Communication

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Tailoring MAPK Pathways: New Therapeutics Avenues for Managing Alzheimer's Diseases

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Abstract: Neurodegenerative diseases like Alzheimer's diseases are irreversible, progressive, and refractory in nature and managed very poorly. AD is manifested with the aggregation of unfolded proteins, synaptic pathology and dementia and poses challenges to the health care system globally. Only very few treatments with minimal effect are available to the patients and their caregivers. Despite numerous clinical trials which were launched for AD, unfortunately, most of them failed in satisfying the pharmacological criteria. At cellular levels, many signaling pathways have been proposed for the sterile / refractory behavior of degenerating neurons. Among those, Mitogen activated protein kinases (MAPKs) are the critical cellular networks which are involved in the development of Alzheimer's disease. Several studies have demonstrated a favorable impact of MAPK inhibition on inflammatory programming, synaptic plasticity, and memory problems in mouse models of AD. In view of this, various clinical trials were launched with several MAPK inhibitors (with good safety profile and less side-effects) have yielded positive results in AD patients suggesting that MAPK targeting may be effective for reducing the pathogenesis of AD, but due to selectivity, dosing and patient stratification, this aspect still need development. In view of selectivity and off-target effects, only a few MAPK inhibitors have been employed in clinical trials against AD indicating a scope of development in this area. Therefore, this study focuses on MAPK based interventions as an upcoming and innovative approach for alleviating AD with special emphasis on clinical studies.

Keywords: alzheimers diseases; MAPK; neuro-immunological interaction; neuronal fibroblast; microglia; Th1/17 responses

Highlights

- MAPK are decisive for neuro-immunological interaction and synapses
- Imbalance of MAPK pathways disrupts neuronal immune-homeostasis
- Readjusting MAPKinome improves immuno-epigenetic response
- MAPK based clinical trials offer therapeutic advantage for AD

Introduction

In recent decades, kinases have emerged as a prominent focus of research in pharmacology due to their central roles in regulating a diverse range of cellular processes [1]. Substantial efforts have been dedicated to developing molecules that specifically target the human kinome, reflecting their significance as potential drug targets [2]. Currently, there are over 250 kinase inhibitors in clinical trials, with 48 already approved by the U.S. Food and Drug Administration (FDA), primarily for treating malignancies. These inhibitors have had a significant impact on cancer therapy, particularly in cases driven by a single oncogenic kinase, such as chronic myeloid leukemia and gastrointestinal stromal tumors[3]. In contrast to oncology, MAPK / kinome based therapeutic approaches are still under early stage of development in neurodegenerative disorders like Alzheimer's disease (AD) and the precise contribution of dysregulated human kinome in the context of neurodegeneration remains elusive. In particular, understanding the neuronal functions of various kinases is a critical area that requires further exploration. The roles of many kinases in neuronal tissues are yet to be fully characterized therefore filling this lacuna in managing / modifying neuro-degenerative diseases is paramount.

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Understanding the precise role of MAPK family members across different brain regions during progression of neurodegenerative diseases conditions will shed light on potential therapeutic strategies. Mammalian cells possess four primary MAPK pathways that trigger the activation of extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), p38, and extracellular signal-regulated kinase 5 (ERK5), also known as Big MAP kinase-1 (BMK1). The mammalian pathways exhibit increased complexity due to the presence of multiple gene products, such as ERK1 and ERK2, JNK1, JNK2, and JNK3, as well as p38α, p38β, p38γ, and p38δ. Due to their critical roles in human diseases, mitogen-activated protein kinases (MAPK) have been targeted / explored for modifying pathology / pathogenesis of various disease models [4].

During the last few years, Ras/Raf/MAPKs pathway has emerged as potential / plausible drug targets in many neurodegenerative diseases (NDDs) such as Parkinson's, Alzheimer's, stroke, aging, and neurodegeneration[5-8] etc. Due to this, the current study highlights the importance of targetable MAPK in NDDs, with a particular emphasis on clinical trial / studies.

Alzheimer's Disease: Progressive Neurodegenerative Ailment

Alzheimer's disease is a terminal dementing neurodegenerative disease of elderly population and is clinically recognized as a slow decline in memory and cognitive function as well as other abnormalities. The majority of AD patients have the sporadic form of the disease. The mortality rate among AD patients rose by 71% from 2000 till 2013 in the United States, where it is ranked as the sixth greatest cause of death. Less than 5% of AD patients have a familial history of disease, which is associated with the mutations in APP, PS1, and PS2 genes [9].

The brain in AD patients is characterized by the extracellular accumulation of senile plaques, intracellular neuro fibrillary tangles. Neuro-pathological lesions of AD are vascular in nature with fibrotic lesions showing oxidative stress and tau pathology. AD is manifested with the aggregation of Amyloid beta, synaptic loss, microglial cell reactivity, excitotoxicity, loss of mitochondrial membrane potential and intracranial accumulation of glycation end products[10,11]. Very little is known on the key factors / mechanism which trigger the pathogenesis of AD in the healthy brain.

Beta Amyloid Specific Interventions for AD

Perturbation in glia-neuron axis and breakage of homeostasis is believed to trigger the pathogenesis of AD which is manifested by the infiltration of effector immune cells and their interaction with damaged neurons subsequently leads to neuronal fibrosis in the cerebral region [12]. This is orchestrated by the release of beta amyloid from damaged neurons which trigger pathogenic inflammation in brain, which is accompanied with the accumulation of βA peptide, which subsequently leads to synaptic loss and augment neuronal cell death which is overriding pathological feature of AD [13].

Inflammation is mainly mediated by microglial cells which are resident immune cells in the central nervous system (CNS). In AD, microglia has been known to be chronically activated, resulting in impairment of Aβ clearance, overexpression of pro-inflammatory signals, and consequently, neurotoxicity. Therefore, the regulation of microglial activation may be an important therapeutic strategy of AD by lowering excessive pro-inflammatory immune chemotaxis and enhancing neuroprotective function, leading to the modulation of neuro-inflammation [13,14].

Infact, for the last couple of decades, several clinical trials involving AD patients / subjects have targeted beta-amyloid (Aβ) for limiting the progression and pathology of AD as shown in Table 1.

According to recent studies, either development of various inhibitors of Amyloid beta and tau protein synthesis or mimetics for their degradation seems to be the most pertinent strategies for modifying AD. So far none of tau-related agents have been approved by regulatory authorities for the treatment of AD [15]. Till date, 187 trials have been launched which assessed 141 drugs targeting various signaling components involved in the progression of AD[15] as shown in Figure 1.

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Table 1. Humanized monoclonal antibodies in the current Alzheimer's disease pipeline. (Data is downloaded from https://clinicaltrials.gov/).

NCT	Agent	Study title	Status/result	Target	Phase	study summary	Comments
NCT00890890	Avagacestat	A Multicenter, Double Blind, Placebo Controlled, Safety and Tolerability Study of BMS-708163 in Patients With Prodromal Alzheimer's Disease	Terminated/ No	Gamma secretase inhibitor	II	The purpose of this study is to determine the safety and tolerability of BMS-708163 in patients with Prodromal Alzheimer's disease over a treatment period of a minimum of 104-weeks. In addition patients will be seen for safety visits at 4 and 12 weeks post treatment.	Safety and tolerability of BMS-708163 in patients with Prodromal Alzheimer's disease as measured by adverse events, vital signs, laboratory assessments, electrocardiograms (ECGs) and Safety Head Magnetic resonance imaging (MRI) findings, Every 12 weeks up to week 220|
NCT00810147	BMS-708163	A Phase II, Multicenter, Double Blind, Placebo-Controlled Safety, Tolerability Study of BMS-708163 in Patients With Mild to Moderate Alzheimer's Disease	Completed/No		2	The purpose of this study is to determine the safety and tolerability of BMS-708163 in patients with mild to moderate Alzheimer's disease over a treatment period of 12-weeks and the course of any potential effects during a 12-week wash-out period	Adverse Events
NCT01039194	BMS-708163	Drug-Drug Interaction to Study the Effect of BMS-708163 on Pharmacokinetics (PK) of Galantamine Extended Release (ER)	Completed/No		1	The purpose of the study is to find out if the plasma concentration of galantamine extended release is changed when BMS-708163 is administered at the same time.	Safety and tolerability
NCT00726726	BMS-708163 + Cooperstown Cocktail	Drug Interaction Study With a Potential Alzheimer's Disease Compound	Completed/No		1	The purpose of this study is to determine whether BMS-708163 will affect the pharmacokinetics of the commonly prescribed medicines midazolam, warfarin, caffeine,omeprazole and dextromethorphan	Adverse events
NCT01042314	BMS-708163	Drug-Drug Interaction Study With AriceptÂ® (Donepezil)	**Completed/No**		1	The purpose of this study is to find out if the plasma concentration of donepezil is changed when BMS-708163 is administered at the same time	**Safety and tolerability**
NCT01079819	BMS-708163	Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of BMS-708163	**Completed/No**		1	The purpose of the study is to evaluate the pharmacokinetics, safety and tolerability of BMS-708163 administered as single and multiple doses in Chinese subjects	**Adverse events**

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NCT	Agent	Study title	Status/result	Target	Phase	study summary	Comments
NCT01035138	Semagacestat	A Study of Semagacestat for Alzheimer's Patients	Completed/ yes	Monoclonal antibodies to Aβ or its oligomers or fibrils	3	The primary objective of the original study was to assess the safety of semagacestat in Alzheimer's disease (AD) patients during 24 months of open-label treatment. Baseline for the efficacy measures is defined as the baseline for feeder studies LFAN (NCT00594568) and LFBC (NCT00762411). For all safety analyses (adverse events), baseline for patients will be week 0 of this study (LFBF).	semagacestat did not slow disease progression and was associated with worsening of clinical measures of cognition and the ability to perform activities of daily living. Preliminary results from LFAN and LFBC showed Study drug was stopped in all studies. Very few participants from LFBC rolled over into LFBF (N = 9). Due to insufficient sample size, the data for LFBC participants who rolled into LFBF were not analyzed.
NCT00663026	Bapineuzumab	Study Evaluating Bapineuzumab In Alzheimer Disease Subjects	Completed/ yes	Monoclonal antibodies to Aβ or its oligomers or fibrils	2	The study will evaluate the safety and effectiveness of bapineuzumab for the treatment of mild to moderate Alzheimer disease. Subjects will be in the study for six months and will receive subcutaneous injections once per week.	Adverse events and serious adverse events.
NCT00676143	Bapineuzumab	Study Evaluating the Safety and Efficacy of Bapineuzumab in Alzheimer Disease Patients	Terminated / yes	Monoclonal antibodies to Aβ or its oligomers or fibrils	3	This is a study to evaluate the efficacy and safety of multiple doses of bapineuzumab in patients with mild to moderate Alzheimer Disease. Patients will receive either bapineuzumab or placebo. Each patient's participation will last approximately 1.5 years.	Alzheimer's Disease Assessment Scale- Cognitive (ADAS-Cog)/11 Subscale Total Score at Week 78,
NCT00996918	Bapineuzumab	A Long-Term Safety And Tolerability Study Of Bapineuzumab In Alzheimer Disease Patients	Terminated / yes	Monoclonal antibodies to Aβ or its oligomers or fibrils	3	The purpose of this study is to assess the long- term safety and tolerability of bapineuzumab in subjects with Alzheimer Disease who participated in study 3133K1-3000 (NCT00667810). Over 250 sites will participate in over 26 countries. Subjects will receive bapineuzumab. Each subject's participation will last approximately 4 years.	Adverse events

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NCT	Agent	Study title	Status/result	Target	Phase	study summary	Comments
NCT03639987	Aducanumab	A Study of Aducanumab in Participants With Mild Cognitive	Terminated/ yes	Monoclonal antibodies to Aβ	2	The primary objective of the study is to assess the safety impact of continuing aducanumab	Number of Participants with Clinically Impactful Amyloid-related Imaging
NCT02484547	Aducanumab	221AD302 Phase 3 Study of Aducanumab (BIIB037) in Early	Terminated/ yes	Monoclonal antibodies to Aβ	3	The primary objective of the study is to evaluate the efficacy of monthly doses of	Change From Baseline in Clinical Dementia Rating Scale - Sum of Boxes
NCT02477800	Aducanumab	221AD301 Phase 3 Study of Aducanumab (BIIB037) in Early	Terminated/ yes	Monoclonal antibodies to Aβ	3	The primary objective of the study is to evaluate the efficacy of monthly doses of	Change From Baseline in Clinical Dementia Rating Sum of Boxes (CDR-
NCT05108922	Aducanumab	A Study of Donanemab (LY3002813) Compared With Aducanumab in	Active not recruiting/ No	Monoclonal antibodies to Aβ	3	The main purpose of this study is to compare donanemab to aducanumab on amyloid plaque	
NCT01677572	Aducanumab	Multiple Dose Study of Aducanumab (BIIB037) (Recombinant, Fully	TERMINATED/ No	Monoclonal antibodies to Aβ	1	The primary objective of this study is to evaluate the safety and tolerability of multiple	Number of Participants with Adverse Events, Baseline to week 518
NCT01397539	Aducanumab	Single Ascending Dose Study of BIIB037 in Participants With	COMPLETED/ No	Monoclonal antibodies to Aβ	1	The primary objective of the study is to evaluate the safety and tolerability of a range	Number of Participants with Adverse Events as a Measure of Safety and
NCT05310071	Aducanumab	A Study to Verify the Clinical Benefit of Aducanumab in Participants With	RECRUITING/ No	Monoclonal antibodies to Aβ	3	The primary objective of this study is to verify the clinical benefit of monthly doses of	Change From Baseline in CDR-SB Score at Week 78, impairment. Positive
NCT02782975	Aducanumab	Absolute Bioavailability of a Single, Fixed Subcutaneous Dose of	COMPLETED/ No	Monoclonal antibodies to Aβ	1	The primary objectives of this study are to evaluate the absolute bioavailability of a single,	PK parameter of SC dose of aducanumab: Absolute Bioavailability,
NCT04241068	Aducanumab	A Study to Evaluate Safety and Tolerability of Aducanumab in participants With Alzheimer's	ACTIVE_NOT_RECRUITING/ No	Monoclonal antibodies to Aβ or its oligomers	3	The primary objective is to evaluate the safety and tolerability of aducanumab over 100 weeks of treatment after a wash-out period imposed	Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs): Number of Participants

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NCT	Agent	Study title	Status/result	Target	Phase	study summary	Comments
NCT02434718	Aducanumab	Single and Multiple Ascending Dose Study of Aducanumab (BIIB037) in Japanese Participants With Alzheimer's Disease	COMPLETED/ No	Monoclonal antibodies to Aβ or its oligomers or fibrils	1	The primary objective of the study is to evaluate the safety and tolerability of single and multiple intravenous (IV) infusions of Aducanumab in Japanese participants with mild to moderate Alzheimer's Disease (AD). The secondary objectives of this study are as follows: To evaluate the serum pharmacokinetics (PK) of Aducanumab after single and multiple intravenous (IV) infusions of Aducanumab; To evaluate the effect of single and multiple IV infusions of Aducanumab on immunogenicity.	Incidence and nature of adverse events (AE) / serious adverse events(SAE), Up to week 42 abnormalities in neurological and physical examinations, Up to week 42|Brain magnetic resonance imaging (MRI) findings to assess amyloid- related imaging abnormalities (ARIA), including incidence of ARIA-E (edema) or ARIA-H (hemosiderosis), Up to week 42
NCT01767311	Lecanemab	A Study to Evaluate Safety, Tolerability, and Efficacy of Lecanemab in Subjects With Early Alzheimer's Disease	Active not Recruiting/No	Monoclonal antibodies to Aβ or its oligomers or fibrils	2	This is a multinational, multicenter, double-blind, placebo-controlled, parallel-group study using a Bayesian design with response adaptive randomization across placebo or 5 active arms of lecanemab to determine clinical efficacy and to explore the dose response of lecanemab using a composite clinical score (ADCOMS).	adverse events (AEs) and serious adverse events (SAEs)
NCT03887455	Lecanemab	A Study to Confirm Safety and Efficacy of Lecanemab in Participants With Early Alzheimer's Disease	Active_not_recruiting/ No	Monoclonal antibodies to Aβ or its oligomers or fibrils	3	This study will be conducted to evaluate the efficacy of lecanemab in participants with early Alzheimer's disease (EAD) by determining the superiority of lecanemab compared with placebo on the change from baseline in the Clinical Dementia Rating-Sum of Boxes (CDR- SB) at 18 months of treatment in the Core Study. This study will also evaluate the long- term safety and tolerability of lecanemab in participants with EAD in the Extension Phase and whether the long-term effects of lecanemab as measured by the CDR-SB at the end of the Core Study is maintained over time in the Extension Phase.	Adverse event that emerges during treatment or within 30 days of the last dose of study drug. Worsens in severity during treatment relative to the pretreatment state, when the adverse event was continuous

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NCT	Agent	Study title	Status/result	Target	Phase	study summary	Comments
NCT04468659	Lecanemab	AHEAD 3-45 Study: A Study to Evaluate Efficacy and Safety of Treatment With Lecanemab in Participants With Preclinical Alzheimer's Disease and Elevated Amyloid and Also in Participants With Early Preclinical Alzheimer's Disease and Intermediate Amyloid	Recruiting/No	Monoclonal antibodies to Aβ or its oligomers or fibrils	3	The primary purpose of this study is to determine whether treatment with lecanemab is superior to placebo on change from baseline of the PACC5 at 216 weeks of treatment (A45 Trial) and to determine whether treatment with lecanemab is superior to placebo in reducing brain amyloid accumulation as measured by amyloid (PET) at 216 weeks of treatment (A3 Trial).	Preclinical Alzheimer Cognitive Composite 5 (PACC5) Score at Week 216
NCT05738486	Donanemab	A Study of Different Donanemab (LY3002813) Dosing Regimens in Adults With Early Alzheimer's Disease (TRAILBLAZER-ALZ 6)	RECRUITING/No	Monoclonal antibodies to Aβ or its oligomers or fibrils		This study will investigate different donanemab dosing regimens and their effect on the frequency and severity of ARIA-E in adults with early symptomatic Alzheimer's disease (AD) and explore participant characteristics that might predict risk of ARIA.	Percentage of Participants with Any Occurence of Amyloid-Related Imaging Abnormality-Edema/Effusion (ARIA-E), 24 Weeks
NCT05108922	Donanemab	A Study of Donanemab (LY3002813) Compared With Aducanumab in Participants With Early Symptomatic Alzheimer's Disease (TRAILBLAZER-ALZ 4)	ACTIVE_NOT_RECRUITING/No	Monoclonal antibodies to Aβ or its oligomers or fibrils		The main purpose of this study is to compare donanemab to aducanumab on amyloid plaque clearance in participants with early symptomatic Alzheimer's Disease (AD).	
NCT05508789	Donanemab	A Study of Donanemab (LY3002813) in Participants With Early Symptomatic Alzheimer's Disease (TRAILBLAZER-ALZ 5)	RECRUITING/No	Monoclonal antibodies to Aβ or its oligomers or fibrils		The reason for this study is to assess the safety and efficacy of donanemab in participants with early Alzheimer's disease. The study duration including screening and follow-up is up to 93 weeks.	Change from Baseline on the Integrated Alzheimer's Disease Rating Scale (iADRS), Change from Baseline on the iADRS in at least one of 'the low medium tau pathology population or
NCT05026866	Donanemab	A Donanemab (LY3002813) Prevention Study in Participants With Alzheimer's Disease (TRAILBLAZER-ALZ 3)	RECRUITING/No	Monoclonal antibodies to Aβ or its oligomers or fibrils		The main purpose of this study is to evaluate the safety and efficacy of donanemab in participants with preclinical Alzheimer's Disease (AD).	Time to clinical progression as measured by Clinical Dementia Rating Global Score (CDR-GS), participant's stage on the spectrum of AD dementia., Estimated Up to Week 182

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NCT	Agent	Study title	Status/result	Target	Phase	study summary	Comments
NCT04640077	Donanemab	A Follow-On Study of Donanemab (LY3002813) With Video Assessments in Participants With Alzheimer's Disease (TRAILBLAZER- EXT)	ACTIVE_NOT_RECRUITING/No	Monoclonal antibodies to Aβ or its oligomers or fibrils		The main goals of this study are to further determine whether the study drug donanemab is safe and effective in participants with Alzheimer's disease and to validate video scale assessments.	Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog13). A summary of serious and other non- serious adverse events regardless of causality is located in the Reported Adverse Events module., Up to 72 Weeks
NCT04437511	Donanemab	A Study of Donanemab (LY3002813) in Participants With Early Alzheimer's Disease (TRAILBLAZER-ALZ 2)	ACTIVE_NOT_RECRUITING/No	Monoclonal antibodies to Aβ or its oligomers or fibrils		The reason for this study is to see how safe and effective the study drug donanemab is in participants with early Alzheimer's disease. Additional participants will be enrolled to an addendum safety cohort. The participants will be administered open-label donanemab.	Change from Baseline on the integrated Alzheimer's Disease Rating Scale (iADRS), Change from Baseline on the iADRS in participants with early symptomatic AD in at least one of 'the low-medium tau pathology population or the overall population'., Baseline, Up to Week 76
NCT01224106	Gantenerumab	A Study of Gantenerumab in Participants With Prodromal	Completed/Yes	Monoclonal antibodies to Aβ	3	This multi-center, randomized, double-blind, placebo-controlled parallel-group study.	Adverse Events (AEs) or Serious Adverse Events (SAEs)
NCT02051608	Gantenerumab	A Study of Gantenerumab in Participants With Mild Alzheimer Disease	Completed/Yes	Monoclonal antibodies to Aβ or its oligomers or fibrils	3	Part 1 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study will evaluate the efficacy and safety of gantenerumab in participants with mild Alzheimer disease. Participants will be randomized to receive either gantenerumab subcutaneously every 4 weeks or placebo subcutaneously every 4 weeks. Approved Alzheimer medication is allowed if on stable dose for 3 months prior to screening. Part 2 is an open-label extension (OLE).	Adverse Events (AEs) or Serious Adverse Events (SAEs)
NCT01998841	Crenezumab		Completed/Yes		2	Study evaluates the efficacy and safety of Crenezumab versus Placebo in participants who carry the PSEN1 E280A autosomal-dominant mutation and do not meet the criteria for mild cognitive impairment due to	Adverse Events (AEs) and Serious Adverse Events (SAEs)

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NCT	Agent	Study title	Status/result	Target	Phase	study summary	Comments
						AD or dementia due to AD and are thus, in a preclinical phase of AD.	
NCT01723826	Crenezumab		Completed/Yes		2	study will evaluate the long-term safety and tolerability of crenezumab in participants with mild to moderate Alzheimer's disease who have participated in and completed the treatment period of the Phase II Study ABE4869g (NCT01343966) or ABE4955g (NCT01397578). Participants who received placebo in Study ABE4869g (NCT01343966) or ABE4955g (NCT01397578) will receive crenezumab. Anticipated time on study treatment is 144 weeks.	Adverse Events (AEs)
NCT02760602	Solanezumab	A Study of Solanezumab (LY2062430) in Participants With Prodromal Alzheimer's Disease	Terminated/yes		3	The main purpose of this study is to investigate the safety and efficacy of the study drug solanezumab in participants with prodromal Alzheimer's disease (AD).	AlzheimerÂ´s Disease Assessment Scale- Cognitive Subscale (ADAS-Cog14) Score
NCT01900665	Solanezumab	Progress of Mild Alzheimer's Disease in Participants on Solanezumab Versus Placebo	Terminated/yes		3	To test the idea that solanezumab will slow the cognitive decline of Alzheimer's Disease (AD) as compared with placebo in participants with mild AD.	ADAS-Cog14
NCT01127633	Solanezumab	Continued Safety Monitoring of Solanezumab (LY2062430) in Alzheimer's Disease	Terminated/yes		3	This study is an open-label extension study in Alzheimer's patients who have completed participation in either solanezumab Clinical Trial H8A-MC-LZAM (NCT00905372) or H8A-MC LZAN (NCT00904683).	A summary of serious and other non- serious adverse events regardless of causality is located in the Reported Adverse Events module., Baseline through Week 104
NCT01739348	Verubecestat	An Efficacy and Safety Trial of Verubecestat (MK-8931) in Mild to Moderate Alzheimer's Disease (P07738)	Terminated/yes	BACE1 inhibitor	02-Mar	This study assesses the efficacy and safety of verubecestat (MK-8931) compared with placebo administered for 78 weeks in the treatment of Alzheimer's Disease (AD).	ADAS-Cog11

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NCT	Agent	Study title	Status/result	Target	Phase	study summary	Comments
NCT01953601	Verubecestat	Efficacy and Safety Trial of Verubecestat (MK-8931) in Participants With Prodromal Alzheimer's Disease (MK-8931-019)	Terminated/yes		3	The study assesses the efficacy and safety of verubecestat (MK-8931) compared with placebo administered for 104 weeks in the treatment of amnestic mild cognitive impairment (aMCI) due to Alzheimer's Disease (AD), also known as prodromal AD.	Adverse events
NCT02910739	Verubecestat	An Open-Label Study Investigating MK-8931 in Participants With Mild and Moderate Hepatic Insufficiency (MK-8931-016)	Complete/yes		1	The purpose of this study is to compare the plasma pharmacokinetics of verubecestat (MK- 8931) following administration of a single oral dose of 40 mg MK-8931 to participants with moderate hepatic insufficiency (HI) to that of healthy matched controls.	
NCT02569398	Atabecestat	An Efficacy and Safety Study of Atabecestat in Participants Who Are Asymptomatic at Risk for Developing Alzheimer's Dementia	Terminated/No		2/3	The purpose of this study is to evaluate whether treatment with atabecestat slows cognitive decline compared with placebo treatment, as measured by a composite cognitive measure, the Preclinical Alzheimer Cognitive Composite (PACC), in amyloid-positive participants who are asymptomatic at risk for developing Alzheimer's dementia.	
NCT02972658	Lanabecestat	A Study of Lanabecestat (LY3314814) in Early Alzheimer's Disease	Terminated/Yes		3	This study is an extension of study I8D-MC-AZES (NCT02245737), the AMARANTH study.	ADAS-Cog13
NCT02783573	Lanabecestat	A Study of Lanabecestat (LY3314814) in Participants With Mild Alzheimer's Disease Dementia	Terminated/Yes		3	The main purpose of this study is to evaluate the efficacy of the study drug known as lanabecestat in participants with mild Alzheimer's disease (AD) dementia.	ADAS-Cog13
NCT02245737	Lanabecestat	An Efficacy and Safety Study of Lanabecestat (LY3314814) in Early Alzheimer's Disease	Terminated/Yes		2/3	The purpose of this study is to assess the efficacy and safety of lanabecestat compared with placebo administered for 104 weeks in the treatment of early AlzheimerÂ´s disease.	ADAS-Cog13

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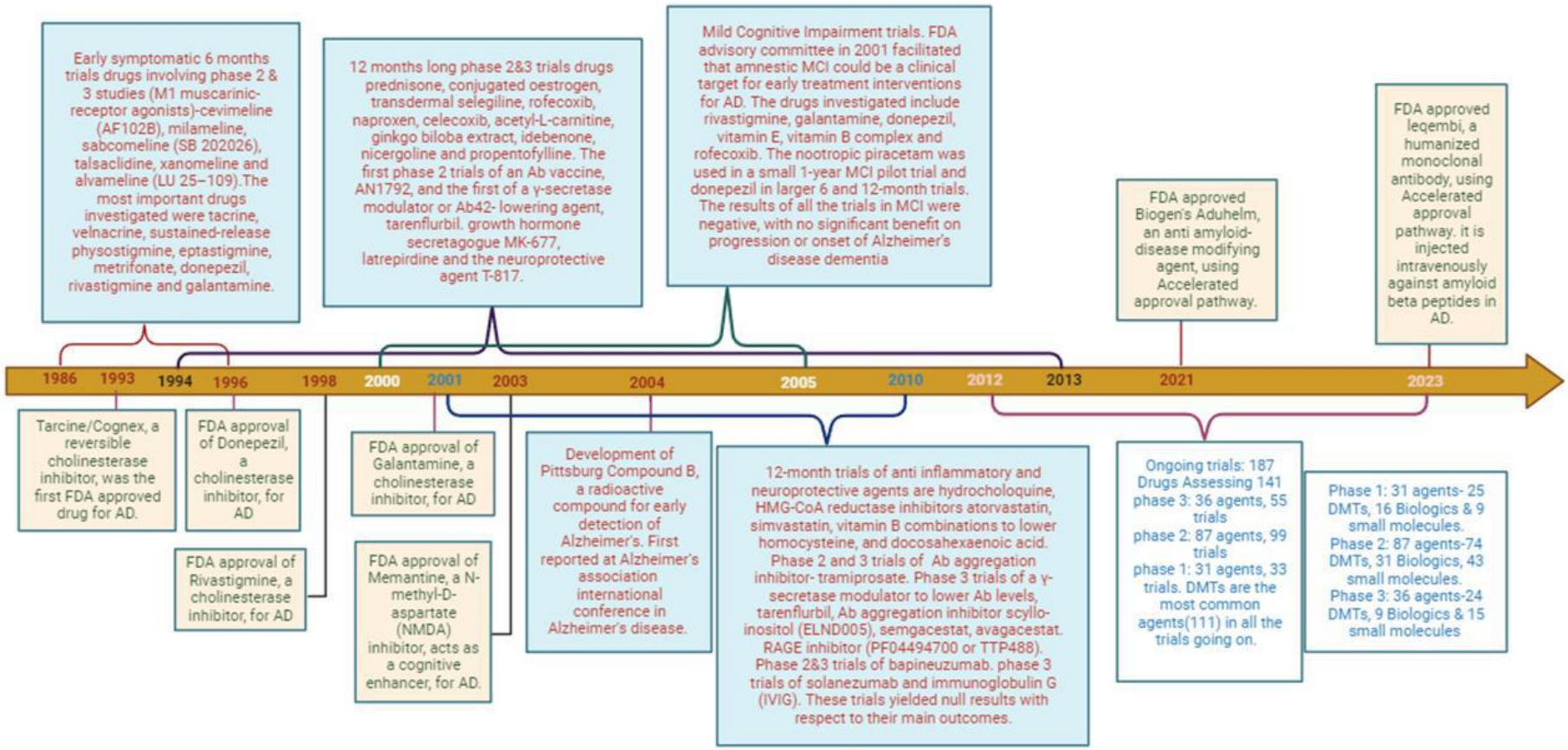

Figure 1. Evolution of Alzheimer;s therapeutics: Shown here is the comprehensive journey of MAPK inhibitors which have been explored in various single / multicentre clinical trials for developing AD therapeutics.

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MAPK Based Intervention of Alzheimer Diseases

Out of several signaling pathways which are involved in the pathogenesis of AD, MAPK pathways are the most intricate pathways which promote stress related adaptation and orchestrate desmoplastic reactions leading to the pathogenic inflammation, neuronal death[7,16]. MAPK is a non-canonical pathway that gets activated by aberrant neuronal-microglia interaction [17](also known as stromal reactions) as shown in Figure 2a.

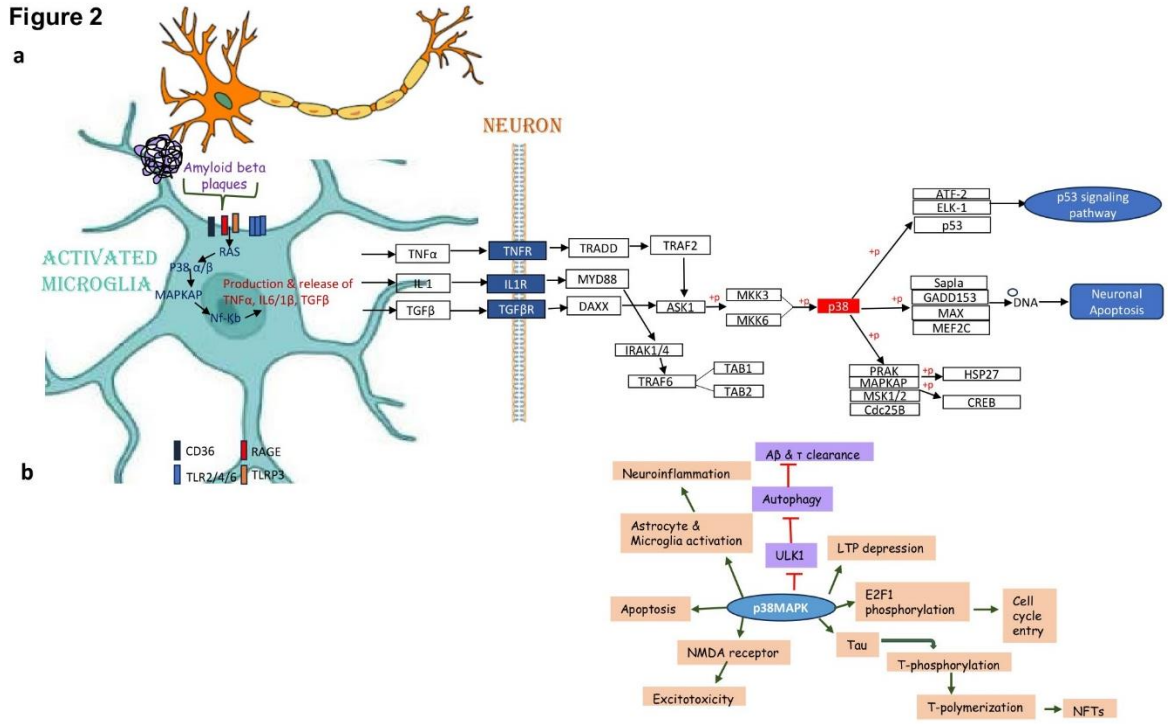

Figure 2. Impact of p38 mitogen-activated protein kinase (MAPK) pathway in the pathogenesis of Alzheimer's disease (AD) (a) This diagram shows the interaction between microglia and neuron in Alzheimer's. The build up of amyloid beta plaques activates microglia leading to chronic inflammation and activation of p38MAPK pathway causing neuronal apoptosis. The CD36 along with TLR2/4/6, and RAGE binds to amyloid beta and trigger the activation of p38 MAPK signalling pathway in microglia leading to the production of pro-inflammatory cytokines, such as TNFα, TGFβ binding to their receptors on neurons. TRADD / TRAF are proteins involved in the signalling pathway of TNFα leading to activation of ASK1. GADD153 and Sapla are proteins induced by p38 MAPK. GADD153 has been shown to be involved in the apoptosis of neurons in AD while Sapla is involved in the regulation of gene expression in neurons. ATF-2 is a transcription factor that gets activated by p38 MAPK. It has been shown to be involved in p53 signalling pathway. Cdc25B is a phosphatase that is activated by p38 MAPK. It has been shown to be involved in the regulation of cell cycle progression. However, in Alzheimer's disease, CDC25B activity increases the abnormal expression of Cdc2/cyclin B, resulting in various downstream indicators of mitotic events and eventually leading to neuro-degeneration. A substantial increase in p53 activity and its level has been documented in AD and intracellular Aβ42 may cause p53-dependent neuronal apoptosis through activation of the p53 promoter; thus, demonstrating an alternative pathogenesis in AD[45-47]. b) the figure showing the central role of p38MAPK leading to the activation and inhibition of several processes in AD.

MAPK constitutes several proteins and among them p38 is one of the three MAPKs family members which are primarily activated by pro-inflammatory cytokines (Th1/ Th17 effectors) and environmental stresses caused by dying neurons. p38 MAPKs have four isoforms which are further categorized in p38α, β, γ and δ [18]. Among these, p38α andβ MAPKs are highly expressed in the adult mouse brain and involved in AD pathogenesis[19]. p38α regulates inflammatory programming of the

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brain via tempering microglia[20] and astrocytes[21]. MAPK is a complex and multifaceted pathway which also connects different neurological disorders as shown in Figure 2a like Alzheimer's and ischemic stroke[8,22,23]. Research is also going in this area whereby inhibiting the MAPK pathway using MAPK inhibitors both neurological diseases can be ameliorated as shown in Figure 3.

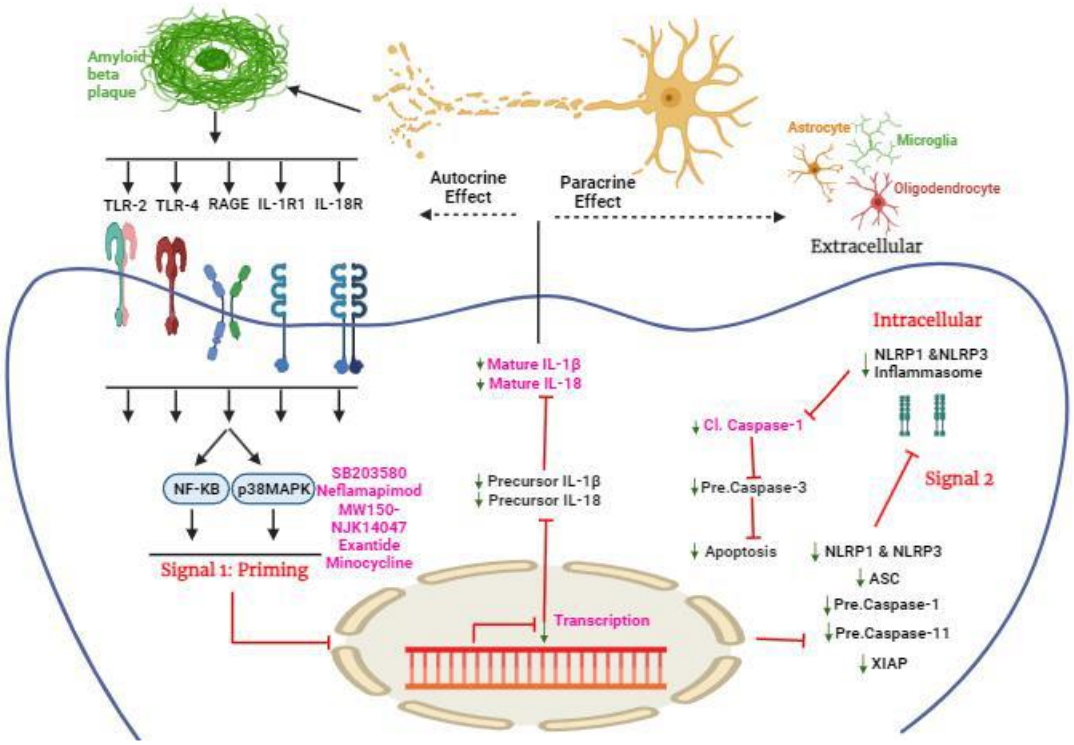

Figure 3. p38MAPK inhibitions in amyloid beta induced neurotoxic environment: The amyloid beta is produced primarily in the intracellular compartments of neurons by the proteolytic cleavage of Amyloid Precursor Proteins which is then secreted outside to form the sticky plaques that causes the death of brain cells. The amyloid beta toxicity initiates the p38MAPK pathway that further initiates the transcription of pro-inflammatory cytokines, pro-apoptotic proteins and inflammasome proteins as shown. However, the p38MAPK inhibitors that are in the clinical trials have shown a significant impact in AD patients and have demonstrated themselves very useful in ameliorating the neurotoxic environment by reducing the chronic inflammation and brain cell death.

During the progression of AD, p38 expression is enhanced in damaged neurons, contributing to amyloid-beta toxicity, inflammation, and tau phenomena on synaptic clefts as shown in Figure 2b. Study with transgenic animals (APP/PS1, aged rats, Tau mice) revealed that deleting the p38α selective kinase reverses the AD symptom which were induced by amyloid-beta, inflammation, or tau. The study also links neuronal p38α signalling to the impairment of memory and synaptic plasticity seen in 5XFAD animals. This is because it regulates the build-up of amyloid-β in the brain as well as how this accumulation is relayed to trigger an inflammatory response, which results in cognitive deficiencies[24]. A highly selective p38α inhibitor was administered as part of a clinical investigation on sixteen patients diagnosed with early AD. The findings suggest that selective p38α inhibition may enhance episodic memory and perhaps influence the development of β-amyloid in patients with early AD. These first clinical results lend support to carrying out a longer-term, placebo-controlled investigation, especially to validate the effects on episodic memory function[25]. A compelling study has indicated that two neuron specific micro RNA, miR-124/128 directed loss of p38α in primary mouse cerebral granule cell culture, leads to the down regulation of signal transduction of p38α MAPK pathway and declining neuro-pathogenesis[26]. Mechanistically, p38α disrupts proteostasis in neurons by promoting unfolded protein responses (UPR) impair autophagy-mediated protein degradation and endolysosome functions[27] which are essential for synaptic function[28]. Clinical trials with several MAPK specific inhibitors have (Tables 2 and 3) have shown their impact in ameliorating AD pathology.

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Table 2. Inflammation targeted therapies in Alzheimer's Disease pipeline. (Data downloaded from clinicaltrials.gov/).

DRUG	PHASE	TARGET	No of participant	duration	OUTCOME
		Inhibits the activation of microglia			
Masatinib	3	TKI	600	24 weeks	Recovered spetial learning performance and synaptic markers (10)
AL002	2	TREM 2Antibody Monoclonal IgG1 antibody	265	96 weeks	Diminished dystrophic neurites, lowered filamentous Aβ plaques, and encouraged microglia activation and Aβ phagocytosis
NE3107	3	NFkB/ERK/ MAPK pw inhibitor	316	30 weeks	Decreasing hyperglycemia, hyperinsulinemia, and mediation of insulin resistance (12)
BCG	2	Immunomodulator	15	364 days	BCG vaccination prevented cognitive impairment, raised circulating IFNγ, attracted macrophages to cerebral Aβ plaques, and boosted cerebral anti-inflammatory cytokines in a transgenic mouse model of AD (17)
Semaglutide	3	GLP-1 agonist	1840	173 weeks	Anti-inflammatory in AD (cummings)
Baricitinib	1-2	JAK STAT inhibitor	20	24 weeks	CSF concs of basatinib, CCL2
Canakimumab	2	Anti-interlukin 1b antibody	90	24 weeks	Change in NTB total score
Daratumumab	2	Anti-CD38 antibody	15	24 weeks	ADAS-cog11
Dasatinib+quercetin	2	SER kinase inhibitor and upregulator of SIRT1 and senolytics	48	48 weeks	Adverse/serious events
			20	11 weeks	Safety and tolerability
			12	12 weeks	Neuro vascular, coupling, executive function, Gait speed
Sagramostim	2	Synthetic GM-CSF	42	24 weeks	Adverse events
Senicapoc	2	KCA3,1 inhibitor	55	52 weeks	ADAS-cog13 scores csf markers

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DRUG	PHASE	TARGET	No of participant	duration	OUTCOME
Rapamycin	2	mTOR Inhibitor	10-40	8weeks/ 12months	BBB penetration, adverse events, metabolic pannel
Proleukin	2	Recombinant human interleukin 2	45	18 months	CDR
Pepinemab	01-Feb	Anti-SEMA4D antibody	40	40 weeks	Adverse events
Montelukast	2	Leukotriene antagonist	70	26 weeks	Global neuro physiological test battery
L-serine	2	Reduces inflammation	40	12 months	Cognitive assessment, health check (blood tests), adverse events
Lenatidomide	2	Proinflammatory cytokines inhibitor	30	18months	ADAS-COG, ADAS-ADL
TB006	2	Anti-galactin 3 antibody	140	104 days	Severity of dementia
T-Dap vaccine	01-Feb	immunomodulator	50	6 months	Change in abeta42/40 ratio and tau in plasma
Valacyclovir	2	HSV antiviral	120	18months	
XProl 595	2	s-TNF inhibitor	201	23 weeks	
CpG 1018	1	Actives TLR9	39	18 weeks	Adverse events, rheumatoid factor, anti-nuclear antibody, and anti-neutrophil ab in their blood
Emtricitabine	1	NRTI for HIV	35	8 months	Adverse events
IBC-ab002	1	PD 1 inhibitor	40	48 weeks	Abnormalities in brain, suicidal thoughts, vital signs, significant changes in hematology
Salsalate	1	P300/CBP inhibitor	40	12 months	Adverse events
VT301	1	Regulatory T cells	12	3	Adverse events
		SYNAPTIC PLASTICITY DRUGS			
Blarcamesine	02-Mar	Sigma 1/ muscarinic agonist	500	48 weeks	
Simufilam	3	Binds to filamin to prevent interaction of abeta and A7 nicotinic acetylcholine receptor	750	52 weeks	
AGB101	02-Mar	SB2A INHIBITOR	164	78 weeks	CDRSB

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DRUG	PHASE	TARGET	No of participant	duration	OUTCOME
Fosgonimeton	02-Mar	Hepatocyte growth factor/MET activator	475	26 weeks	
Bryostatin	2	PKC activator	100	30 days	SIB, safety
AL001	01-Feb	GSK3 beta inhibitor	72	14 days	Safety and toleralibity
Tertomotide	3	Telomerase RT mimic	936	6 month	Sib, CDRSB
CY6463	2	Positive allostreric modulator of guanylate cyclase	30	14 days	Safety and tolerability
Endonerpic	2	Specific target under defined may be collapsin response mediator protein 2	200	78 weeks	Change in CSF p Tau 181
Dalzanemdor	2	N methyl d aspartate receptor, allosteric modulator	150	84 days	
Elayta CT1812	2	Sigma 2receptor antagonist	450	18 months	CDRSB
X039	2	Enhance n methyl d aspartate receptor activity	120	28 weeks	
ExPlas	2	Human plasma with multiple constituents	60	1 year	Adverse events
Levetiracetam	2	SV2A inhibitor	85	5 months	
			65	1 year	
			30	4 weeks	Hippocampal function
MW150	2	MAPK P38alpha inhibitor	24	84 days	Safety measures
Neflamapimod	2	MAPK P38alpha inhibitor	40	12 Weeks	Brain inflammation by translocator protein tracer
Centella asiatica	1	Multimiodel herb derives traditional Chinese medicine	48	6 weeks	Brain AA/CR ratio assessed by MR spectroscope

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Table 3. p38MAPK inhibitors interventional therapy in Alzheimer's Disease Pipeline(Data downloaded from clinicaltrials.gov/).

Drug	Phase	Study title	Target	NCT	Study status/result	Study summary	Outcome measures
Neflamapimod	2	Proof-of-Concept Study of a Selective p38 MAPK Alpha Inhibitor, Neflamapimod, in Subjects With Mild Alzheimer's Disease	P38 MAPK inhibitor	NCT03402659	Completed/ yes	This is a phase 2b, double-blind, placebo controlled proof-of-concept study of a an oral small molecule selective inhibitor of p38 alpha kinase, neflamapimod, administered for 24 weeks in subjects with mild Alzheimer's disease. The primary objective is to demonstrate significant improvement relative to placebo-treatment in episodic memory function, as assessed by the Hopkins Verbal Learning Test. Secondary endpoints include Clinical Dementia Rating scale (CDR), Wechsler Memory Scale (WMS), Mini- Mental-Status-Examination (MMSE) and Cerebrospinal fluid (CSF) biomarkers of AD disease activity and progression.	Total and Delayed Recall on the Hopkins Verbal Learning Test - Revised (HVLT-R), Combined change from baseline in z-scores of total and delayed recall on the Hopkins Verbal Learning Test - Revised (HVLT-R) in neflamapimod-treated subjects compared to placebo. The primary endpoint was analyzed using Mixed Model for Repeated Measures (MMRM) with fixed effects for treatment, background AD- specific therapy, CDR-Global Score of 0.5 versus 1.0, scheduled visit (nominal) and scheduled visit by treatment interaction, random effect for subject and baseline Z-score as a covariate.For baseline total and delayed recall, a z- score for each subject is defined by z=(x-m)/s where x is the subject's recall at baseline, and m and s are the overall mean and overall standard deviation of recall at baseline across all subjects. A composite baseline z-score for each subject is calculated using equal weighting in the following way: Z=0.5*z-score for total recall at baseline + 0.5*z- score for delayed recall at baseline. For HVLT-R, higher score indicates improvement., Baseline and 24 weeks
VX-745	2	Clinical Pharmacology of p38 MAP Kinase Inhibitor, VX- 745, in Mild Cognitive Impairment Due to Alzheimer's Disease (AD) or Mild AD	P38 MAPK inhibitor	NCT02423200	Completed/ yes	This study will assess the effects of VX-745 on markers of disease in the central nervous system of patients with MCI due to AD or with mild AD. The study will also evaluate the safety and tolerability of VX-745 in these patients during 6 weeks of dosing, as well as the plasma and cerebrospinal fluid concentrations of VX- 745 during dosing.	Percent Change From Baseline to End of Treatment in Cerebrospinal Fluid Levels of Cytokines, Cytokines: Of nine cytokines assessed, only CSF IL-8 quantifiable at all time points. And so, only IL-8 levels are being reported herein. The analysis was exploratory and no statistical analysis was performed., Baseline and Day 42 of dosing with VX-745

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Drug	Phase	Study title	Target	NCT	Study status/result	Study summary	Outcome measures
VX-745	2	A PET Study of the Effects of p38 MAP Kinase Inhibitor, VX- 745, on Amyloid Plaque Load in Alzheimer's Disease (AD)	P38 MAPK inhibitor	NCT02423122	Completed/ yes	This study will assess the effects of administration of VX-745 for 12 weeks on amyloid plaque burden in Alzheimer's disease (AD). Subjects who meet entry criteria will undergo 11C-PiB (Carbon-11-labeled Pittsburgh Compound B) positron emission tomography (PET) at baseline and after 45 days of dosing with VX-745. Cognitive testing will also be conducted at baseline and day 45.	Percent Change From Baseline in Amyloid Plaque Burden by 11C-PiB PET, Percent change in global cortical amyloid specific PET signal (BPND), Baseline compared to following 12 weeks' dosing with VX-745|Number of 11C-PiB Responders, Number of patients meeting protocol pre-specified definition of response: \> 7% reduction in global cortical BPND, Day 84
Exantide	2	A Pilot Clinical Trial of Exendin-4 in Alzheimer's Disease	P38 MAPK inhibitor	NCT01255163	terminated	Researchers were interested in studying the safety and comparing the effects of Exendin-4 with placebo on cognitive performance, clinical progression of dementia, various chemicals measured in blood and cerebrospinal fluid, and brain MRI, in individuals with early-stage Alzheimer's disease or MCI. Objectives were to determine the safety and tolerability of twice daily administration of Exendin-4, as well as to acquire preliminary evidence for effects on cognitive performance, clinical progression of dementia, various chemicals measured in blood and cerebrospinal fluid, and brain MRI, in individuals with early-stage Alzheimer's disease or mild cognitive impairment. * Eligible participants were divided into two groups (double-blind randomization). One group received Exendin-4 SC twice daily, and the other will received a placebo. Participants kept a medication diary and scheduled for additional study visits 1 and 2 weeks after the start of the treatment. Participants had regular followup visits with blood tests, cognitive tests, imaging studies, and other examinations 6, 12, and 18 months after the start of the treatment. Another lumbar puncture was performed optionally at the 18- month followup visit.	Number of Participants With Incidence of Nausea, Tolerability of exenatide (nausea is the most common expected adverse event of exenatide), 18 months

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Drug	Phase	Study title	Target	NCT	Study status/result	Study summary	Outcome measures
Minocycline	2	Minocycline in Patients With Alzheimer's Disease	P38 MAPK inhibitor	NCT01463384	completed	Cognitively normal individuals, patients with Mild Cognitive Impairment (MCI) or Alzheimer's Disease (AD) will undergo clinical screening, neuropsychological tests, blood and urine analyses, quantitative magnetic resonance imaging (MRI) and proton (1H) and carbon 13 (13C) magnetic resonance spectroscopy (MRS). Each individual will receive minocycline oral administration for 4 weeks initially, after which MRI, MRS and neuropsychological results will be recorded. If no adverse side effects occur, subjects will continue minocycline administration for an additional 5 months.	Values are reported below for Baseline, averaged for 1-3 months, and averaged for 4-6 months during minocycline administration., Baseline values, 1-3 Months Values (averaged), 4-6 Months Values (averaged)|Hippocampal Volumes Measured in three Groups: Alzheimer Disease (AD), Mild Cognitive Impairment (MCI) and Normal, Age- matched Controls (NC)., Using magnetic resonance images acquired, hippocampal volume was measured monthly for 6 months. Biomarkers NAA/mI Measured in Three Groups: Alzheimer Disease (AD), Mild Cognitive Impairment (MCI) and Normal, Age-matched Controls (NC).two biomarkers, N acetylaspartate (NAA, a neuronal marker) and myo-inositol (mI, a glial marker) were quantified and then used to calculate NAA/mI (an index currently widely used for AD and MCI diagnosis). Scale of MRS biomarkers for aged- matched controls: NAA = 1.43, mI = 0.60, NAA/mI = 2.38. Any value lower than NAA/mI of 2.38 are considered not normal.
MW150	2	MW150 Stress Kinase Inhibitor in Mild to Moderate Alzheimer's Disease	P38 MAPK inhibitor	NCT05194163	Not yet recruiting	This study is a phase 2a randomized double-blind, placebo-controlled, study, in mild-to-moderate Alzheimer's disease, of the oral investigational drug MW150, a p38alphaMAPK kinase inhibitor. The primary goals of this study are to investigate the safety and tolerability, and drug movements in the body. The secondary goals of the study are to investigate the effects of the drug on cognitive performance, activities of daily living, and behavior, and the biological effects of the drug on blood biomarkers.	Drug Safety- Blood tests, Number of participants with treatment-related adverse events as assessed by laboratory test abnormalities., 84 days treatment|Drug Safety- Electrocardiographic, Number of participants with emergent abnormal electrocardiograms., 84 days treatment|Drug Safety- C-SSRS, Development of any suicidality on COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) score (minimum 0, no maximum, higher number worse)., 84 days treatment|Drug Tolerability- Adverse events, Incidence of adverse events (AE)., 84 days treatment.
Mastinib	3	Masitinib in Patients With Mild to Moderate Alzheimer's Disease	TKI	NCT05564169	Not yet recruiting/N o	Masitinib is an orally administered tyrosine kinase inhibitor that targets activated cells of the neuroimmune system (mast cells and microglia). Study AB21004 will evaluate masitinib as an adjunct to cholinesterase inhibitor and/or memantine in patients with mild-to-moderate Alzheimer's disease.	Absolute change from baseline in ADAS-Cog-11 score, Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog) (scores range from 0 to 70, with higher scores indicating worse dementia), 24 weeks|Absolute change from baseline in ADCS-ADL score, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory scale (ADCS-ADL) (scores from 0 to 78, with lower scores indicating worse function), 24 weeks

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Drug	Phase	Study title	Target	NCT	Study status/result	Study summary	Outcome measures
Nilotinib	3	Evaluating the Efficacy and Safety of Nilotinib BE in Subjects With Early Alzheimer's Disease	TKI	NCT05143528	Not yet recruiting/N o	This study will investigate the safety and efficacy of a Tyrosine Kinase Inhibitor (TKI) called Nilotinib BE (bioequivalent) in individuals with Early Alzheimer's disease (EAD). This is a multi-center double blinded, Phase 3 study, that will enroll patients for three years in approximately 50 centers nationwide. The total duration of the study will be for five years.	Changes From Baseline in Clinical Dementia Rating Scale - Sum of Boxes (CDR-SB) Score at Week 72 [Time Frame: Baseline, Week 72], CDR-SB integrates assessments from 3 domains of cognition (memory, orientation, judgment/problem-solving) and 3 domains of function (community affairs, home/hobbies, personal care). Following a systematic patient examination, the rater assigns a score describing the participant's current performance level in each of these domains of life functioning. Prespecified severity anchors range from none = 0, questionable = 0.5, mild = 1, moderate = 2 to severe = 3 (the personal care domain omits the 0.5 score). "Sum of boxes" scoring methodology sums the score for each of the 6 domains and provides a value ranging from 0 to 18 that can change in increments of 0.5 or greater. Higher scores indicate greater disease severity. A positive change from baseline indicates clinical decline., 72 weeks
Bumetanide	2	Bumetanide in Patients With Alzheimer's Disease		NCT06052163	Not yet recruiting/No	Bumetanide is a potent diuretic administered orally and is FDA approved for the treatment of edema and hypertension. Repurposing bumetanide as a medication for AD has been proposed based on data that demonstrated its ability to "flip" the APOE genotype-dependent transcriptomic signatures in AD mouse and cell culture models. Critically, this discovery was subsequently explored in Electronic Health Record cohorts, which revealed that among individuals over the age of 65, bumetanide exposure was significantly associated with a lower prevalence of AD in three independent datasets.	Incidence of Treatment-Related Adverse Events, Number of participants with adverse events including clinical signs and symptoms, change in vital signs, ECGs, laboratory safety tests, and suicidality assessments., 6 months

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Redefining New Strategies for Managing AD

Several drugs like gantenerumab, solanezumab, and aducanumab have been explored in AD patients for either inhibiting Aβ production (e.g., β- and γ-secretase inhibitors), enhancing Aβ clearance, or neutralizing it with humanized monoclonal antibodies however these interventions could only modify the AD symptoms only minimally and transiently with less stable outcomes of these interventions have not been encouraging as shown in Table 1. To circumvent challenges in designing prevention trials for late-onset sporadic AD, the innovative DIAN-TU (Dominantly Inherited Alzheimer Network Trials Unit) was initiated. DIAN-TU, a phase 2/3 trial, focused on primary prevention for the autosomal dominant form of AD, which has a known link to Aβ dysfunction and early cognitive decline[29]. Regrettably, a preliminary analysis of the trial revealed that both investigational anti-amyloid drugs, Roche's gantenerumab and Lilly's solanezumab, did not meet the primary endpoint criteria (DIAN-Multivariate Cognitive Endpoint)[30]. In October 2019, phase 3 study was conducted using aducanumab's which also could not offer clinical advantage and could not modify the diseases severity[31]. The negative outcomes with the above biological agents lead to the beginning of newer approaches targeting intracellular signaling components (e.g. MAPK) in AD and related neurodegenerative dementias. Due to stringent involvement of MAPK in AD pathogenesis, p38 specific inhibitors were employed in ameliorating the AD pathology. Some of MAPK inhibitors have been used in interventional studies while some of them are not used in clinical trials yet but have been tested both in vivo / vitro. .

p38 inhibitors

Neflamapimod

Vertex Pharmaceuticals originally developed neflamapimod for rheumatoid arthritis, progressing to phase 2a. Later EIP Pharma acquired rights in 2014, using it against CNS disorders. Neflamapimod (formerly known as VX-745) is a potent ATP competitive inhibitor of p38α kinase, showing strong inhibition of p38α *in vitro* with an IC50 of 9nM in bringing down beta amyloid / tau-induced toxicity and neuro-inflammation. This is currently under phase 2b trial for abolishing synaptic dysfunction. Neflamapimod targets neuronal mechanisms, addressing synaptic dysfunction, a key factor in early Alzheimer's disease. Phase 2a study results showed memory improvement prompting a planned 2b study[32]. Another compelling study showed that selective inhibition of p38α with neflamapimod improved episodic memory and inhibited the turnover of amyloid turnover viz –a viz autophagy in repaired neuronal cells[33]. A 6-month placebo-controlled study has recently been initiated to confirm these preliminary clinical findings which targeted Neflamapimod targets like ABL1, ABL2, p38β, PDGFRβ, and SRC[34].

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SB203580

SB203580 is a traditional p38α/β MAPK inhibitor and had shown therapeutic effects in mouse model of AD as well as the LPS-induced depression model[35]. SB203580 inhibits p38 catalytic activity by binding to the ATP binding pocket[36]. Administration of SB203580 in animals with AD significantly reversed the altered phosphorylation levels of p38 in the habenula, neuro-inflammation induced depressive-like behaviors, which were accompanied by increased levels of TNF-α and p-p38 in the habenula[37]. The p38 inhibitor SB203580 reduced the level of TNF-α and up-regulated the levels IL-10 in the habenula[37]

MW150-

MW-150, also showed therapeutic effects in the AD mouse model. Although, intervention of AD mice with MW150 attenuated the increased levels of IL-1β and TNFα, yet it increased the IBA1+ microglia within amyloid plaques, without significantly affecting overall microglia or plaque volume[38]. MW150 is capable of reducing neuro-inflammatory responses while dispensing physiological functions of microglia. These results potentially indicated the therapeutic impact of inhibiting microglia specific p38MAPK in modulating disease biology of AD[38]. Additional research indicates that MW150 can selectively block the stress-activated p38α MAPK, thereby attenuating the entorhinal cortex dysfunctions linked to neuro-inflammation during the early stages of Alzheimer's disease progression[39].

NJK14047-

NJK14047 as a selective p38α/β MAPK inhibitor reduces the level of phospho-p38 MAPKs in the brain and attenuates spatial memory loss in 9-month-old 5XFAD mice[40]. In a study, with NJK14047; a novel and selective p38 inhibitor, it was shown for the first time that it suppressed activation and reduced the secretion of pro-inflammatory cytokines in LPS stimulated microglia such as TNF-α, IL-1β and IL-6 through the inhibition of p38 MAPK activation in BV2 microglia in mouse model[41]. It reduced the expression of iNOS and COX-2 proteins which are the marker of M1 effector microglia which are involved in pathogenic neuro- inflammation[41].

Exantide

This molecule alleviated mitochondrial dysfunction and cognitive impairment in the 5XFAD mouse model of Alzheimer's disease. In conclusion, it was shown that exenatide treatment improved cognitive impairment, reduced Aβ1-42 deposition, and alleviated synaptic degradation in 5XFAD mice suggesting that exenatide may be a promising new therapeutic candidate for AD[42].

Minocycline

Minocycline is a semisynthetic tetracycline derivative that inhibits the p38 mitogen-activated protein kinase (MAPK) pathway. One animal study shows that intrathecal administration with minocycline not only attenuates morphine anti-nociceptive tolerance, but also activation of spinal microglia / astrocyte induced by chronic morphine treatment[43].

Limitations/Bottlenecks

In spite of available MAPK inhibitors which we have discussed above, only a few have been studied in clinical trials (Table 3) with heterogeneous outcome as disease modifying potential. The ability of these inhibitors to cross impermeable BBB is one of the main constraints for many inhibitors which are currently in clinical trials. This is not limited to protein kinase inhibitor drugs, however, as it is estimated that >95% of approved drugs lack sufficient brain tissue exposure. CNS exposure limitation is most often linked to the molecular properties of the small molecule drugs and this barrier can be addressed through medicinal chemistry refinement[44]. Therefore designing / screening BBB permeable inhibitors is paramount requirement for enhancing the efficacy of MAPK for AD. The p38

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MAPK pathway contributes to neuro-inflammation mediated by microglia and astrocytes. p38α appears to be the main isoform involved in the inflammatory response. p38MAPK mediated pro-inflammatory programming of CNS contribute to the development of AD. p38α and p38β, expressed in the brain, are often activated in animal models of neurodegeneration, leading to altered physiological properties, activation of responsive genes and neurotoxicity.

Conclusions

Taken together, these observations are consistent with the hypothesis that specific p38 MAPK isoforms have a role in the pathogenesis of neurodegenerative diseases, potentially making them attractive therapeutic targets. Although proof of principle experiments in preclinical models have shown that inhibitors of p38MAPK can have neuroprotective effects, an evaluation of inhibitors that are able to bypass the blood–brain barrier is needed to evaluate this in human clinical trials. Combinatorial therapy must be taken into consideration where a cocktail of P38 inhibitors should be formulated to see the synergistic effects on neuro-inflammation. More target engagement biomarkers, better clinical measures, and new approaches to assessment, such as computerized tests and digital biomarkers, may improve the ability to characterize drug-placebo differences and advance novel therapies for AD.

Abbreviation

MAPK	Mitogen Activated Protein Kinase
ERK	Extracellular Signal-Regulated Kinase
TNFα	Tumor Necrosis Factor Alpha
TNFR	Tumor Necrosis Factor Receptor
IL1	Interleukin-1
IL1R	Interleukin-1 Receptor
TGFβ	Transforming Growth Factor-Beta
TGFβR	Transforming Growth Factor-Beta Receptor
TRADD	TNFR1-Associated Death Domain Protein
MYD88	Myeloid Differentiation Factor 88
DAXX	Death Domain Associated Protein
TRAF	TNF Receptor-Associated Factor
ASK1	Apoptosis Signal-Regulating Kinase 1
IRAK	Interleukin-1 Receptor-Associated Kinase
MKK	Mitogen Activated Protein Kinase Kinase
TAB	Transforming Growth Factor Beta-Activated Kinase 1-Binding Protein
CDC25B	Cell Division Cycle 25B
ATF	Activating Transcription Factor
ELK	ETS Like-1 Protein
SAPLA	Regulatory Subunit of Serine/Threonine-Protein Phosphotase 6
GADD	Growth Arrest and DNA Damage-Inducible Protein
MAX	MYC Associated Factor X
MEF2C	Myocyte-Specific Enhancer Factor 2C
TLR	Toll-Like Receptors
RAGE	Receptor for Advanced Glycation Endproducts
NF-KB	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells

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XIAP	X-Linked inhibitor of Apoptosis Protein
ASC	Apoptosis-Associated Speck-Like Protein
NLRP1/3	NLR Family Pyrin Domain Containing 1/3
5XFAD	Familiar Alzheimer Disease Mice Bear 5 AD-Linked Mutation

References

1. Cano, M., Guerrero-Castilla, A., Nabavi, S. M., Ayala, A. & Argüelles, S. Targeting pro-senescence mitogen activated protein kinase (Mapk) enzymes with bioactive natural compounds. *Food and Chemical Toxicology* **131**, 110544 (2019).
2. Islam, S., Wang, S., Bowden, N., Martin, J. & Head, R. Repurposing existing therapeutics, its importance in oncology drug development: Kinases as a potential target. *British Journal of Clinical Pharmacology* **88**, 64-74 (2022).
3. Kannaiyan, R. & Mahadevan, D. A comprehensive review of protein kinase inhibitors for cancer therapy. *Expert review of anticancer therapy* **18**, 1249-1270 (2018).
4. Ahmed, T. *et al.* Map kinase signaling as therapeutic target for neurodegeneration. *Pharmacological research* **160**, 105090 (2020).
5. Oxford, A. E., Stewart, E. S. & Rohn, T. T. Clinical trials in Alzheimer's disease: a hurdle in the path of remedy. *International Journal of Alzheimer's Disease* **2020** (2020).
6. Son, S. H. *et al.* Chemical Knockdown of Phosphorylated p38 Mitogen-Activated Protein Kinase (MAPK) as a Novel Approach for the Treatment of Alzheimer's Disease. *ACS Central Science* **9**, 417-426, doi:10.1021/acscentsci.2c01369 (2023).
7. Falcicchia, C., Tozzi, F., Arancio, O., Watterson, D. M. & Origlia, N. Involvement of p38 MAPK in synaptic function and dysfunction. *International journal of molecular sciences* **21**, 5624 (2020).
8. Eskandari, S. *et al.* Targeting common signaling pathways for the treatment of stroke and Alzheimer's: A comprehensive review. *Neurotoxicity research* **39**, 1589-1612 (2021).
9. Goel, P. *et al.* Neuronal cell death mechanisms in Alzheimer's disease: An insight. *Front Mol Neurosci* **15**, 937133, doi:10.3389/fnmol.2022.937133 (2022).
10. Takahashi, R. H., Nagao, T. & Gouras, G. K. Plaque formation and the intraneuronal accumulation of β-amyloid in Alzheimer's disease. *Pathology international* **67**, 185-193 (2017).
11. Kril, J. J., Patel, S., Harding, A. J. & Halliday, G. M. Neuron loss from the hippocampus of Alzheimer's disease exceeds extracellular neurofibrillary tangle formation. *Acta neuropathologica* **103**, 370-376 (2002).
12. Finger, C. E., Moreno-Gonzalez, I., Gutierrez, A., Moruno-Manchon, J. F. & McCullough, L. D. Age-related immune alterations and cerebrovascular inflammation. *Molecular Psychiatry* **27**, 803-818, doi:10.1038/s41380-021-01361-1 (2022).
13. Long, H.-Z. *et al.* The role of microglia in Alzheimer's disease from the perspective of immune inflammation and iron metabolism. *Frontiers in Aging Neuroscience* **14**, 888989 (2022).
14. Plastira, I. *et al.* MAPK signaling determines lysophosphatidic acid (LPA)-induced inflammation in microglia. *Journal of Neuroinflammation* **17**, 1-17 (2020).
15. Cummings, J. *et al.* Alzheimer's disease drug development pipeline: 2023. *Alzheimer's & Dementia: Translational Research & Clinical Interventions* **9**, e12385 (2023).
16. Kim, E. K. & Choi, E.-J. Pathological roles of MAPK signaling pathways in human diseases. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* **1802**, 396-405, doi:https://doi.org/10.1016/j.bbadis.2009.12.009 (2010).
17. Fagiani, F., Lanni, C., Racchi, M. & Govoni, S. Targeting dementias through cancer kinases inhibition. *Alzheimer's & Dementia: Translational Research & Clinical Interventions* **6**, e12044 (2020).
18. Bachstetter, A. D. & Van Eldik, L. J. The p38 MAP Kinase Family as Regulators of Proinflammatory Cytokine Production in Degenerative Diseases of the CNS. *Aging Dis* **1**, 199-211 (2010).
19. Germann, U. A. & Alam, J. J. P38α MAPK Signaling—A Robust Therapeutic Target for Rab5-Mediated Neurodegenerative Disease. *International Journal of Molecular Sciences* **21**, 5485 (2020).
20. Origlia, N. *et al.* Microglial receptor for advanced glycation end product-dependent signal pathway drives beta-amyloid-induced synaptic depression and long-term depression impairment in entorhinal cortex. *J Neurosci* **30**, 11414-11425, doi:10.1523/jneurosci.2127-10.2010 (2010).
21. Choudhury, G. R. *et al.* Involvement of p38 MAPK in reactive astrogliosis induced by ischemic stroke. *Brain research* **1551**, 45-58 (2014).

22. Chi, N.-F., Chien, L.-N., Ku, H.-L., Hu, C.-J. & Chiou, H.-Y. Alzheimer disease and risk of stroke: a population-based cohort study. *Neurology* **80**, 705-711 (2013).
23. Fann, D. Y.-W. *et al.* Evidence that NF-κB and MAPK signaling promotes NLRP inflammasome activation in neurons following ischemic stroke. *Molecular neurobiology* **55**, 1082-1096 (2018).
24. Colié, S. *et al.* Neuronal p38α mediates synaptic and cognitive dysfunction in an Alzheimer's mouse model by controlling β-amyloid production. *Scientific Reports* **7**, 45306, doi:10.1038/srep45306 (2017).
25. Scheltens, P. *et al.* An exploratory clinical study of p38α kinase inhibition in Alzheimer's disease. *Annals of clinical and translational neurology* **5**, 464-473 (2018).
26. Lawson, S. K., Dobrikova, E. Y., Shveygert, M. & Gromeier, M. p38α mitogen-activated protein kinase depletion and repression of signal transduction to translation machinery by miR-124 and-128 in neurons. *Molecular and cellular biology* **33**, 127-135 (2013).
27. Li, W. *et al.* Phosphorylation of LAMP2A by p38 MAPK couples ER stress to chaperone-mediated autophagy. *Nature communications* **8**, 1763 (2017).
28. Shah, S. Z. A., Zhao, D., Hussain, T. & Yang, L. The role of unfolded protein response and mitogen-activated protein kinase signaling in neurodegenerative diseases with special focus on prion diseases. *Frontiers in aging neuroscience* **9**, 120 (2017).
29. Moulder, K. L. *et al.* Dominantly Inherited Alzheimer Network: facilitating research and clinical trials. *Alzheimer's research & therapy* **5**, 1-7 (2013).
30. Joseph-Mathurin, N. *et al.* Amyloid-Related Imaging Abnormalities in the DIAN-TU-001 Trial of Gantenerumab and Solanezumab: Lessons from a Trial in Dominantly Inherited Alzheimer Disease. *Annals of neurology* **92**, 729-744 (2022).
31. Budd Haeberlein, S. *et al.* Two randomized phase 3 studies of aducanumab in early Alzheimer's disease. *The journal of prevention of Alzheimer's disease* **9**, 197-210 (2022).
32. Alam, J., Blackburn, K. & Patrick, D. Neflamapimod: clinical phase 2b-ready oral small molecule inhibitor of p38alpha to reverse synaptic dysfunction in early Alzheimer's disease. *J. Prev. Alzheimers Dis* **4**, 273-278 (2017).
33. Scheltens, P. *et al.* An exploratory clinical study of p38α kinase inhibition in Alzheimer's disease. *Ann Clin Transl Neurol* **5**, 464-473, doi:10.1002/acn3.549 (2018).
34. Falcicchia, C., Tozzi, F., Arancio, O., Watterson, D. M. & Origlia, N. Involvement of p38 MAPK in Synaptic Function and Dysfunction. *Int J Mol Sci* **21**, doi:10.3390/ijms21165624 (2020).
35. Zhao, Y.-w., Pan, Y.-q., Tang, M.-m. & Lin, W.-j. Blocking p38 signaling reduces the activation of pro-inflammatory cytokines and the phosphorylation of p38 in the habenula and reverses depressive-like behaviors induced by neuroinflammation. *Frontiers in pharmacology* **9**, 511 (2018).
36. Cuenda, A. *et al.* SB 203580 is a specific inhibitor of a MAP kinase homologue which is stimulated by cellular stresses and interleukin-1. *FEBS letters* **364**, 229-233 (1995).
37. Zhao, Y. W., Pan, Y. Q., Tang, M. M. & Lin, W. J. Blocking p38 Signaling Reduces the Activation of Pro-inflammatory Cytokines and the Phosphorylation of p38 in the Habenula and Reverses Depressive-Like Behaviors Induced by Neuroinflammation. *Front Pharmacol* **9**, 511, doi:10.3389/fphar.2018.00511 (2018).
38. Zhou, Z. *et al.* Retention of normal glia function by an isoform-selective protein kinase inhibitor drug candidate that modulates cytokine production and cognitive outcomes. *J Neuroinflammation* **14**, 75, doi:10.1186/s12974-017-0845-2 (2017).
39. Rutigliano, G., Stazi, M., Arancio, O., Watterson, D. M. & Origlia, N. An isoform-selective p38α mitogen-activated protein kinase inhibitor rescues early entorhinal cortex dysfunctions in a mouse model of Alzheimer's disease. *Neurobiol Aging* **70**, 86-91, doi:10.1016/j.neurobiolaging.2018.06.006 (2018).
40. Gee, M. S. *et al.* A selective p38α/β MAPK inhibitor alleviates neuropathology and cognitive impairment, and modulates microglia function in 5XFAD mouse. *Alzheimers Res Ther* **12**, 45, doi:10.1186/s13195-020-00617-2 (2020).
41. Gee, M. S. *et al.* A novel and selective p38 mitogen-activated protein kinase inhibitor attenuates LPS-induced neuroinflammation in BV2 microglia and a mouse model. *Neurochemical research* **43**, 2362-2371 (2018).
42. An, J. *et al.* Exenatide alleviates mitochondrial dysfunction and cognitive impairment in the 5× FAD mouse model of Alzheimer's disease. *Behavioural brain research* **370**, 111932 (2019).
43. Cui, Y. *et al.* A novel role of minocycline: attenuating morphine antinociceptive tolerance by inhibition of p38 MAPK in the activated spinal microglia. *Brain, behavior, and immunity* **22**, 114-123 (2008).
44. Chico, L. K., Van Eldik, L. J. & Watterson, D. M. Targeting protein kinases in central nervous system disorders. *Nature reviews Drug discovery* **8**, 892-909 (2009).
45. Ohyagi, Y. *et al.* Intracellular Aβ42 activates p53 promoter: a pathway to neurodegeneration in Alzheimer's disease. *The FASEB Journal* **19**, 1-29 (2005).

 doi:10.20944/preprints202312.1509.v1

46. De la Monte, S., Sohn, Y. K., Ganju, N. & Wands, J. R. P53-and CD95-associated apoptosis in neurodegenerative diseases. *Laboratory investigation; a journal of technical methods and pathology* **78**, 401-411 (1998).
47. Cenini, G., Sultana, R., Memo, M. & Butterfield, D. A. Elevated levels of pro-apoptotic p53 and its oxidative modification by the lipid peroxidation product, HNE, in brain from subjects with amnestic mild cognitive impairment and Alzheimer's disease. *Journal of cellular and molecular medicine* **12**, 987-994 (2008).