this reactive phenotype of microglia was less evident in TREM2-R47H and TREM2-R62H carriers than in noncarriers. Collectively, we believe this data suggests ineffective amyloid-β recognition and binding, leading to reduced pro-survival microglial responses in the presence of TREM2 loss-of-function mutations.

Are TREM2 Mutations Always Deleterious In Vivo?

While most evidence is supportive of TREM2 activity being protective against amyloid pathology, there are some conflicting reports on the impact of TREM2 modulation on amyloid levels, including a 2017 paper from the same Jiang group mentioned above. This report suggested that in contrast to TREM2 overexpression in 7-month-old (about middle-aged) APPswe/PS1dE9 mice, overexpression at 18 months (considered advanced age) had no beneficial effect on AD-related neuropathology and spatial cognitive functions. This differing result could be somewhat explained by reduced phagocytic microglial capacity in cells isolated from the aging mice. This was consistent with the conclusions from Jay, et al., 2017, which demonstrated using the same APPPS1 mouse then crossed with a TREM2 knockout mouse that TREM2 deficiency exacerbates amyloid pathology and is associated with reduced myeloid cell count in midstage disease (8 months old). Interestingly, TREM2 knockout mice showed reduced plaque burden in early stages of disease (2 months old), suggesting the timing of neuroinflammation-focused interventions could be important given the dynamic role of microglia. This finding echoes that from Ulrich, et al., 2014, which showed that while heterozygous TREM2 knockout in APPPS1 mice showed no significant differences in amyloid deposition, heterozygous knockout did result in a marked decrease in the number and size of plaque-associated microglia in 3-month-old mice (early disease stage) and trends toward

decreased expression of NOS2, C1qa, and IL1a cytokines at this time point as well. While we view these time-variable results as interesting, we emphasize differences in disease pathology and immune system function between mice and humans as potentially limiting broad translation.

Dhandapani, et al., 2022 sought to explore the impact of stabilized TREM2 on AD pathology and generated a mouse deficient in ADAM-protease TREM2 cleavage through mutation of the cleavage site. This resulted in increased membrane-associated TREM2, which resulted in myeloid cell survival and enhanced phagocytic activity, consistent with prior reports. Next, the authors sought to determine the impact on AD pathology of increased TREM2 stabilization and therefore crossed these mice with APP23xPS45 mice. In mice with increased membrane-associated TREM2, there was an increase in total plaque load as well as the number of small plaques. However, there was a reduction in earlier disease stages in soluble amyloid-β levels in mice with enhanced membrane-bound TREM2 and more TREM2-positive microglia around the plaques. The authors also suggested enhanced TREM2 stabilization drove microglia to a more pronounced activation state in early disease stages as determined by transcriptional signatures via single-cell RNAseq. This was a similar phenotype to that seen in more advanced disease stages, which the authors suggest increases pro-inflammatory cytokine release that in excess can cause immune dysregulation and impaired amyloid-β clearance later in disease stages.

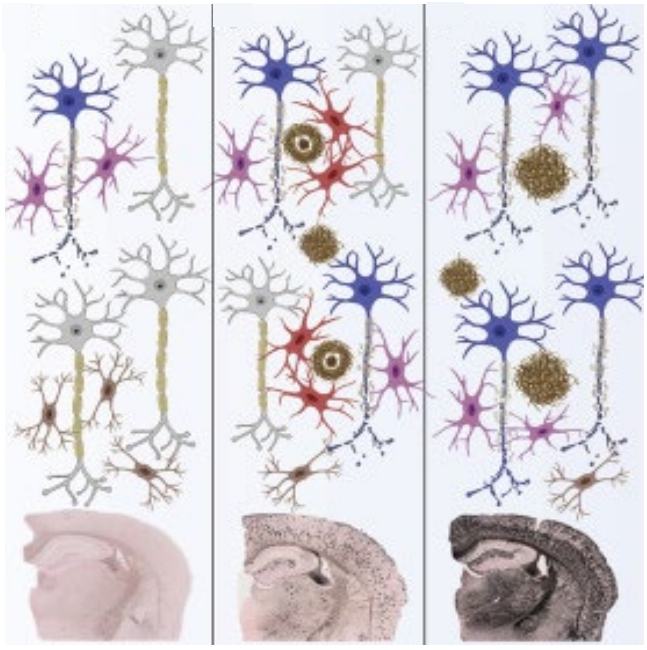
This finding is interesting in the context of findings from Rachmian, et al., 2023, which identified senescent microglia that express high levels of TREM2 but also exhibit a distinct signature from TREM2-dependent DAM using high-throughput mass cytometry in the 5xFAD mouse model. This senescent microglial protein signature was found in various mouse models that show cognitive decline, including aging, amyloidosis, and tauopathy, and together these results suggest potential for microglial dysregulation and exhaustion with excessive TREM2 activation. However, lack of TREM2 has also been linked to reduced survival and motility of microglia as discussed above, which collectively supports beneficial effects of TREM2 modulation, in our view, although we acknowledge outstanding questions on the timing and duration of this type of intervention will need to be addressed in the clinic.

Relatedly, questions remain on the potential implications for tau pathology with TREM2 modulation. For example, Gratuze, et al., 2021 showed that both TREM2 knockout and microglial ablation dramatically enhance tau seeding and spreading around plaques in 5xFAD mice injected unilaterally with 1 µg of tau isolated from human AD patients (AD-tau) in each of the dentate gyrus and overlaying cortex at 6 months old. This reinforces results previously published by Leyns, et al., 2019, which similarly showed that germline knockout of TREM2 or the expression of the TREM2^{R47H} variant reduce microgliosis around amyloid-β plaques and facilitate the seeding and spreading of neuritic plaque (NP) tau aggregates. This is somewhat at odds with results from Jain, et al., 2023, which showed that, when using the same 5xFAD mouse with unilateral AD-tau injection, a TREM2-agonizing antibody increased seeding of neurite plaque associated tau (NP-tau) pathology in dystrophic neurons surrounding amyloid-β plaques, and to a certain extent the spreading of tau pathology compared to an IgG control treatment. There was also increased loss of the pre-synaptic marker synapsin. However, we note and the authors acknowledge that in the study the TREM2 agonizing antibody did not decrease amyloid-β deposition or alter plaque confirmation. This may be a function of the disease state at the age of 6 months in 5xFAD mice, which show robust plaque load, and we would expect a lack of amyloid-β reduction to be associated with downstream tau pathology. Indeed, a 2019 study from He and colleagues suggests that in studies using this same AD-tau injection model, amyloid-β plaques created a unique environment that facilitated the rapid amplification of proteopathic AD-tau seeds into large tau aggregates, initially appearing as NP tau, which was followed by the formation and spread of neurofibrillary tangles, likely through secondary seeding events. Therefore, delayed intervention with TREM2 agonist antibodies in the presence of excessive amyloid-β plaques could result in different outcomes, and we look forward to future studies involving earlier intervention and different models to add to the body of evidence.

In studies of genetic tauopathy using mice engineered with P301S mutation, the silencing of brain TREM2 via injection of a lentivirus containing TREM2 shRNA was able to exacerbate tau phosphorylation through neuroinflammation-induced hyperactivation of tau kinases (Jiang, et al., 2016). Moreover, data presented in this study suggests an exacerbation of neurodegeneration and higher spatial learning deficits in PS19 mice expressing TREM2 shRNA compared to mice not deficient in TREM2. In the second study, the authors induced TREM2 overexpression in microglia of PS19 mice with a lentivirus containing TREM2 cDNA. In agreement with their first study, they observed that overexpression of TREM2 in microglia reduced neurodegeneration, spatial cognitive impairments, and tau hyperphosphorylation through the suppression of neuroinflammation-induced hyperactivation of tau kinases (Jiang, et al., 2015). For additional review of these and similar studies, see Gratuze, et al., 2018.

In another attempt to examine the potential interplay between amyloid aggregation and tau mutants and impact of TREM2 signaling, Lee et al., 2021 examined *Trem2* knockout in a pR5-183 mouse model expressing mutant tau alone or in TauPS2APP mice, in which β-amyloid pathology exacerbates tau pathology and neurodegeneration. Results indicated that tau pathology was not impacted by TREM2 presence or absence in the tau-only condition (pR5-183 mouse), with neither early tau accumulation nor later hippocampal atrophy affected by *Trem2* deletion. In the combination amyloid/tau accumulation TauPS2APP mice, presence of TREM2 showed reduced amyloid-β aggregation compared to TauPS2APP mice without TREM2, which was also associated with increased tau burden, phosphorylated tau, and atrophy. Collectively, this supports the hypothesis that TREM2-mediated microglial activation leading to enhanced response to, and compaction/clearance of, Aβ is beneficial in preventing the seeding/spread/exacerbation of a cycle of Aβ and tau aggregates leading to neurotoxicity (exhibit 18) and is overall in line with reports from other mouse systems, summarized in exhibit 19.

Exhibit 18
Impact of TREM2, Amyloid Deposition, and Tau Mutation on Brain Atrophy in AD Mouse Model



Source: Lee, et al., 2021; adapted by William Blair Equity Research

Exhibit 19
Summary of Key Findings From Select AD Mouse Model Studies

Mouse Model	Type of Pathology	Changes in Amyloid Burden	Changes in Tau	Reference
5xFAD: TREM2 Knockout	Amyloid	Increased Aβ accumulation	NA	Wang, et al. 2015
5xFAD: TREM2 Knockout	Amyloid	Increased Aβ accumulation	NA	Griciuc, et al., 2019
5xFAD: TREM2 H157Y	Amyloid	Reduced oligomeric Aβ42 levels and plaque density; no reduction in plaque size or fibrillary Aβ levels	NA	Qiao, et al., 2023
5xFAD: TREM2 R47H	Amyloid	Reduced envelopment of amyloid deposits; less compact plaques with branched amyloid fibrils resulting in greater surface exposure to adjacent neurites	NA	Yuan, et al., 2016
5xFAD: TREM2 R47H	Amyloid	Reduced plaque-associated microgliosis and microglial activation	NA	Song, et al., 2018
5xFAD: TREM2 R47H	Amyloid	Reduced size and number of microglia that display impaired interaction with plaques	NA	Tran, et al., 2023
5xFAD: TREM2 Overexpression	Amyloid	Reduced amyloid burden including filamentous Aβ	NA	CYD Lee, et al., 2018
Ps2APP: TREM2 Knockout	Amyloid	Increased Aβ plaque in females at early stage; diminished in late stages in both male & female; across all ages, plaque morphology was more diffuse and fibrillar Aβ oligomers also increased; axonal dystrophy was exacerbated from 6 to 7 months onward in PS2APP:Trem2ko	NA	Meilandt, et al., 2020
APPswe/PS1dE9: TREM2 Overexpression	Amyloid	Reduced Aβ deposition, synaptic loss, and neuronal death (7 month old mice)	NA	Jiang, et al., 2014
APPswe/PS1dE9: TREM2 Overexpression	Amyloid	No benefit on AD-related neuropathology in late-stage disease (18 month old)	NA	Jiang, et al., 2017
APPswe/PS1dE9: TREM2 Knockout	Amyloid	TREM2 knockout reduces amyloid pathology early (2 months) but exacerbates in mid-stage (8 months) disease progression; TREM2 deficiency decreases plaque-associated myeloid cell accumulation by reducing cell proliferation in midstage pathology	NA	Jay, et al., 2017
APPswe/PS1dE9: TREM2 Heterozygous Knockout	Amyloid	No significant change in Aβ deposition but marked decrease in number and size of plaque-associated microglia	NA	Ulrich, et al., 2014
APP23xPS45: Membrane Stabilized TREM2 Increase	Amyloid	Reduction in earlier disease stages in soluble Aβ levels and more TREM2-positive microglia around the plaques early in disease; increased membrane-associated TREM2 associated with increase in total plaque load and number of small plaques later in disease	NA	Dhandapani, et al., 2022
5xFAD + hTau Injection:TREM2 Knockout or Mg Ablation	Amyloid + Tau	Increased Aβ pathology in 5XFAD mice with repopulated or TREM2 KO microglia	Both TREM2 knockout and microglial ablation dramatically enhance tau seeding and spreading around plaques	Gratuze, et al., 2021
APPswe/PS1dE9 + hTau Injection:TREM2 Knockout or TREM2 R47H	Amyloid + Tau	Reduced microgliosis around amyloidβ plaques	Elevated neuritic plaque tau aggregates in absence of TREM2 or presence of R47H mutant	Leyns, et al., 2019
5xFAD + hTau Injection + TREM2 Agonist Antibody	Amyloid + Tau	No change in total Aβ burden or plaque conformation in 6-month-old 5xFAD mice	Antibody increased seeding of neurite plaque associated tau	Jain, et al., 2023
TauPS2APP: TREM2 Knockout	Amyloid + Tau	In the presence of β-amyloid pathology, Trem2 deletion further exacerbated tau accumulation and spreading and promoted brain atrophy. Without β-amyloid pathology, Trem2 deletion did not affect these processes.		Lee, et al., 2021
P301S: TREM2 Knockout	Tau	NA	Increased tau pathology	Jiang, et al., 2015
P301S: TREM2 Overexpression	Tau	NA	Reduced tau pathology	Jiang, et al., 2016

Source: William Blair Equity Research

With these various and somewhat conflicting lines of animal model evidence in mind, we emphasize the limitations of these types of murine systems in general given mice and other animals, including nonhuman primates, do not demonstrate the complete behavioral and pathologic phenotype of AD, including amyloid-β plaques, neurofibrillary (tau) tangles, and dementia (reviewed in Walker & Jucker, et al., 2017). In this context, we highlight discordant results in animal models based on differences in stages of target pathology (i.e., amyloid-β or tau); differences in timing, degree, and type of protein accumulation between model systems (i.e., 5xFAD or APPPS1); and type and timing of TREM2 modulation (i.e., knockout, partial loss of function, antibody). We also highlight that significant differences exist in immune cell activation states between mice and humans, even in the context of responding to environmental stimuli such as amyloid-β.

Specifically, a recent study from Zhou, et al. 2020 highlighted this, comparing single-nucleus RNA-seq on tissue from AD patients with and without the R62H and R47H TREM2 variants, and 5xFAD mice with and without TREM2. Results showed significant differences in transcriptional signatures between mice and human samples in the presence of amyloid, with human microglial signatures more similar to those seen in IRF8-driven reactive microglia, which respond to peripheral-nerve injury (Masuda, et al., 2012) In both TREM2 knockout mice and humans with loss-of-function TREM2 mutations, there was less pronounced reactive phenotypes in microglial signatures, suggesting a role of TREM2 in activation across species. Overall, mixed results from imperfect animal models place even greater importance on the observations from the human genetic studies, in our view. Ultimately, the potential for these therapeutics will be determined in the clinic, with multiple critical updates in the coming months discussed below.

Promising Preclinical TREM2 Therapeutic Intervention Data In Vivo

Given the increasingly supportive role of TREM2 activity in improving disease pathology, drug developers have sought to expand on these genetic studies through TREM2 agonizing approaches. For example, a monoclonal antibody with a stalk region epitope close to the TREM2 cleavage site demonstrated dual mechanisms of action by stabilizing TREM2 on the cell surface and reducing its shedding, and concomitantly activating phospho-SYK signaling. This antibody, referred to as 4D9, led to elevation in TREM2 expression while decreasing markers of microglial homeostasis in a mouse model, indicating a shift to an activated state (Schlepckow, et al., 2020). This was particularly evident in microglia clustered around amyloid-β plaques and was further associated with reduced amyloid plaque load, including filamentous noncompact plaques. Additional studies of this antibody and related humanized version ATV:TREM2 involved engineering a monovalent transferrin receptor (TfR) binding site (antibody transport vehicle [ATV]), to the anti-TREM2 antibody to facilitate blood–brain barrier transcytosis (van Lengerich, et al., 2023). Using the 5xFAD mouse crossed with a human TfR expressing mouse, the authors showed ATV:TREM2 treatment increased mitochondrial TSPO expression in microglia, which is associated with an activated state. This ATV:TREM2 asset was initially developed by Denali Therapeutics but has since been discontinued due to dose-limiting safety signals discussed further below.

Using a different TREM2-directed antibody, AL002c (a humanized mouse IgG1 anti-hTREM2 mAb with an epitope within the extracellular stalk region of the receptor), Wang and colleagues showed that a single injection of AL002c expanded unique subpopulations of metabolically active and proliferating microglia in both CV-KO-5XFAD and R47H-KO-5XFAD mice, as assessed by single-cell RNA sequencing. Repeat treatments with AL002c reduced formation of filamentous plaques and rescued neurite dystrophy. However, we note that microglial coverage of amyloid-β plaques was not increased by AL002c in the hippocampi of CV-KO-5XFAD or R47H-KO-5XFAD mice, and was in fact slightly reduced in the cortex of CV-KO-5XFAD mice, despite suggestions of increased

microglial surveillance and phagocytic activities. In addition, the effect of AL002c on filamentous and inert plaques was more significant in the CV than the R47H genotype, suggesting that the ability of TREM2 to bind ligands, which is impaired in the R47H variant, may impact the effectiveness of AL002c treatment. Other variants of AL002 have shown increases in plaque-associated microglia, and a clinical variant is currently in clinical development by Alector, discussed further below. We note that this antibody was tested in the 5xFAD + hTau injection model system discussed above in the Jain, et al., 2023 paper and showed potential worsening of tau seeding. However, the paper also unexpectedly noted no improvement on amyloid-β pathology. We see two potential explanations for this. First, the AL002 antibody does not recapitulate the TREM2-mediated effects on amyloid-β seen in overexpression studies, with chronic TREM2 activation resulting in pathology exacerbation. Or second, and more likely in our view, the aggressive amyloid deposition seen at 6 months in the 5xFAD model is beyond rescue with TREM2 antibody approaches, resulting in no benefit on either amyloid-β or tau pathology, suggesting a limitation of the model. We will need to see clinical data to determine therapeutic potential for TREM2 agonizing antibodies.

Current Clinical Data and Upcoming Company Catalysts

Alector—INVOKE-2 Top-Line Data Expected Fourth Quarter 2024

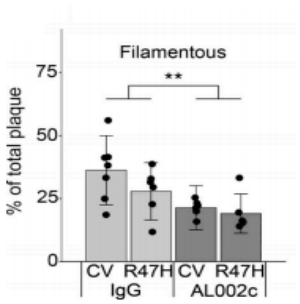
Alector is currently developing the most clinically advanced TREM2 program in AD, AL002. AL002 is a monoclonal antibody designed to stabilize the stalk region of extracellular TREM2 receptors on microglia to promote phosphorylation cascades in the presence of endogenous ligands as discussed above. The rationale here is that AL002 will upregulate TREM2-mediated microglial function to correct dysregulated neuroinflammation, improve clearance of protein aggregates including amyloid-β, and ultimately spare neuronal death and cognitive decline. Importantly, AL002 has been shown in preclinical studies to not interfere with binding sites critical for proper response to damage signals in the cellular environment, and instead stabilizes through interactions within the stalk region (Wang, et al., 2020; Alector company reports; see Leveraging Neurogenetics to Usher in a New Era of Chronically Dosed, Targeted CNS Therapy; Initiating at Outperform).

AL002 has been evaluated in a suite of preclinical animal studies reviewed above and an initial Phase I trial in healthy volunteers (clinicaltrials.gov: NCT03635047). Briefly, studies using the 5xFAD mouse model of amyloid accumulation in AD crossed to either the common variant TREM2 or R47H mutant TREM2 and treated with weekly 30 mg/kg intraperitoneal AL002c for 12 weeks displayed decreased filamentous amyloid-β plaques, reduced dystrophic neurites adjacent to plaques, and displayed anxiety benefits in the elevated plus maze (exhibit 20; Wang, et al., 2020). We note that reductions in compact plaques were not observed, and inert plaque load actually increased with AL002c; however, using another candidate, the AL002s variant, did result in a total amyloid-β plaque coverage and an increase in microglial recruitment to those plaques. Despite some differences in amyloid-β plaque removal kinetics, the preclinical data from the two candidates trend in the same direction, in our view, supporting AL002's ability to induce microglial proliferation, activation, and amyloid-β phagocytosis. Additional preclinical data from Alector indicates AL002 enhances binding to ApoE relative to an IgG control, promotes phospholipid binding, induces signaling cascades as evidenced by increased tyrosine phosphorylation, and induces lysosomal enzymes, which collectively suggests potential for increased response to and clearance of endogenous damage ligands (exhibit 21). AL002 also promotes changes in gene expression and cell viability relative to an IgG control, which could support sustained responses if replicated in vivo by increasing responsive microglial populations.

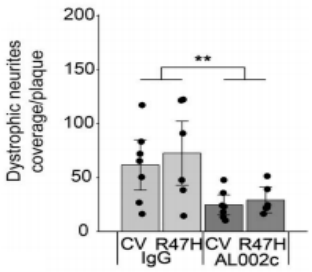
Exhibit 20
Preclinical Data of AL002-Treated 5xFAD Mice

AL002c Preclinical Data

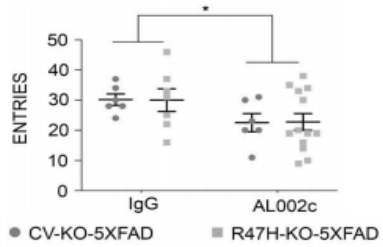
Filamentous Aβ Plaques



Dystrophic Neurites Surrounding Plaque

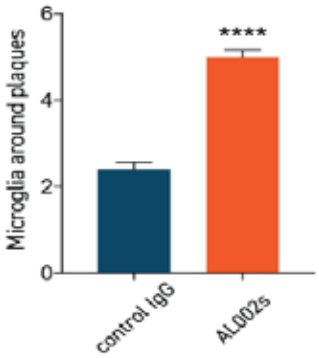


Elevated Plus Maze Open Arm Entries

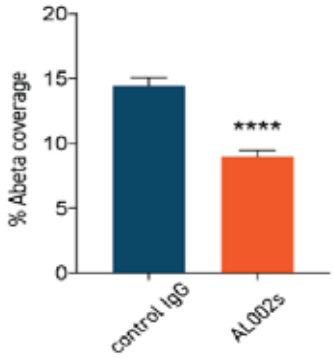


AL002s Preclinical Data

Plaque-Localized Microglia

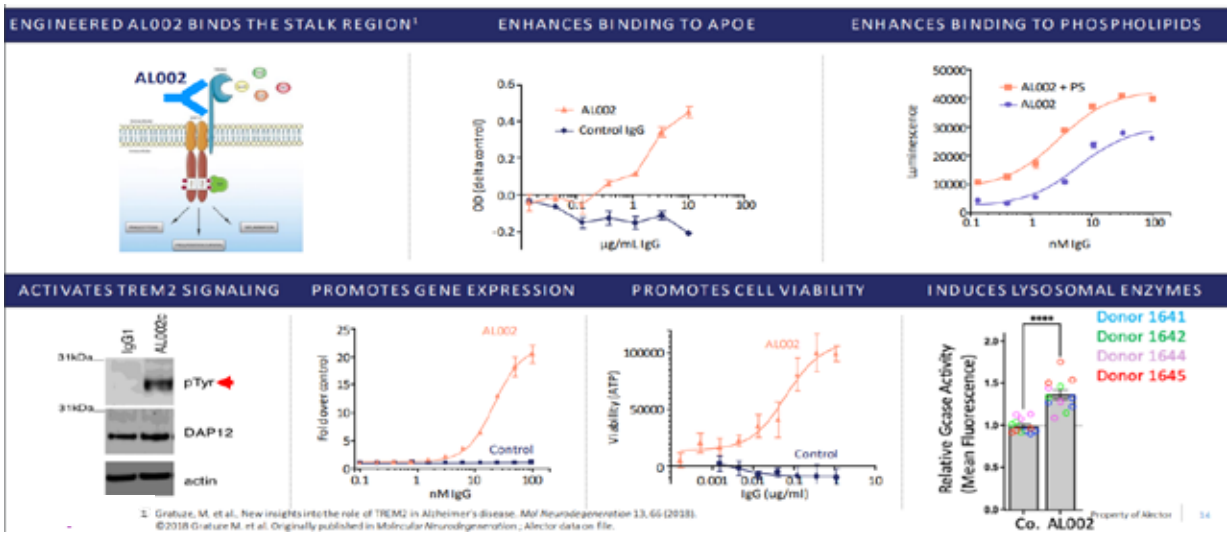


Aβ Plaque Coverage



Sources: Alector company presentation; Wang S et al., 2020. JEM

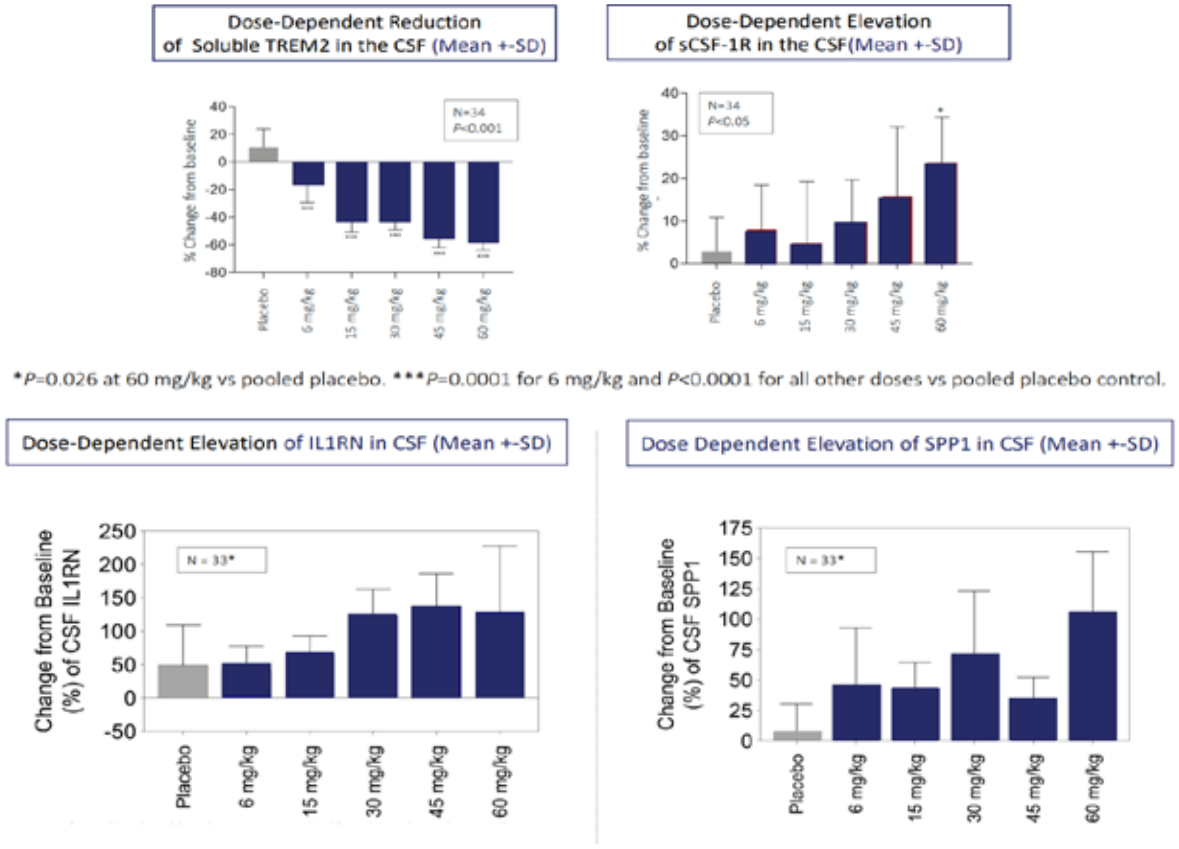
Exhibit 21
Preclinical Data From AL002 Shows Potential for Broad Impact on Microglial Function



Sources: Alector company presentation

Alector subsequently advanced AL002 into a single-ascending dose Phase I trial in healthy volunteers. The trial enrolled 56 healthy adult participants into 10 cohorts to receive a single IV dose of AL002, ranging from 0.003 mg/kg to 60 mg/kg. For higher-dose cohorts, lumbar punctures were taken before and 2 days after dosing to obtain CSF for biomarker analysis, and subjects were followed for an additional 12 weeks after dosing for safety data. As shown in exhibit 22, dose-dependent decreases in CSF sTREM2 (the product of proteolytic cleavage of cell-surface TREM2) and increases in sCSF-1R, a proposed marker of microglia proliferation, as well as increases in IL1RN levels (an anti-inflammatory signaling activator) and SPP1 levels (a regulator of microglial activation), were observed in the CSF of AL002-treated healthy volunteers. We believe this is preliminary evidence of clinical target engagement by AL002, promoting activation of TREM2 signaling processes while preventing its proteolytic degradation due to the antibody binding dynamics. AL002 was also safe and well tolerated, with no drug-related serious adverse events or dose-limiting toxicities. A single patient in the 6 mg/kg cohort experienced a serious adverse event of traumatic injury, but this was deemed not related to drug.

Exhibit 22
AL002 Shows Dose-Dependent Changes in Downstream Signaling Systems



Source: Alector company materials

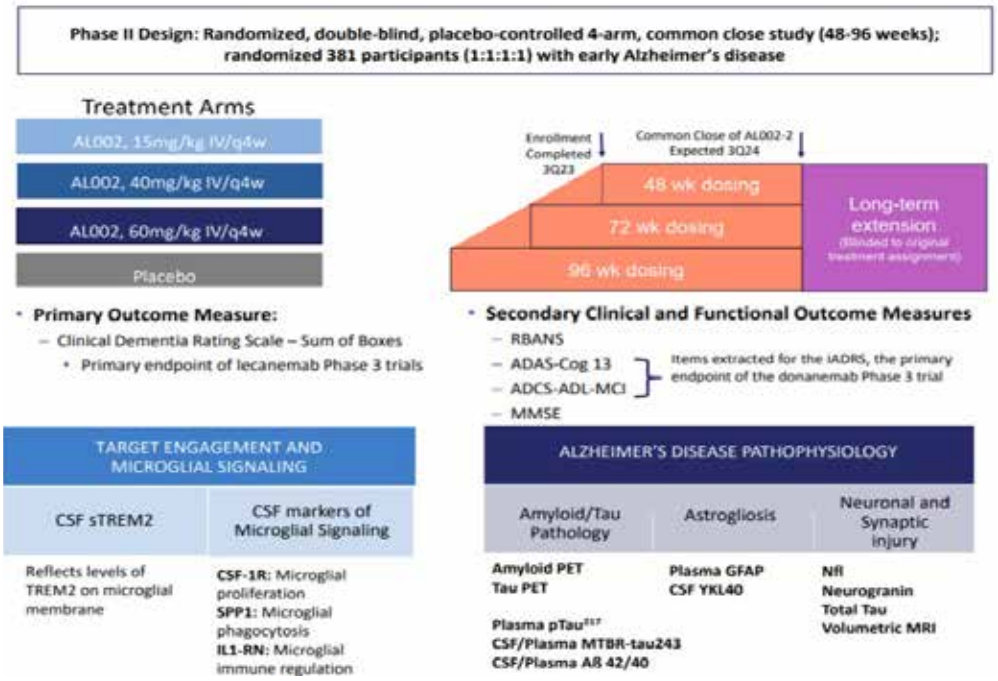
INVOKE-2 trial design and patient demographic considerations

Alector is evaluating AL002 in the Phase II INVOKE-2 study, a randomized, double-blind, placebo-controlled, four-arm, common close study (48-96 weeks) enrolling 381 participants with early AD. Participants will be enrolled 1:1:1:1 to placebo or monthly infusions of 15 mg/kg, 40 mg/kg, or 60 mg/kg. Monthly dosing frequency was selected in part by preclinical studies of receptor turnover and expression regulation, with more frequent administration leading to downregulation of TREM2 expression related to receptor internalization, while monthly dosing alleviated this issue,

per our conversations with management. The study completed enrollment in third quarter 2023 and will close data collection in third quarter 2024, with data expected in fourth quarter 2024 from roughly 250 participants who reached the 48-week completion time point. The primary endpoint is CDR-SB (a widely accepted regulatory endpoint) with a number of secondary endpoints of cognitive measures such as MMSE, RBANS, ADCS-ALD-MCI, and ADAS-Cog13 (exhibit 23).

The study will use a proportional analysis method to incorporate all data from the common close design (minimum 48 weeks of treatment), and the overall study is powered to detect a 40% benefit over placebo on clinical outcomes using a proportional MMRM analysis method to account for varying follow-up time points. Biomarkers being collected include NfL levels, various measures of amyloid and tau burden including both PET imaging and plasma biomarkers, CSF markers of microglial signaling similar to the Phase I study, and others. We believe this study will provide a wealth of information on both cognitive and pharmacodynamic outcomes at various doses and should provide key proof-of-concept data if positive.

Exhibit 23
INVOKE-2 Trial Design and Outcomes and Biomarker Measures



Sources: Alector company presentation

At the 2024 AAIC meeting, Alector presented baseline characteristics and demographics for those enrolled in the study. In the INVOKE-2 study, 67.2% of participants were diagnosed with mild cognitive impairment (MCI) due to AD and 32.8% with mild dementia due to AD. In addition, 62.7% of participants are APOE4 carriers, although only 3.9% of participants are APOE4 homozygotes after the company elected to discontinue enrollment of APOE4 homozygotes following an increased incidence of ARIA in these patients, discussed further below. INVOKE-2 patients show baseline amyloid PET centiloid levels of 100.1, a mean CDR-SB value of 3.4, and mean MMSE score of 24.5. While comparing across trials is often challenging due to differences in methodology, details from the poster indicate the patient population is largely similar to those enrolled in studies of Biogen/Eisai's lecanemab and Lilly's donanemab, with the biggest difference in APOE4 genotype due to differences in enrollment criteria (exhibit 24). The CLARITY study of lecanemab showed statistically significant benefit on the CDR-SB as early as 6 months and the TRAILBLAZER-2 study began

Exhibit 24
Participant Baseline Characteristics Across Select Alzheimer's Disease Clinical Trials

	AL002	Lecanemab			Donanemab		
	INVOKE-2	Phase II	CLARITY-AD		TRAILBLAZER-ALZ	TRAILBLAZER-ALZ2 (Combined Tau)	
Cohort	*All*	*All*	*Placebo*	*Lecanemab*	*All*	*Placebo*	*Donanemab*
N	381	854	875	859	272	876	860
Age (min, max)	71 (51, 85)	72 (50, 90)	71.0±7.8	71.4±7.89	75.2±5.5	73±6.2	73±6.2
Female %	50.1%	50%	53%	52%	53.3%	57.4%	57.3%
Race %							
White	93.7%	90%	77.4%	76.3%	94.9%	92.1%	90.9%
Asian	1.0%		16.9%	17.1%	1.1%	5.4%	6.6%
Black/AA	0.8%	10%	2.70%	2.3%	2.9%	2.4%	2.2%
Multiple	0.3%		0%	0%	0.0%	0.1%	0.0%
NA	4.2%		3.0%	4.3%	1.1%	0.0%	0.1%
Ethnicity %							
Hispanic/Latino	4.5%	NR	12.3%	12.5%	3.3%	NR	
Not Hispanic/Latino	91.3%						
NA	4.2%						
Clinical Diagnosis %						Mild Cognitive Impairment (MMSE ≥27)	
Mild Cognitive Impairment due to AD	67.2%	64%	62.2%	61.5%	NR	15.7%	17.0%
Mild Dementia due to AD	32.8%		37.8%	38.5%		Mild Alzheimer Disease (MMSE 20-26)	
						84.3%	82.9%
APOE Genotype %							
APOE4 Carrier	62.7%	71%	68.6%	68.9%	73.0%	71.2%	69.8%
Non-APOE4	37.3%	29%	31.4%	31.1%	27.0%	28.7%	30.2%
E2/E3	1.3%		APOE4 Heterozygotes		0.7%	2.3%	2.1%
E2/E4	1.6%		53.5%	53.1%	1.5%	2.9%	2.6%
E3/E3	36.0%	NR	APOE4 Homozygotes		26.3%	26.4%	28.1%
E3/E4	57.2%		15.1%	15.8%	50.7%	51.6%	50.5%
E4/E4*	3.9%				20.7%	16.7%	16.7%
Amyloid PET Centiloids, Mean (SD)	100.1 (38.9)	Cohort Means Range: 78.0 - 90.3	75.03 (41.82)	77.92 (44.84)	104.2 (34.8)	101.6 (34.5)	103.5 (34.5)
CDR-GS %							
0		Global CDR, Mean (SD)				0.5%	0.2%
0.5	78.0%	0.6 (0.2)	80.70%	80.80%	NR	61.2%	60.8%
1	22.0%		19.30%	19.20%		35.4%	36.0%
>1	0%					2.9%	3.0%
CDR-SB, Mean (SD)	3.4 (1.4)	3.0 (1.4)	3.22 (1.34)	3.17 (1.34)	3.5 (1.9)	3.9 (2.1)	4.0 (2.1)
MMSE, Mean (SD)	24.5 (2.4)	25.6 (2.4)	25.6 (2.2)	25.5 (2.2)	23.5 (3.1)	22.2 (3.9)	22.4 (3.8)
RBANS, Mean (SD)	66.4 (12.1)	NR	NR		NR	NR	
ADAS-Cog13, Mean (SD)	29.2 (8.6)				27.6 (7.6)	29.3 (8.9)	28.7 (8.8)
ADCS-ADL-MCI, Mean (SD)	40.3 (7.2)		40.9 (6.9)	41.2 (6.6)	NR	NR	
ADCOMS, Mean (SD)	0.43 (0.16)	0.4 (0.2)	0.400 (0.147)	0.398 (0.147)			
Source	ALEC AAIC 2024 Presentation	Swanson, et al., 2021; ESAIY CTAD 2021 Presentation; McDade, et al., 2022	van Dyck, et al., 2023 NEJM		Mintun, et al., 2021 NEJM	Sims, et al., 2023 JAMA	

* APOE4 homozygote enrollment discontinued following protocol amendment announced in 2022

Source: William Blair Equity Research

showing statistical separation versus placebo at 12 weeks, with both showing rapid amyloid clearance (>50 centiloid reduction by 12 months; van Dyck, et al., 2023; Sims, et al., 2023). These changes were seen within the same time frame being evaluated in INVOKE-2, although we emphasize these pivotal studies were notably larger and better powered than INVOKE-2 (see: AAIC Update: INVOKE-2 Baseline Characteristics Largely Similar to Peer Programs; Catalytic Data Expected in Fourth Quarter).

Interim safety data presented at the 2023 AAIC meeting showed ARIA-E and ARIA-H incidence each in 8 of 15 (71%) APOE4 homozygotes patients, with mean radiographic severity of ARIA-E of 2.5 (Std.Dev=1.6; scale 1-5) and 5 of 8 ARIA-H incidences rated at severe (2 moderate and 1 mild). With the removal of APOE4 homozygotes from the prior INVOKE-2 protocol amendment, ARIA-E incidence dropped to 41 of 206 (19.9%) patients, with only 5 of 41 (12%) cases symptomatic and a mean radiographic severity score of 2.3 (Std.Dev=1.4). ARIA-H incidence was reduced to 46 of 206 (29%) patients, with no isolated ARIA-H incidences symptomatic and 72% of overall ARIA-H incidences mild or moderate. Overall, the company reported 2 of 206 (1%) clinically serious ARIA events in APOE4 non-homozygotes, compared to 3 of 15 described clinically serious events seen in APOE4 homozygotes prior to enrollment criteria updates (characterized by transient focal signs, seizures, and mental status changes requiring hospitalization). These events all resolved with discontinuation of study drug and initiating corticosteroid treatment.

Of the total 49 ARIA-E events across all genotypes, the mean and median time to onset were 72.0 and 54.0 days, respectively, and time to resolution in 42 of the 49 events was a mean and median of 105.0 days and 85.5 days, respectively. Per the presentation and our prior conversations with management, an independent data monitoring committee is reviewing the data regularly and has recommended to continue the trial. It is important to note that the study remains blinded, and the data presented assume all ARIA events occurred in treated patients, although this may not ultimately be the case given instances of ARIA in placebo-treated patients in other studies. Over 90% of eligible patients from INVOKE-2 have elected to continue into the open-label extension portion of the study, and we view this as an encouraging signal of tolerability and potential benefit.

Overall, we see this ARIA characterization as fairly similar to that seen with anti-amyloid antibodies, although higher than Biogen/Eisai's Leqembi, which showed an overall rate of 9.9% ARIA-E in the 10 mg/kg twice-monthly dose cohort in the Phase II study and 12.6% in CLARITY AD. However, AL002 ARIA rates appear lower than for Eli Lilly's donanemab, according to AAIC data, which showed slightly higher overall ARIA-E rates at 24.0%, in addition to higher ARIA-H rates at 31.4% in donanemab-treated patients. The Phase II study of donanemab also had higher ARIA-E and ARIA-H rates of 27.5% and 30.5%, respectively, compared to that seen in INVOKE-2 of 22.2% and 24.4%. When removing APOE4 homozygotes, 5 of 206 patients (2.4%) or 5 of 41 (12%) of ARIA-E events were symptomatic, compared to 2.8% in CLARITY AD and 6.1% in TRAILBLAZER-ALZ. However, head-to-head comparison here is particularly challenging with the removal of homozygotes in INVOKE-2 only, given the well-characterized increased risk in these patients and differences in mechanism of action, with AL002 designed to activate microglia to clear amyloid via TREM2- signaling rather than bind to amyloid itself. As highlighted by Lilly, other metrics like amyloid levels at baseline and presence of superficial siderosis can also impact the underlying rate of ARIA incidence (see AAIC Update: INVOKE-2 Update Shows Similar ARIA Incidence to Amyloid Antibodies; Top-Line AL002 Data on Track for Late 2024).

While we see these signals as potentially suggestive of efficacy, the trial is not without significant risk. For example, getting sufficient levels of therapeutic antibody into the CNS and distributed to regions of interest remains a significant challenge for the field broadly. In addition, treated patients are split across multiple dose groups, potentially diluting efficacy signals (although management has noted prespecified analysis plans including pooling patients at the highest doses

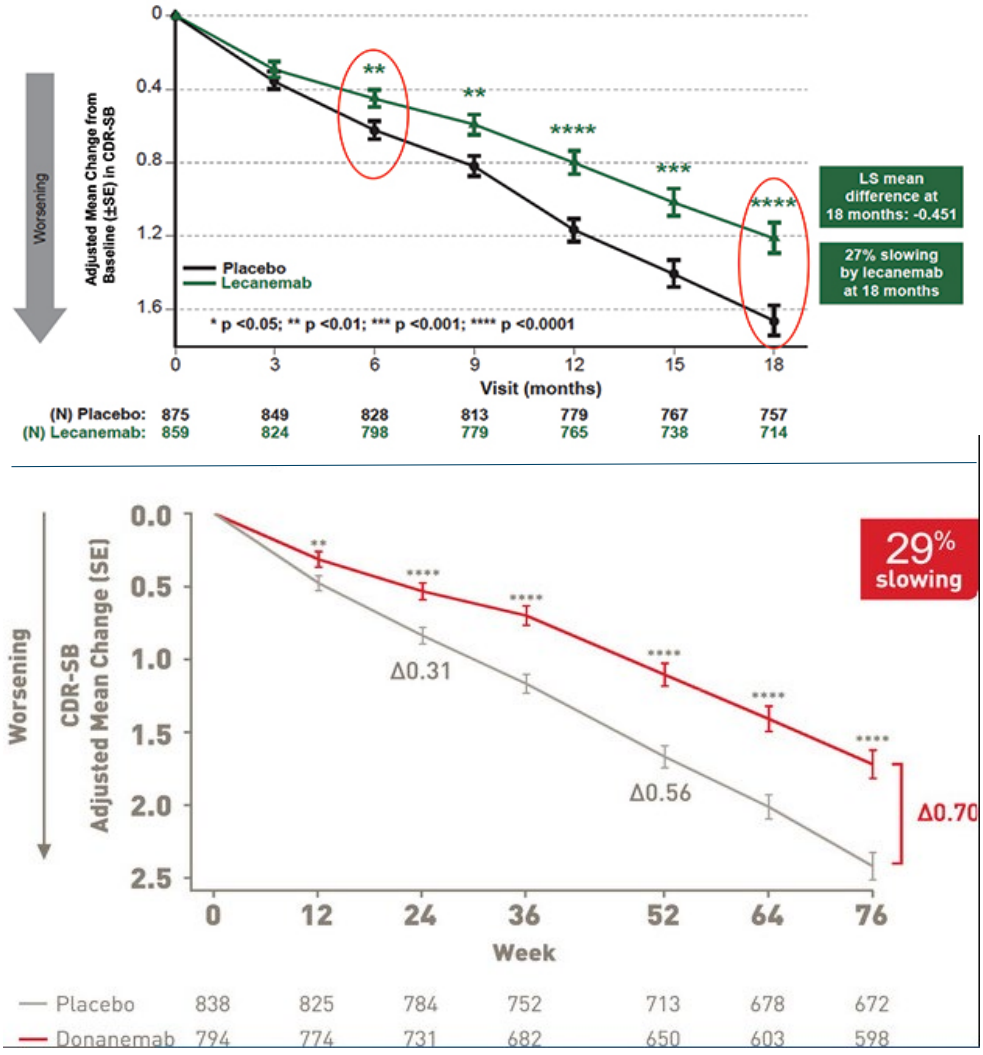
given similar pharmacodynamic profiles). Patients will also have variable lengths of follow-up related to the common-close design, particularly challenging on complex, variable measures like the CDR-SB.

We also believe the minimum 48 weeks of follow-up, with potential for 96 weeks, to be a benefit, with the pivotal trials of lecanemab and donanemab showing separation on cognitive measures versus placebo as early as 6 months (exhibit 25) and maintained through at least 3 years of treatment, and potentially widening benefit when considering an external control (exhibit 26; see: Second-Quarter Earnings: Continued Momentum as Biogen Seeks Return to Growth; AAIC Update Builds on Leqembi Benefit Potential). Further, these studies also demonstrated rapid (less than 6 months) amyloid clearance and improvements in other biomarkers on a similar timescale, well within the data window collected here, and we believe biomarker data will be the most important piece of the preliminary data readout to determine therapeutic potential.

Cognitive data collected from patients closer to the 96-week mark could therefore provide a clear, albeit likely underpowered, signal of potential for benefit given the study is designed to detect a 40% slowing of disease on the CDR-SB. We note that the use of the proportional MMRM could be a statistical benefit here though, with this type of analysis carrying a potential 20%-30% gain in power versus traditional MMRM analysis given the ability to use all post-baseline data (Wang, et al., 2022). We look forward to the completed trial dataset in the fourth quarter to draw further comparisons between Alector's approach and anti-amyloid antibody therapies, but remain optimistic heading into the INVOKE-2 results based on evidence of target engagement, human genetic validation, and preliminary biomarker signals.

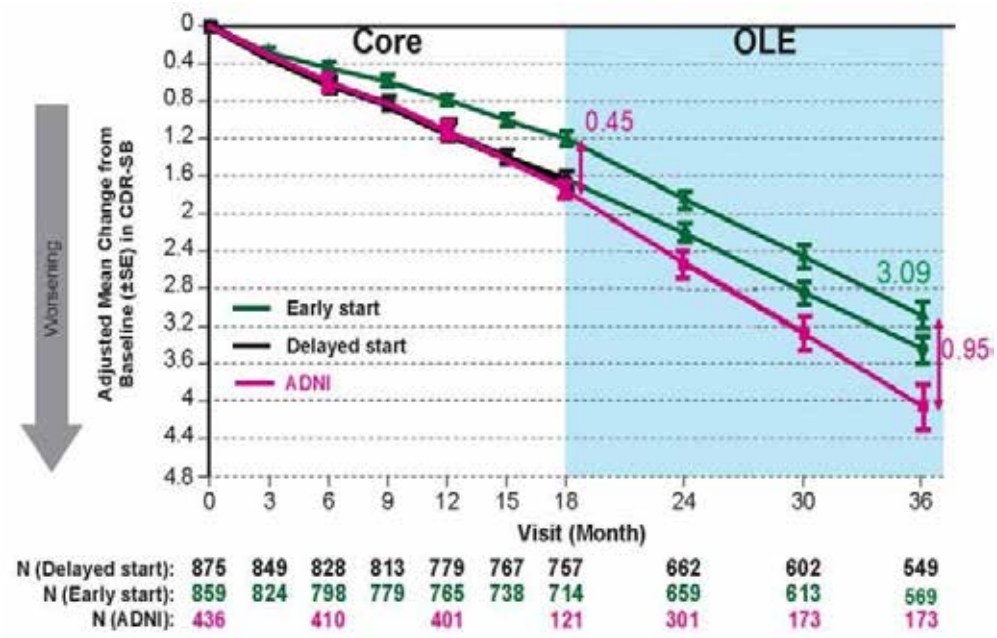
Beyond the initial data readout, Alector is set up for additional catalysts, including the ability for AbbVie to opt in to a license agreement to advance global development and commercialization of AL002 within 90 days of receipt of the data package (expected around the same time as public release of data with a decision expected in the first quarter). If AbbVie moves forward with the license, Alector would be eligible for additional option exercise and milestone payments totaling up to $487.5 million. Both companies would share the development costs and would split global profits equally if AL002 is ultimately approved. In addition, Alector has indicated plans to share additional analyses from the study in 2025 once more patients have reached the 96-week time point, providing opportunity for additional insights on potential benefit and additional data catalysts in the next 6 or so months.

Exhibit 25
Lecanemab (Top) and Donanemab (Bottom) Show 27% and 29% Slowing of Disease at About 18 Months, Respectively



Source: ESAIY company materials; Klein, et al., 2024

Exhibit 26
Three-Year Update Shows Maintenance of Disease Slowing vs. Lecanemab Late-Start and External Control Cohorts



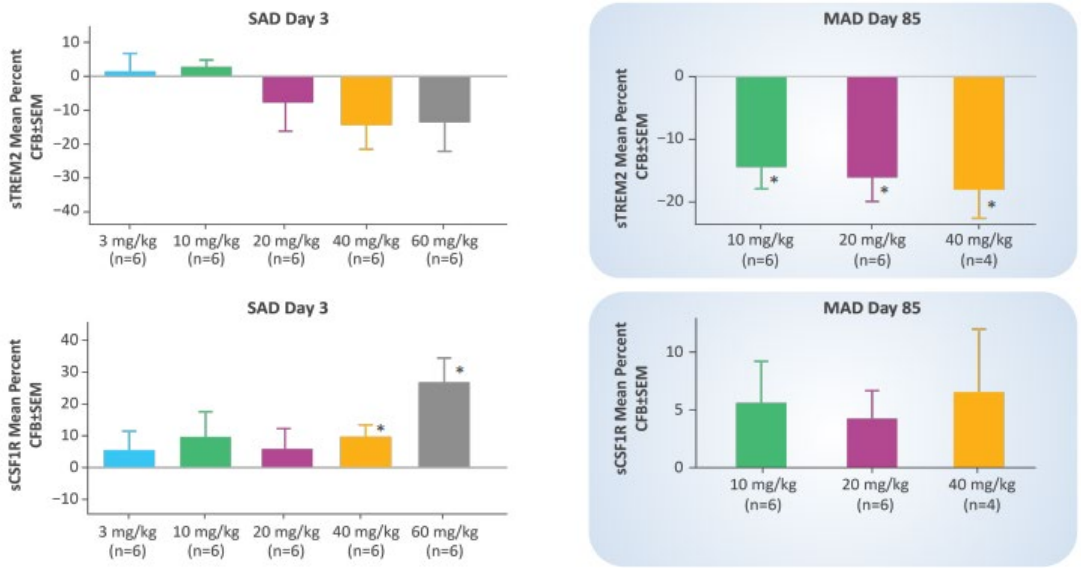
Source: Biogen company reports

Vigil—Top-Line Data From Phase II IGNITE Trial Expected First Half 2025

Vigil is a clinical-stage biotech company developing two TREM2-targeting assets, a TREM2-targeting monoclonal antibody (iluzanebart) and a small-molecule TREM2 agonist (VG-3927). Iluzanebart binds with high affinity to the extracellular domains of two TREM2 receptors, sequestering TREM2 in the active state (regardless of absence/presence of endogenous ligand) and is being evaluated in the Phase II IGNITE study in patients with adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP). ALSP is a rare and fatal neurodegenerative disease caused by mutations in the colony-stimulating factor 1 receptor (CSF1R) gene leading to microglial dysfunction and white matter changes, resulting in progressive cognitive and motor impairment.

A Phase I study of iluzanebart (fka VGL101) enrolled 136 volunteers to receive placebo (n=23) or iluzanebart (n=113) at doses ranging from 1 to 60 mg/kg (SAD) or monthly infusions for 3 months of 10, 20, 40, or 60 mg/kg (MAD). Results showed iluzanebart to be safe and well tolerated with no severe or serious adverse events and predominantly mild TEAEs. The study also indicated iluzanebart has a half-life of about 29 days (supporting monthly dosing) and brain penetrance of 0.1%-0.2% CSF-to-serum ratio (all doses), with the low level in line with what is typically seen for CNS-targeted therapeutic antibodies without a BBB-shuttling mechanism (Meier, et al., 2023; Kouhi, et al., 2021). In addition, iluzanebart showed dose-dependent reductions in CSF sTREM2 including sustained reductions through the day 85 visit of mean ranges about 14%-18% (28 days after the third and final dose; exhibit 27). Iluzanebart also showed increases in CSF sCSF1R of about 6%-8% and osteopontin levels, and collectively we view this data as supportive of meaningful target engagement, although we note less sTREM2 reduction and CSF1R increase than seen with AL002 (shown above in exhibit 22) of about 60% and 25%, respectively, with the usual cross-trial comparison caveats applying here.

Exhibit 27
sTREM2 and sCSF1R Pharmacodynamic Markers of Iluzanebart Target Engagement

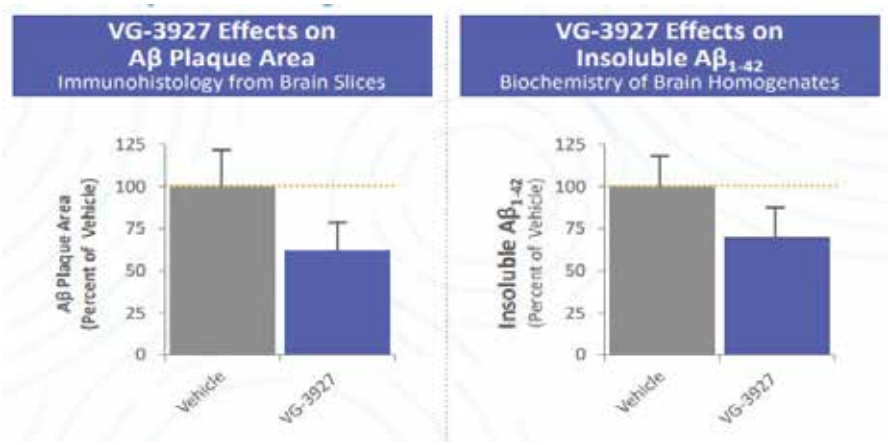


Source: Vigil company materials

The ongoing Phase II IGNITE study is a 12-month open-label study in a planned 15 patients receiving monthly infusions of 20 mg/kg or 40 mg/kg iluzanebart. Interim data from 6 patients at 6 months receiving 20 mg/kg showed a consistent safety profile with the Phase I study, with no severe TEAEs and one serious AE of abdominal pain, asthenia, vomiting, and diarrhea deemed not related to treatment. Of the 6 patients with interim data, 5 showed directional improvements in reduced rate of ventricular enlargement and 3 showed directional change supporting reduced rate of atrophy. In addition, 4 showed an increase over baseline (range: 16%-34%) in sCSF1R, while 3 patients showed changes in serum NfL trajectory. Further, 2 patients with low serum NfL baseline (age-normal range) showed low absolute changes in serum NfL at 6 months, and 2 patients showed reduced CSF NfL at 6 months. Overall, we view this result as supportive of the target engagement findings from the Phase I study. The company recently announced plans to provide full data from the 12-month IGNITE study in the first half of 2025 (rather than prior guidance of an interim update later this year) to support potential filing for accelerated approval (AA). We are encouraged by the early profile and believe AA is a viable option if the data next year bears out, given the high unmet need in ALSP and no FDA-approved therapies currently available.

In addition to iluzanebart, Vigil is developing the small-molecule TREM2 agonist VG-3927. VG-3927 acts as a molecular glue to stabilize the TREM2 complex and is extremely selective for TREM2 over TREM1. VG-3927 has shown rescue of in vitro TREM2 activity (relative pSYK induction) in response to sulfatides in TREM2 variants of increased AD risk and has also shown dose-dependent increases in IP-10 and suppression of the pro-inflammatory cytokine IL-1b. In vivo, 6 weeks of oral dosing showed reduction in amyloid-β plaques and also reduced the levels of insoluble amyloid-$\beta_{1\text{-}42}$ in mouse brain homogenates (exhibit 28). Target engagement was confirmed in nonhuman primates with dose-dependent reductions in CSF sTREM2, with stabilized TREM2 leading to reduced cleavage and sTREM2 in the CSF.

Exhibit 28
Preclinical Rodent Data Showed VG-3927 Reduced Amyloid Plaques and Insoluble Aβ Isoform Levels

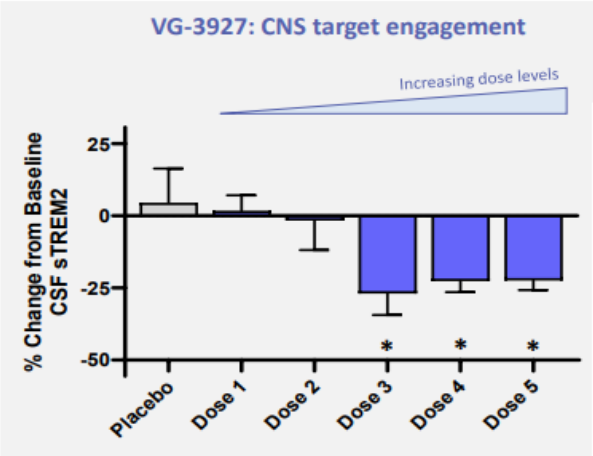


Source: Vigil company materials

Vigil is conducting a Phase I healthy volunteer study of VG-3927, and interim data was presented at the 2024 AAIC meeting showing statistically significant reductions of roughly 20% or greater in CSF sTREM2 in the three highest doses tested (exhibit 29). The presentation also noted that all adverse events were mild or moderate and resolved without intervention, with no serious AEs reported thus far. This clinical and additional non-clinical data led to the recent removal of a partial clinical hold from the FDA which had limited maximum drug exposure. The company continues to explore the pharmacodynamic profile and has initiated dosing of an AD cohort, with plans to report the full Phase I data in the first quarter of 2025.

Lastly, the company recently announced a $40 million strategic investment from Sanofi for the exclusive right of first negotiation for an exclusive license for the small-molecule TREM2 agonist program. Overall, we continue to see concordant results of VG-3927 with TREM2 antibodies in terms of target engagement and markers of microglial engagement and inflammatory modulation as supportive of the overall approach of TREM2 targeting.

Exhibit 29
VG-3927 Induces CSF TREM2 Reductions



* t-test, p < 0.05; N=6 for each dose group and N=10 for the placebo group
Note: Data are preliminary; CSF collection was conducted for select dose cohorts

Source: Vigil company materials

Denali

Denali Therapeutics is developing a diverse platform of assets to treat neurodegenerative disease and leveraging its transport vehicle platform technology to promote delivery to the central nervous system. The company had previously been developing DNL919 (ATV:TREM2), a high-affinity TREM2 antibody designed to stabilize the stalk region and activate TREM2 signaling engineered with a monovalent transferrin receptor (TfR) binding site in the Fc domain to enable active transport into the CNS. Preclinical data from this program was published by Schlepckow, et al., in 2020 and van Lengerich, et al., in 2023 and confirmed improved delivery of a TREM2 antibody into the brain parenchyma and engagement with microglia when incorporating the TfR-binding region. Similar to other studies, single-cell transcriptomics data confirmed induction of disease-associated microglial activation states with antibody treatment, including in the presence of pathological stimuli such as amyloid. The paper also demonstrated activation of specific downstream cascades promoting cell proliferation such as mTOR and AKT within microglia and mediated by TREM2 receptor activation. In vivo modeling using a 5xFAD mouse showed treatment increased translocator protein positron emission tomography (TSPO-PET), a potential indicator of microglial activity. Relatedly, imaging of brain glucose uptake by fluorodeoxyglucose-positron emission tomography (FDG-PET) showed significant regional association with the TSPO-PET signal, collectively supporting increased microglial activation in the presence of amyloid-β when treated with ATV:TREM2.

In August of last year, Denali provided an update on the program. Phase I clinical data indicated robust target engagement and effects on microglial biomarkers (e.g., CSF1R, SPP1, IL1RA, IP10, MIP1b, MCP-1), which were consistent with the preclinical studies. However, safety signals of moderate, transient anemia were observed at the highest dose tested, suggesting a narrow therapeutic window for the Alzheimer's disease patient population, which ultimately led to discontinuation of the program. The company and partner Takeda indicated the signal was unique to DNL919 and the companies are focused on backup molecules in preclinical development, including exploration of potential combination therapy given recent new drug approvals in AD, and we continue to monitor the company's evolving portfolio.

A note on TfR-targeting conjugates for enhancing CNS bioavailability

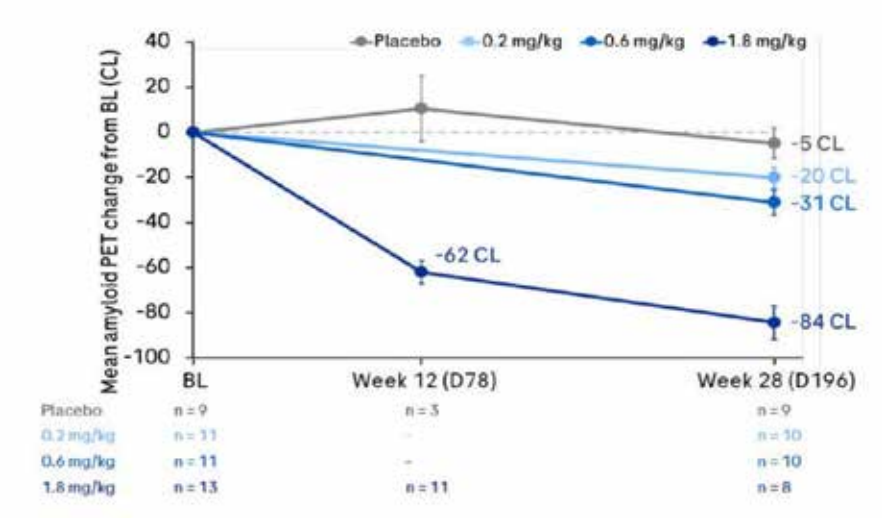
We continue to believe the anemia signal observed in the DNL919 program was not related to TREM2 targeting specifically but rather a result of TREM2 activation in the presence of an active Fc region needed to bind to TfR. Given TfR is also expressed on reticulocytes and immature cells in the bone marrow, and the propensity of TREM2 activation to induce phagocytic activation states in both microglia and macrophages, we believe this activation close to reticulocytes results in engulfment and depletion, leading to anemia. This has been observed previously in other bispecific TfR-binding antibodies with active effector regions, while antibodies engineered to lack or reduce Fc interactions with immune cells were able to reduce this effect (Couch, et al., 2013; Pardridge, et al. 2018; Lo, et al., 2017; Castellanos, et al., 2020; Pardridge, et al., 2023).

In addition, similar effects on anemia have been reported recently in other clinical-stage antibodies incorporating TfR-mediated shuttling, notably Roche's trontinemab. Trontinemab is a second-generation bispecific version of the company's anti-amyloid mAb therapy gantenerumab engineered with a TfR-binding region. Interim data presented at last year's CTAD meeting showed 6-17x greater brain exposure than gantenerumab and 8x increase in CSF/plasma ratio in healthy volunteers. In AD patients, trontinemab showed impressive dose-dependent amyloid reduction of a mean 84 centiloids at week 28 with the 1.8 mg/kg dose, and 4 of 11 (36%) participants in this dose group were below the amyloid positivity threshold at week 12, increasing to 6 of 8 (75%) at week 28 (exhibit 30; see CTAD 2023 Recap: More Amyloid Antibody Data, Biomarker Advances, and Other Landscape Updates). However, treatment increased incidence of anemia and increases in C-reactive protein, particularly at higher doses. We will be interested to see if this brain-shuttled anti-amyloid antibody can find a suitable therapeutic window for chronic repeat dosing.

Notably, Avidity Biosciences incorporates TfR1-targeting monoclonal antibodies conjugates to oligonucleotide therapeutics (siRNA) to improve delivery to muscle for degenerative diseases like DMD and DM1. Importantly, the mAB used is effector region null and does not dual-engage with an immune stimulatory target. In addition to exon skipping and dystrophin increases confirming target engagement, the company reported no symptomatic hemoglobin changes with del-zota treatment in DMD patients in its recent data update. Dyne Therapeutics has also not observed any anemia or reticulocyte count reductions in clinical development of its FORCE platform, a TfR-targeting antibody conjugated to an oligonucleotide drug payload (currently ASO) in development for DM1 and DMD subtypes.

Overall evidence from other TfR-conjugated therapies suggests to us that an antibody targeting TREM2 alone is unlikely to lead to significant anemia concerns. However, this leaves significant BBB penetration as a challenge for TREM2-targeting antibodies and biologic treatments for CNS diseases in general. Efforts are ongoing to optimize other shuttling systems for enhanced delivery across the BBB. For example, Alector's CD98hc-ABC platform leverages the CD98 receptor and has shown preclinical evidence for improving CNS delivery 10-20x over an unconjugated antibody (see: Blood-Brain Barrier R&D Day Highlights Path for Next-Gen Pipeline; INVOKE-2 Data on Track for Fourth Quarter). We see this as an area ripe for innovation in the coming years and a topic for additional analysis in future reports.

Exhibit 30
Trontinemab Shows Dose-Dependent Reduction in Amyloid Burden

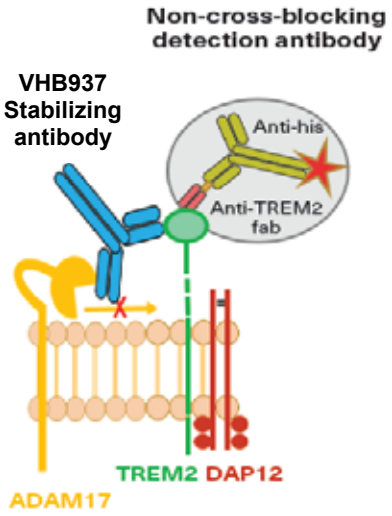


Source: Roche company materials

Novartis

At the 2024 American Academy of Neurology (AAN) meeting, Novartis presented preclinical data on its TREM2 stabilizing antibody, VHB937. VHB937 is a fully human antibody that binds selectively to the IgSF domain of TREM2 to stabilize the receptor in the plasma membrane and activate TREM2 signaling to reestablish functional microglia (exhibit 31). Treatment with VHB937 improves remyelination in the well-established cuprizone-treated mouse model, promotes dopaminergic neuron survival following MPTP-induced cytotoxicity in another murine system, and demonstrates microglial activation signatures in multiple in vitro systems. While VHB937 does not yet appear to be in clinical testing, we see continued enthusiasm from large pharma in the target as further validation.

Exhibit 31
Schematic of VHB937 Mechanism of Action

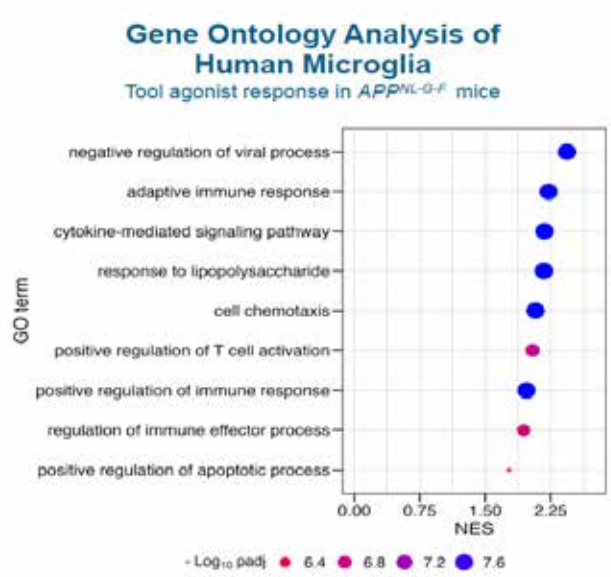


Source: Novartis company materials

Muna

Muna Therapeutics is a private preclinical-stage company based in Denmark focused on developing therapies to treat neurodegenerative diseases including Alzheimer's and Parkinson's. The company is developing multiple microglial-targeting therapies, with the lead program a small-molecule TREM2 agonist. A presentation of preclinical data at the 2023 Clinical Trials in Alzheimer's Disease (CTAD) annual meeting showed multiple molecule candidates promoting dose-dependent TREM2 stabilization and dimerization, resulting in increasing SYK phosphorylation. Using a xenograft model of human microglia incorporated into $APP^{NL\text{-}G\text{-}F}$ mice, treatment with a small-molecule TREM2 agonist led to differential gene expression linked to activation states of microglia subtypes in the presence of amyloid-β pathology (7-month-old $APP^{NL\text{-}G\text{-}F}$ mice) and upregulation of immune-related signaling pathways (exhibit 32). The program remains in preclinical development, and we look forward to future updates.

Exhibit 32
Tool TREM2 Agonist Induces Supportive Microglial State



Source: Muna CTAD 2023 presentation

Summary

We believe TREM2 is one of the most promising emerging clinical targets to correct microglial function and modulate neuroinflammation in several neurodegenerative diseases. To be clear, targeting neuroinflammation is a separate therapeutic class from those that target the proteinopathy component of these disorders (e.g., anti-amyloid and anti-α-synuclein antibody, oligonucleotide therapeutics, and small molecule inhibitors), and given that these disorders converge on dysregulated neuroinflammatory signaling, we believe this new class could be broadly applicable across disease indications.

Several important clinical catalysts for the TREM2 space specifically are expected in the next six to nine months and could act as a tailwind for numerous players targeting neuroinflammation as a therapeutic strategy. These include upcoming top-line data from Alector's INVOKE-2 trial of a TREM2 agonist antibody, AL002, in early AD expected in the fourth quarter of 2024, Vigil's full IGNITE dataset in the first half of 2025, and additional data from Vigil's small-molecule TREM2 agonist, including in AD patients, in the first quarter of 2025. Beyond target validation, these studies can inform broader interventional strategies focused on neuroinflammation in terms of potential disease stage, types of patients to enroll, time to potential benefit, and utility of emerging biomarkers. We anticipate significant progress for the field in the next 24 months and look forward to continuing to follow these developments.

Appendix A—List of Selected Development Programs Targeting Neuroinflammation

Exhibit 33
Select Neuroinflammation-Targeted Drug Discovery Programs

Company		Asset	Indication	Target	Mechanism/modality	Phase	Timing
AC Immune	Public	ACI-24.060	AD	Aβ	Vaccine	Phase II	TBD
AC Immune	Public	Anti-NLRP3	TBD	NLRP3	Antibody	Preclinical	TBD
AC Immune	Public	ACI-35.030	AD	pTau	Vaccine	Phase II	TBD
AC Immune	Public	ACI-7104.056	PD	α-Synuclein	Vaccine	Phase II	2H24
Acumen	Public	Sabirnetug	AD	oAb	Antibody	Phase II	TBD
AcuraStem, Inc/Takeda	Private/Public	AS-202	ALS	PIKfyve	Antisense Oligonucleotide	Preclinical	TBD
AevisBio	Private	AB103i	PD	TBD	TBD	Preclinical	TBD
AevisBio	Private	AB103e	AD	TBD	TBD	Preclinical	TBD
Alchemab	Private	ATLX-1088	AD	CD33	Antibody	Preclinical	TBD
Alchemab	Private	ATLX-1282	FTD/ALS	Undisclosed	Antibody	Preclinical	TBD
Alector/AbbVie	Public	AL002	AD	TREM2	Antibody	Phase II	2H24
Alector/GSK	Public	Latozinemab	FTD	PGRN	Antibody	Phase III	2025*
Alector/GSK	Public	AL101	AD	PGRN	Antibody	Phase II	Late 2026*
Annexon	Public	ANX005	ALS/HD	C1q	Small Molecule	Phase II	2H24
Aperture Therapeutics	Private			TBD		Preclinical	TBD
Arkuda Therapeutics	Private	TBD	Multiple	PGRN	TBD	Preclinical	TBD
AviadoBio	Private	AVB-101	FTD/ALS	PGRN	Gene Therapy	Phase I	TBD
BioAge	Private	BGE-100	TBD	NLRP3	Small Molecule	Preclinical	TBD
BioHaven	Public	BHV-8000	AD/PD/MS	Tyk2 Inhibitor	Small Molecule	Phase I	TBD
BlueRock Therapeutics	Private	TBD	Multiple	Microglia	Cell Therapy	Preclinical	TBD
Bristol Myers Squibb	Public	BM-986456	TBD	Tyk2 Inhibitor	Small Molecule	Phase I	TBD
Cerevance	Private	CVN293	ALS/AD	KCNK13	Small Molecule	Phase 1	TBD
Contineum Therapeutics	Public	PIPE-791	MS	LPA1R	Small Molecule	Phase I	2024*
Contineum therapeutics	Public	PIPE-307	MS	M1R	Small Molecule	Phase II	2025*
Coya	Public	COYA 302	ALS/FTD/AD/PD	IL-2 + CTLA4-Ig	Antibody	Phase II	2H24
Denali/Sanofi	Public	DNL788	MS	RIPK1	Small Molecule	Phase II	2H25*
Denali/Takeda	Public	DNL593	FTD	PGRN	Biologic/Antibody Conjugate	Phase I/II	TBD
Discoveric Bio	Private	NIDB-3101	AD	Undisclosed	Antibody	Preclinical	TBD
Eisai	Public	TBD	AD	TREM2	TBD		
Elixiron Therapeutics	Private	EL-1071	AD	CSF1R	Small Molecule	Phase I	TBD
FireCyte therapeutics	Private	FCT-201	TBD	CSF1R	TBD	Preclinical	TBD
FireCyte therapeutics	Private	FCT-102	TBD	PGRN	TBD	Preclinical	TBD
Herophilus	Private			TBD		Preclinical	TBD
ImmunoBrain Checkpoint	Private	IBV-ab002	AD	PD-L1	Antibody	Phase Ib	2024*
Imnewrun	Private	INR301	AD	PD-L1	Antibody	Preclinical	TBD
INmune Bio	Public	Xpro1595	AD	sTNFα	Biologic	Phase II	4Q24
Muna	Private	TBD	AD	TREM2	Small Molecule	Preclinical	TBD
Myrobalan Therapeutics	Private	TBD	AD/ALS	CSF1R	Small Molecule	Preclinical	TBD
Myrobalan Therapeutics	Private	TBD	AD/PD	Tyk2 Inhibitor	Small Molecule	Preclinical	TBD
Neumora	Public	NMRA-NLRP3	PD	NLRP3	Small Molecule	Preclinical	TBD
Nodthera	Private	NT-0796	PD	NLRP3	Small Molecule	Phase II	TBD
Novartis	Public	VHB937	Multiple	TREM2	Antibody	Preclinical	TBD
Olatec Therapeutics	Private	Dapansutrile	AD/PD	NLRP3	Small Molecule	Phase II	TBD
PassageBio	Public	PBFT02	FTD/ALS/AD	PGRN	Gene Therapy	Phase I/II	2H24
Prevail/Eli Lilly	Public	PR006	FTD	PGRN	Gene Therapy	Phase II	2029*
Prothena	Public	PRX012	AD	Aβ	Antibody	Phase I	2024
Prothena/BMS	Public	PRX005	AD	Tau	Antibody	Phase II	2027*
Prothena/Roche	Public	Prasinsezumab	PD	Alpha-syn	Antibody	Phase II	2H24
PTC Therapeutics	Public	Vatiquinone	FA	15-Lipoxygenase	Small Molecule	Phase III	TBD
PTC Therapeutics	Public	Utreloxastat	ALS	15-Lipoxygenase	Small Molecule	Phase II	4Q24
Roche	Public	Selnoflast	PD	NLRP3	Small Molecule	Phase I	2025*
Shaperon Inc	Private	NuCerin	AD	NLRP3	Small Molecule	Phase I	TBD
Sudo Biosciences	Private	SUDO-550	TBD	Tyk2 Inhibitor	Small Molecule	Preclinical	TBD
Therini Bio	Private	THN391	AD	Fibrin	Antibody	Phase I	TBD
Vanqua	Private	TBD	AD/MS	C5aR1	Small Molecule	Preclinical	TBD
Ventus	Private	VENT-02	Multiple	NLRP3	Small Molecule	Phase I	TBD
Ventyx	Public	VTX3232	PD	NLRP3	Small Molecule	Phase II	1H25*
Verge Genomics	Private	VRG50635	ALS	PIKfyve	Small Molecule	Phase I	2026*
Vesper Bio	Private	VES001	FTD	PGRN	Small Molecule	Phase I	2H24*
Vigil	Public	Iluzanebart	ASLP	TREM2	Antibody	Phase II	1H25
Vigil	Public	VG-3927	AD	TREM2	Small Molecule	Phase I	1Q25

*In our view/clinicaltrials.gov
Sources: Company materials, Clinicaltrials.gov, William Blair Equity Research

The prices of the common stock of other public companies mentioned in this report follow:

AbbVie Inc. (Outperform)	$193.45
AC Immune SA	$3.46
Acumen Pharmaceuticals, Inc.	$2.48
Alector, Inc. (Outperform)	$5.64
Amylyx Pharmaceuticals, Inc.	$2.92
Annexon, Inc.	$6.99
Avidity Biosciences, Inc.	$42.19
Biogen Inc. (Outperform)	$198.21
Biohaven Ltd. (Outperform)	$39.00
Bristol Myers Squibb Company (Market Perform)	$49.49
Contineum Therapeutics, Inc.	$18.40
Coya Therapeutics, Inc.	$6.14
Denali Therapeutics Inc.	$30.68
Dyne Therapeutics, Inc.	$34.60
Eli Lilly and Company	$906.18
GSK plc	$42.56
Ionis Pharmaceuticals, Inc. (Outperform)	$41.51
INmune Bio, Inc.	$5.55
Neumora Therapeutics, Inc. (Outperform)	$11.73
Novartis AG	$115.70
Passage Bio, Inc.	$0.73
Prothena Corporation plc	$21.94
PTC Therapeutics, Inc. (Outperform)	$35.07
Roche Holding AG	$39.39
Sanofi	$56.91
Takeda Pharmaceutical Company Limited	$14.85
Ventyx Biosciences, Inc.	$2.32
Vigil Neuroscience, Inc.	$3.50

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S&P 500: 5634.58
NASDAQ: 17628.10

Additional information is available upon request.

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Market Perform (Hold)	28	Market Perform (Hold)	1
Underperform (Sell)	1	Underperform (Sell)	0

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