ISSN: 0974-5823 Vol. 6 No. 3 October-December, 2021

International Journal of Mechanical Engineering

RAGE as a Potential Therapeutic Target for Alzheimer's disease

Palaniswamy Rani*
Department of Biotechnology, PSG College of Technology, Coimbatore, Tamilnadu 641004, India

Balasubramanian Ayshwariya
Department of Biotechnology, PSG College of Technology, Coimbatore, Tamilnadu 641004, India

Saravanakumar Vinodh
Department of Biotechnology, PSG College of Technology, Coimbatore, Tamilnadu 641004, India

Dr. P Rani (Corresponding author)
Professor, Department of Biotechnology, PSG College of Technology, Avinashi Rd, Peelamedu, Coimbatore, Tamil Nadu, 641004, India.

Abstract:
Alzheimer's disease (AD) is a chronic neurodegenerative disease which accounts for 60–70% cases of dementia. Worldwide, around 50 million people are affected by dementia and every year nearly 10 million new cases are being reported. Major cause of AD is abnormal accumulation of amyloid beta in the brain cells which in turn forms neurofibrillary tangles that leads to failure of synaptic transmission and neuronal degeneration. Deposition of amyloid beta is governed by various factors in which Receptor for advanced glycation end products (RAGE) plays a critical role in pathogenesis of AD. RAGE is a key pattern recognition receptor of the innate immune response and mediates diverse physiological and pathological effects through cellular signaling pathways leading to inflammatory reactions. In this context, the potential role of RAGE in cognitive impairment and as therapeutic target for AD is an interesting topic to review. In this essence, the contents emphasis on RAGE and its isoforms in human, pattern recognition of RAGE for diverse ligands, role of RAGE in AD through RAGE and amyloid beta interaction, involvement of RAGE activated signaling pathways in neuro-inflammation, role of sRAGE in Amyloid beta clearance, sRAGE as therapeutics for AD and development of RAGE inhibitors. This chapter overviews RAGE as potential therapeutic targets for Alzheimer's disease.

Keywords: Dementia, Alzheimer's disease,Cognitive mpairment,RAGE,Amyloid Beta, Neurodegeneration, Drug development

INTRODUCTION

Dementia is a root for progressive cognitive decline and is caused by various disease conditions such as Alzheimer's disease (AD), Huntington's disease and multiple sclerosis etc. Dementia patients are facing vulnerable conditions in terms of physical and mental health which presents a serious challenge to the healthcare systems and requires early diagnosis and therapy. The incidence of dementia is mostly observed in aging populations over 65 years old. Alzheimer's disease is the most common cause for AD (50-75%). The pattern of symptoms and biomarkers helps to identify Alzheimer's disease. AD generates short-term memory decline, manifestation and repetitive questioning state in patients. Dementia affects essential functions which are memory function, executive ability, language ability, visuospatial ability, and personality and behavior conditions. The association of dementia with pathophysiological conditions observed in normal aging complicates the early identification and leads to overt cognitive decline which give rise to functional impairment. The biomarkers accustomed to AD are extracellular accumulated amyloid beta and intracellular tangles of hyperphosphorylated tau and affect synaptic function that leads to neuronal signal loss. Hippocampal atrophy in the medial temporal lobe also causes early symptoms in AD. The Receptor for Advanced Glycation Endproducts (RAGE) is a multi-ligand pattern recognition receptor that plays an important role in AD pathology. During aging oxidative stress increases in brain cells which lead to the formation of AGEs (Advanced glycation end-products) around the brain cells. This AGE in turn activates

RAGE which leads to influx of Aβ from the blood to brain and causes subsequent inflammatory reactions. Amyloid peptides also bind to RAGE which is further eliciting an inflammatory response through the NF-κB (Nuclear factor kappa B) pathways. Therefore,RAGE plays a major role in AD pathology [1,2,3].

FUNCTIONAL SIGNIFICANCE OF RAGE IN ADD

RAGE is a multi-ligand receptor which belongs to the Immunoglobulin superfamily having a molecular weight of 35kDa and RAGE gene is located in chromosome 6. The full-length RAGE consists of V domain with 23-116 amino acid residues, C1 domain with 124-221 amino acid residues, C2 domain with 227-317 amino acid residues, transmembrane region with 343-363 amino acid residues and the cytoplasmic tail domain with 363-404 amino acid residues [4,5,6,7]. The V and C2 domains are composed of 8 strands linked through 6 loops forming 2 β sheets attached by disulfide bonds respectively whereas the C2 domain folds as C-type immunoglobulin domain. The transmembrane domain contains the "GxxxG" motif which is essential for homodimerization of receptor and signal transduction [8,9]. The cytoplasmic tail has 3 units such as membrane proximal domain (17 amino acids), central domain (17 amino acids) and unstructured C terminus [10]. These structural units are essential for mediating the interaction between RAGE and effector molecules. RAGE binds with a diverse range of ligands relevant to distinct pathological conditions such AD, cardiovascular disease and cancer. Binding of RAGE ligands mediates cellular signal transduction pathways namely MAPK (mitogen-activated protein kinase), NF-κB etc. RAGE expression is exhibited in various locations such as cerebral endothelial cells, astrocytes, neurons of the hippocampus, entorhinal cortex, and superior frontal gyrus. The escalation level of RAGE at the Blood Brain Barrier (BBB) leads to influx of Aβ into the brain. At the same time, in neurons it increases the activity of the Aβ producing β-secretase enzyme (BACE1), which in turn induces Aβ accumulation, tau hyperphosphorylation and neuroinflammation. Accumulation of $A\beta_{1-40}$ and $A\beta_{1-42}$ resulting in RAGE-mediated apoptosis in neurons [11,12,13].
Multiple isoforms of RAGE generated as a result of alternative splice variants of RAGE gene and proteolytic cleavage of f-RAGE. These isoforms exhibit responsibility for a variety of pathophysiological processes depending on the interaction of ligands. Eventually, all the isoforms exhibit similar affinity towards RAGE ligands. In order to understand the RAGE mediated signaling pathways, it is essential to understand the interaction and function of isoforms. Majorly, three isoforms of RAGE represented as a key player in mediating signaling pathways which are full-length RAGE (fRAGE), soluble RAGE (sRAGE) and Dominant Negative RAGE (DNRAGE). Aside from these three predominant types of RAGE, other forms of RAGE are also reported in the human brain which is RAGEB (intracellular modified RAGE), sRAGEB (C domain modified sRAGE), DNRAGEB (C domain modified DNRAGE) and NRAGE (N truncated RAGE). Elucidating the role of these isoforms helps to understand the functional perspective of signaling pathways in neuronal disorders (figure 1) [2,14,15,16].

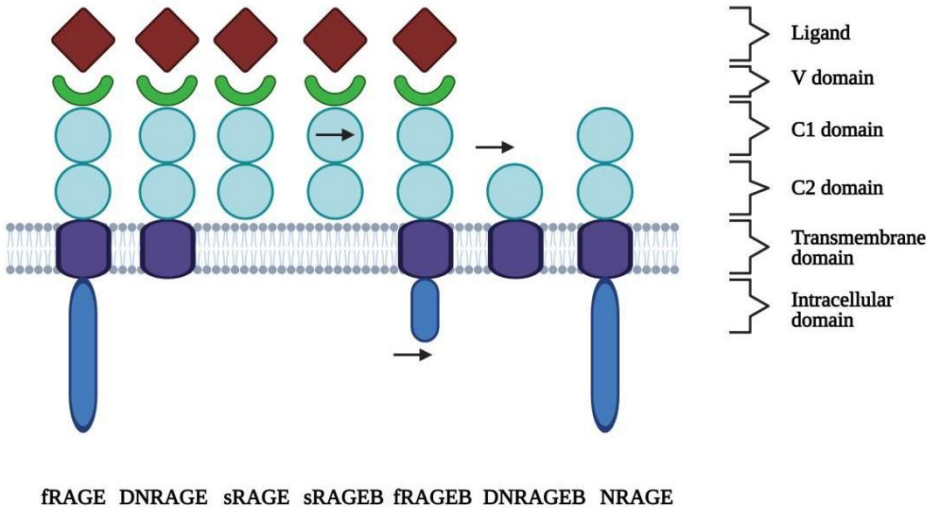


Figure 1: Structure and Isoforms of RAGE. Arrow mark indicates modifications in the domain (Created with BioRender.com)

Full-length RAGE (fRAGE)

Full-length RAGE is a direct mediator of pathophysiological pathways such as chemotaxis, apoptosis, proliferation and

inflammation. fRGAE consists of V domain, C1 and C2 domain, transmembrane domain followed by intracellular cytoplasmic tail domain. The intracellular cytoplasmic domain is essential for activating various signaling pathways such as NF-κB, MAPK etc [17,18,19,20]. Presence of fRAGE induces more accelerated and sustained signaling pathways than the other forms of RAGE. Since, DNRAGE and sRAGE are involved in decaying the binding of ligands towards fRAGE presumably involved in suppressing the effect of fRAGE mediating signaling. Therefore, sRAGE and DNRAGE gained an important role in study of inhibitors in various chronic neuronal diseases. Additionally, interaction of ligands with RAGE generates reactive oxidative species (ROS) which regulate the intracellular signaling pathways [21,22]. RAGE-ligand interactions had shown cell specific effects. Therefore, the signal transduction pathway activation is solely dependent on the specific cell type.

Soluble RAGE (sRAGE)

sRAGE consists of V domain, C1 and C2 domain similar to fRAGE but lacks transmembrane and cytoplasmic tail domain leading to release of sRAGE into the extracellular space. And also, there is a subtype of sRAGE that exists which are esRAGE and cRAGE. The sRAGE is generated from the pre-mRNA by alternative splicing is known as endogenous secretory RAGE (esRAGE) and the one which formed from the cleavage of extracellular domain of RAGE is known as cleaved RAGE (cRAGE) [2,14]. The sRAGE is a key player in decaying fRAGE mediated signaling pathways because sRAGE binds to the RAGE ligands prior to the fRAGE [1,23]. When sRAGE binds with early monomeric or soluble ligands, it further prevents the formation of insoluble complexes. Therefore, sRAGE amends the formation of insoluble aggregates of ligands and thereby prevents the efficacious activation of fRAGE signaling pathway [2,24,25,26].

Dominant Negative RAGE (DNRAGE)

DNRAGE has a similar V type and C type domain as fRAGE but lacks an intracellular cytoplasmic tail domain. DNRAGE competes with fRAGE for binding with ligands to block the fRAGE mediating signal transduction due to lack of intracellular cytoplasmic tail domain. DNRAGE interaction with ligands prevents the initial binding of fRAGE with ligands. At the same time, accumulation of ligands on the surface of the cells further activates influx of more ligands which in turn causes aggregation of ligands and oxidative stress that promotes fRAGE activation [25,27].

Structural feature of RAGE for diverse ligands

RAGE interacted with a diverse variety of ligands with different size and symmetry. The rationale behind the multi-ligand recognition property of RAGE elucidated by negatively charged VC1 domain and ligand-driven multimodal dimerization [4,5]. Since RAGE interacted with acidic ligands and oligomerization had provided high stability between RAGE and ligand interaction. The basic (positive charge) nature of the V domain is provided by the presence of highly conserved Arginine and Lysine residues. At the same time, the C2 domain composed of large negative charge mediates the efficient binding of ligands on VC1 domain by repelling the negatively charged ligands towards VC1 domain. Therefore, the conserved basic cavity exhibited by the RAGE receptor is essential for recognizing multi diverse ligands [4,5,8,35].

ROLE OF RAGE LIGANDS IN AD

Studies have been reported that RAGE is a multi-ligand receptor which binds with variety of ligands mainly advanced glycation end products (AGE), Aβ, HMGB1 (High mobility group box), S100 proteins (S100A12, S100B, S100A7, S100A8/A9 complex), Mac-1 (Macrophage-1 antigen) and Phosphatidylserine [28,29,30].

AGE are the forms of modified proteins that are subjected to glycation and progressively involved in various modifications that in turn result in formation of insoluble cross links. Various types of AGE is reported such as Carboxymethyl-lysine (CML), Carboxyethyl-lysine (CEL), Pentosidine, glyoxal-lysine dimer (GOLD) and methylglyoxal-lysine dimer (MOLD). The rate of formation of AGE is altered by various environmental factors. Accumulation of AGE in intracellular and extracellular space recruits various neuronal related disorders. During aging, oxidative stress is elevated in brain cells which lead to the formation of AGE. This AGE in turn activates RAGE which mediates influx of Aβ from the blood to the brain and causes subsequent inflammatory reactions. RAGE-Aβ interactions induce NF-κB inflammatory response through signaling pathways [31,32,33,34].

AGEs are mostly located in pyramidal neurons. It is evident that AGEs concentration had increased in pyramidal neurons of the AD patients. As AD progress, the elevated level of AGE positive neurons leads to hyperphosphorylation of tau protein which finally causes neurofibrillary tangles (NFTs) and senile plaques [38,39]. AGEs-RAGE interaction leads to dephosphorylation of the Nuclear factor activated T-cells (NFAT-1) elevated a BACE1 expression. NFAT-1 is a crucial controller of BACE1 expression which in turn regulates the APP processing [40,41].Regulation of detoxifying mechanisms such as Glyoxalase 1 (GLO1) detoxifying pre-AGEs methylglyoxal (MG) is prominent activity to mitigate the AD pathogenesis. But essential enzyme cofactor glutathione depletion in AD patients down regulates the GLO1-AGE detoxifying system, thus mediating the elevated production AGEs [42,43,44,45].

RAGE AND AMYLOID PATHOLOGY

Amyloid Beta (Aβ) is a crucial player in mediating pathogenesis of AD. Aβ is toxic to neuronal cells which has the ability to generate reactive oxygen species and causes accumulation of lipid peroxides and hydrogen peroxides. It is a potent inducer of the transcription factor NF-κB in primary neurons and astrocytes. Chemotactic nature of Aβ causes migration of microglia which leads to an increased accumulation of microglial cells surrounding the amyloid plaques. Both the monomeric and complex forms of Aβ interact

with fRAGE. Finally, Aβ interaction potentiates the secretion of the cytokines Interleukin (IL)-6, IL-8 and IL-1b-activated human astrocytoma cells and leads to neuronal damage [4,5,32].

Failure in the RAGE receptor function tends to imbalance the production and clearance of Aβ peptides inside the brain. RAGE is a key player in generating neurotoxicity. RAGE interaction with Aβ oligomers activates proinflammatory responses, ROS activation which causes amyloid pathological change followed by neuronal cell death (figure 2) [36,37].

RAGE is a critical player in AD as follows; i) RAGE increase the formation of Aβ and neurofibrillary tubes (tau hyperphosphorylation). ii) Activates microglia and astrocytes into inflammatory states which tend to develop cellular stress. iii) Enhanced neurodegeneration leads to cognitive impairment. iv) This process continues as a cyclic process and leads to progression of AD [46,47,48,49,50,51,52].

RAGE and Aβ clearance

RAGE is a transporter responsible for mediating influx of Aβ inside the brain whereas efflux of Aβ is controlled by LRP-1 and P-glycoprotein transporters. It has been demonstrated that AD affected brain samples had shown elevated expression of RAGE receptors and decreased level of LRP1 receptors [37]. Up-regulation of RAGE and downregulation of LRP1 receptors leads to re-entry of circulating Aβ peptides into the brain. Further activation of β and γ secretases in turn leads to Aβ generation [36].It is evident that Aβ accumulation distorts the BBB junction via Ca^{2+}calcineurin pathway [53,54,55]. Abundant RAGE-Aβ interaction drives the RAGE-DIAPH1 signaling pathway which is a prominent mediator for activating inflammation and cellular dysfunction [42,56].

Role of oxidative stress in AD

Interaction of RAGE-AGEs tends to elevate through levels of ROS which affects various antioxidant defense systems such as superoxide dismutase, catalase and glutathione related enzymes and also activates protein kinase C [57]. The presence of metal ions along with the AGES initiates the generation of ROS that affects the cellular processes. Peptidyl radicals and nitroxyl radicals are sources for oxidative stress [58,59].

RAGE: Signaling pathways in AD pathology

Neuronal inflammation is a major reason for enhanced generation of Aβ and hyperphosphorylation of tau protein. Interaction of RAGE and Aβ induces various cellular signaling pathways [60]. RAGE-Aβ mediates the activation of CaMKKβ–AMPK (Ca^{2+}/calmodulin dependent protein kinase kinase-beta- AMP-activated protein kinase) signaling pathway which causes chronic neuroinflammation, oxidative stress and tau hyperphosphorylation[51,61]as represented in figure 2. Phosphorylation of ERK1/2 (extracellular signal regulated kinase 1/2) enhances binding of Aβ and increased levels of tau kinases [62,63,64]. RAGE mediated GSK-3 (Glycogen synthase kinase 3) signaling pathway induces the hyperphosphorylation of tau protein [11,45,65]. RAGE mediated NF-κB signaling pathway induces the release of cytokines which leads to oxidative stress and inflammation[66,67,68].

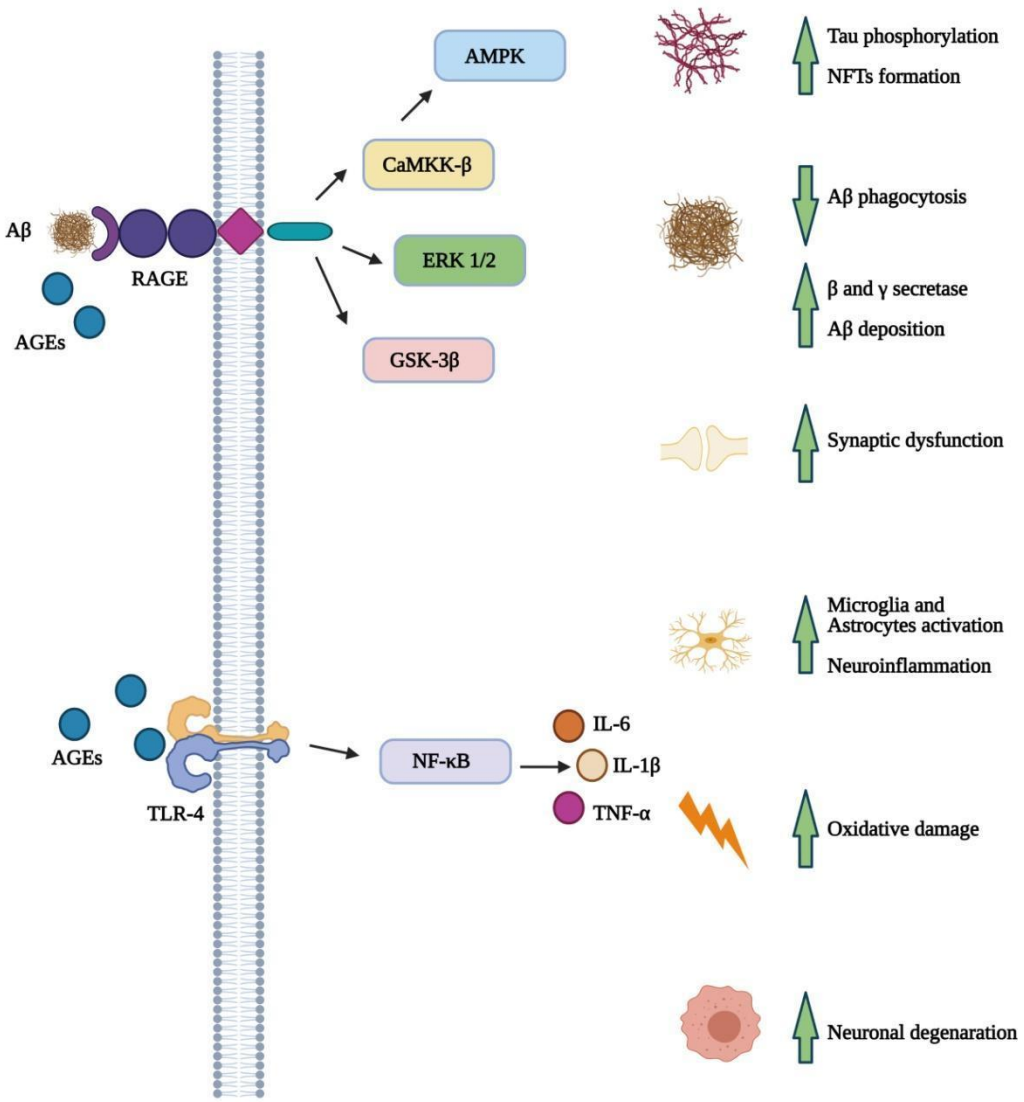


Figure 2: Pathological process in AD mediated by RAGE-Aβ interaction (Created with BioRender.com).

Interaction between sRAGE and Aβ

sRAGE had an inhibitory effect on fRAGE signaling pathways. Elevated aggregation of Aβ leads to formation of highly cross linked complex structures. It is evident that fRAGE mostly binds with highly cross-linked structures than the monomeric Aβ. Therefore, when sRAGE binds with the earliest stage of Aβ prior to the membrane bound RAGE, prevents the fRAGE activation and RAGE ligand generation [24] which is represented in figure 3. Studies also reported that administration of sRAGE into the circulatory system increases peripheral nerve regeneration, prevents the Aβ crossing from blood and reduces the binding of AGEs to the endothelial cell surface [73,74,75]. Additionally, most of the sRAGE is generated by ADAM10 (A disintegrin and metalloproteinase 10) sheddase and polymorphism in ADAM10 might be responsible for lower concentration of sRAGE which leads to the progression of AD [76,77,78,79,80].

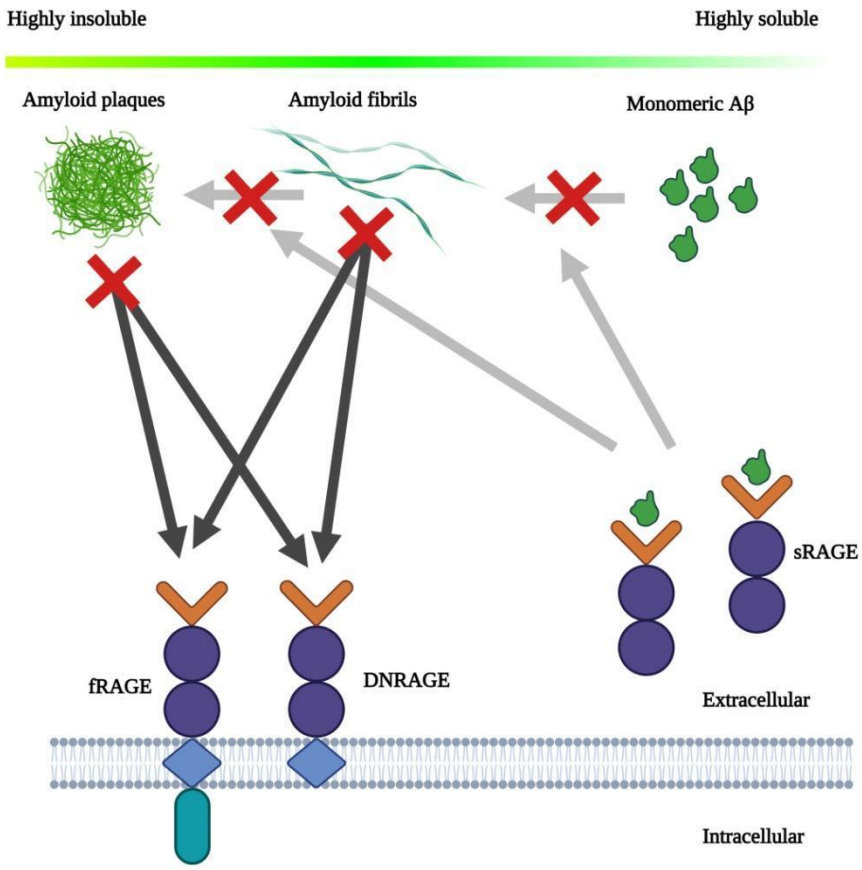


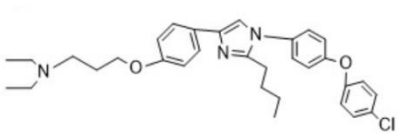
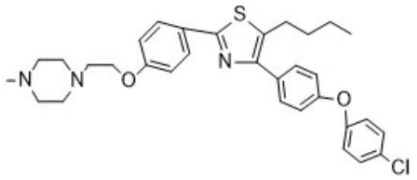
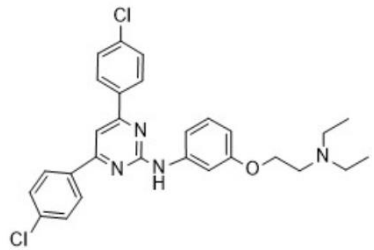
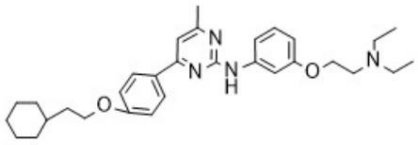
Figure 3: sRAGE as therapeutics for Aβ clearance in AD. Binding of sRAGE with monomeric Aβ prevents the formation of complex Aβ structures thereby preventing fRAGE interaction and proinflammatory signaling pathways. (Created with BioRender.com)

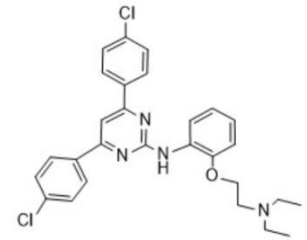
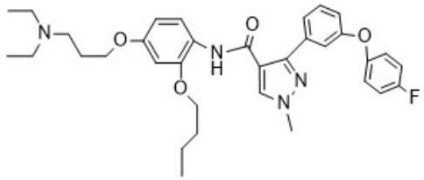
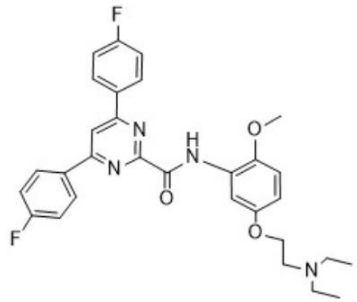
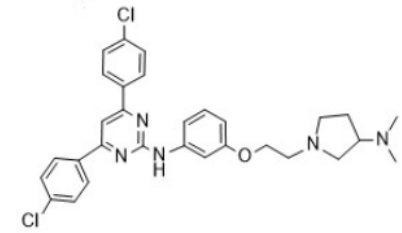
DEVELOPMENT OF RAGE INHIBITORS

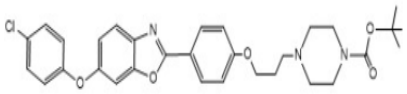
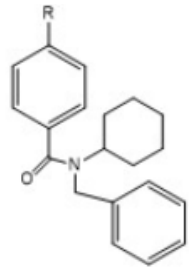
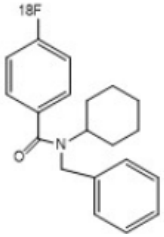
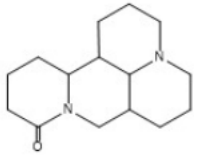
Existing knowledge on the mechanism of RAGE-Aβ interaction in AD pathology paves way for development of RAGE antagonists for AD treatment. Various strategies have been developed for blocking the RAGE-Aβ interaction such as synthetic RAGE analogs and RAGE antibodies to decay the RAGE mediated inflammatory response [81]. Studies had proven that administration of anti-RAGE antibodies hampered the inflammatory signaling pathways leading to reduction in the cytokine expression and interruption in the RAGE up-regulation. Anti-RAGE antibodies also prevent the Aβ mediated monocyte infiltration which induce pro-inflammatory responses and cause neurotoxicity in AD. Even though anti-RAGE antibodies seem to be beneficial, its permeability through blood brain barrier is still implausible [82, 83]. Hence, the development of synthetic RAGE inhibitors gained attractiveness.

In the recent years, various synthetic RAGE inhibitors are developed in rapid pace such as 2-aminopyrimidine series of inhibitors, pyrazole-5-carboximide series of inhibitors, 6-phenoxy-2-phenylbenzoxazole series of inhibitors, FPS-ZM1, [^{18}F] RAGER and Matrine. The details of synthetic RAGE inhibitors are given in table 1.

Table 1: Development of Synthetic inhibitors for RAGE

Inhibitor classification	Inhibitor	Inhibitor name	Inhibitor structure	RAGE inhibitory activity	Model system and method used for RAGE-drug interaction	Therapeutic Effects	References
2-aminopyrimidines analog series	1	PF-04494700 or TTP488 (3-[4-[2-butyl-1-[4-(4-chlorophenoxy) phenyl] imidazol-4yl] phenoxy]-*N, N*-diethylpropan-1-amine)		K_d = 500 nM	Phase III clinical trial Participants with mild to moderate Alzheimer's disease Fluorescent polarization with sRAGE Mouse model of systemic amyloidosis	Inhibition of RAGE-Aβ interaction Reduction of inflammatory markers Cognitive function improvement	84,85,86,87
	2	2,4-phenyl-substituted thiazole derivatives of 2 aminopyrimidines		IC_{50} = 1.21 μM	Structure-Activity relationship study (SAR)	Inhibition of Aβ influx through BBB Downregulation of NF-κB Blocking RAGE-Aβ interaction	88
	3	4,6-Bis(4-chlorophenyl)-N-(3-(2-(diethylamino) ethoxy) phenyl)-pyrimidin-2-amine		K_d = 102 μM IC_{50} = 16.4 μM	Acute model study-mice model Surface plasmon Resonance (SPR) using human RAGE	Inhibition of Aβ BBB entry Downregulation of NF-κB activation Improvement of cognitive function Inhibition of Aβ accumulation	89,90
	4	4-(4-(2-Cyclohexylethoxy) phenyl)-N-(3-(2-(diethylamino) ethoxy)- phenyl)-6-methylpyrimidin-2-amine		Percent inhibition = 49.6 ± 4.4	Acute animal model study- mice model	Inhibition of Aβ-RAGE binding Blocking of Aβ entry into BBB Downregulation of NF-κB of activation	89

	5	4,6-Bis(4-chlorophenyl)-N-(2-(2-(diethylamino) ethoxy) phenyl)-pyrimidin-2-amine		IC_{50} = 4.6 μM	Acute animal model study- mice model SPR using human RAGE	Inhibition of Aβ accumulation Inhibition of Aβ entry into BBB Downregulation of NF-κB activation	89
Pyrazole-5-carboximide analog series	6	N-(2-butoxy-4-(3-(diethylamino) propoxy) phenyl)-3-(4-(4-fluorophenoxy) phenyl)-1-methyl-1H-pyrazole-5-carboxamide)		K_d = 43.4 μM IC_{50} = 1.9 μM	SAR study mice model study SPR analysis	Inhibition of Aβ-RAGE binding Inhibition of Aβ entry into BBB	89,90
	7	N-(2-(2-(Diethylamino) ethoxy)-5-methoxyphenyl)-4,6- bis(4-fluorophenyl) pyrimidine-2-carboxamide)		-	ELISA on human RAGE- $Aβ_{1-42}$	Inhibition of Aβ-RAGE binding Improved hydrophilicity and reduced cytotoxicity	90
	8	4, 6-Bis(4-chlorophenyl)-N-(3-(2-(3(dimethylamino) pyrrolidin-1-yl) ethoxy) phenyl) pyrimidin-2-amine)		-	Molecular docking study ELISA on human RAGE- $Aβ_{1-42}$	Inhibition of Aβ-RAGE binding Improved analog binding efficiency	92

6-phenoxy-2-phenylbenzoxazole analog series	9	4-(3-{4-[6-(4-Chlorophenoxy)-benzoxazol-2-yl]-phenoxy}-propyl)-piperazine-1-carboxylic acid tert-butyl ester)		40% inhibition at 4 μM	AD mice model study Fluorescence resonance energy transfer (FRET) assay	Blocks Aβ transport across the BBB Reduction of amyloid deposition Analogs are protective against cytotoxicity	93
	10	FPS-ZM1 (N-Benzyl-N-cyclohexyl-4-chlorobenzamide)		Ki for $A\beta_{1-40}$ = 25 nM	Rat model study ELISA on human RAGE- $A\beta_{1-42}$ RAGE-$A\beta_{1-40}$	Up-regulatedantioxidant defense system Down-regulated AGE-mediated pro-inflammatory cytokines Reduced $A\beta_{1-40}$ and $A\beta_{1-42}$ production and oxidative stress Improved cognitive function	94,95
	11	[^{18}F] RAGER		K_d = 15 nM	Molecular docking study Autoradiography	Inhibition of Aβ-RAGE binding	96
	12	Matrine		K_d = 24 mM	AD mice model study ELISA on human RAGE- $A\beta_{1-42}$	Inhibits the $A\beta_{42}$-induced cytotoxicity Inhibition of aggregation of $A\beta_{42}$ Suppressed the Aβ/RAGE signaling pathway, proinflammatory cytokines and plaque formation Improved cognitive function	97

2-aminopyrimidines series of inhibitors are derived from one of the RAGE ligand called argpyrimidine-1which is served as a template for the design of inhibitor. This argpyrimidine 1 has two essential moieties which are pyrimidine moiety and amino acid moiety (two parts – linker part and terminal polar part). The modification in these two moieties gave rise to a new class of aminopyrimidines of the RAGE antagonists (Inhibitor 1-5). These classes of inhibitors had pharmacophore composed of two aromatic groups, a pyrimidine central core and alkyl chain having protonable nitrogen [84-89]. Pyrazole-5-carboximide series of inhibitors are designed by introduction of electronegative substituent and modification of ethoxy moiety (Inhibitor 6-8) [90-92]. 6-phenoxy-2-phenylbenzoxazole series of inhibitors have three parts such as 6-phenoxy region, 2-phenyl benzoxazole core and amino alkoxy region. In the 6-phenoxy-2-phenylbenzoxazole class of inhibitors compounds with a (4-(alkoxycarbonyl) piperazin-1-yl) alkyloxy side chain had shown significant inhibition towards the RAGE–Aβ interactions [93]. [^{18}F] RAGER is a first small molecule radiotracer which accumulates in areas of RAGE expression [96]. Matrine (Mat) is derived from Sophora flavescens Ait, a chinese herb medicine used to treat dementia. Matrine could inhibit Aβ42-induced cytotoxicity by preventing the Aβ42 aggregation and reducing the Aβ-RAGE signaling pathway [97]. Even though various RAGE inhibitor synthetic small molecules are under trial, it could not interact with larger surface areas of the protein interface to block the protein-protein interactions. Thereupon, peptides as an inhibitor gained essential attractiveness in therapeutics due to its advantages over small molecule antagonists [98].

CONCLUSION AND FUTURE ASPECTS

RAGE-amyloid interactions plays a major role in pathophysiology of AD through neuroinflammation and amyloid mediated pathogenesis. Blocking this interaction by synthetic small molecule inhibitors, anti-RAGE antibodies and peptides antagonists are novel therapeutic strategy for AD. However as on date there are no RAGE inhibitors approved for clinical use mainly due to the limited bioavailability and permeability of the drug candidates through BBB. Future research on developing drug therapeutics with good bioavailability, permeability, maximum safety and efficacy is warranted.

CONFLICT OF INTEREST

None declare

REFERENCES

[1] Cai Z, Liu N, Wang C, Qin B, Zhou Y, Xiao M et al. Role of RAGE in Alzheimer's Disease. Cellular and Molecular Neurobiology. 2015;36(4):483-49

[2] Ding Q, Keller J. Evaluation of rage isoforms, ligands, and signaling in the brain. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research. 2005;1746(1):18- 27.

[3] Korczyn A. Mixed Dementia-the Most Common Cause of Dementia. Annals of the New York Academy of Sciences. 2002;977(1):129-134.

[4] Yatime L, Andersen G. Structural insights into the oligomerization mode of the human receptor for advanced glycation end-products. FEBS Journal. 2013;280(24):6556-6568.

[5] Xue J, Rai V, Singer D, Chabierski S, Xie J, Reverdatto S et al. Advanced Glycation End Product Recognition by the Receptor for AGEs. Structure. 2011;19(5):722- 732.

[6] Neeper M, Schmidt A, Brett J, Yan S, Wang F, Pan Y et al. Cloning and expression of a cell surface receptor for advanced glycosylation end products of proteins. Journal of Biological Chemistry. 1992;267(21):14998-15004.

[7] AGER - Advanced glycosylation end product-specific receptor precursor - Homo sapiens (Human) - AGER gene & protein [Internet]. Uniprot.org. 2021 [cited 23 January 2021]. Available from: https://www.uniprot.org/uniprot/Q15109

[8] Dattilo B, Fritz G, Leclerc E, Vander Kooi C, Heizmann C, Chazin W. The Extracellular Region of the Receptor for Advanced Glycation End Products Is Composed of Two Independent Structural Units†. Biochemistry. 2007;46(23):6957-6970.

[9] Sakaguchi M, Murata H, Yamamoto K, Ono T, Sakaguchi Y, Motoyama A et al. TIRAP, an Adaptor Protein for TLR2/4, Transduces a Signal from RAGE Phosphorylated upon Ligand Binding. PLoS ONE. 2011;6(8): e23132.

[10] Rai V, Maldonado A, Burz D, Reverdatto S, Yan S, Schmidt A et al. Signal transduction in receptor for advanced glycation end products (RAGE). Solution Structure Of C-Terminal Rage (Ctrage) And Its Binding to Mdia1. Journal of Biological Chemistry. 2012;287(14):11283.

[11] Li J, Liu D, Sun L, Lu Y, Zhang Z. Advanced glycation end products and neurodegenerative diseases: Mechanisms and perspective. Journal of the Neurological Sciences. 2012;317(1-2):1-5.

[12] Röcken C, Kientsch-Engel R, Mansfeld S, Stix B, Stubenrauch K, Weigle B et al. Advanced Glycation End Products and Receptor for Advanced Glycation End Products in AA Amyloidosis. The American Journal of Pathology. 2003;162(4):1213-1220.

[13] Ramasamy R, Vannucci S, Yan S, Herold K, Yan S, Schmidt A. Advanced glycation end products and RAGE: a common thread in aging, diabetes, neurodegeneration, and inflammation. Glycobiology. 2005;15(7):16R-28R.

[14] Hudson B, Carter A, Harja E, Kalea A, Arriero M, Yang H et al. Identification, classification, and expression of RAGE gene splice variants. The FASEB Journal. 2007;22(5):1572-1580.

[15] Kaji Y, Usui T, Ishida S, Yamashiro K, Moore T, Moore J et al. Inhibition of Diabetic Leukostasis and Blood-Retinal Barrier Breakdown with a Soluble Form of a Receptor

for Advanced Glycation End Products. Investigative Opthalmology & Visual Science. 2007;48(2):858.
[16] Yonekura H, Yamamoto Y, Sakurai S, Petrova R, Abedin M, Li H et al. Novel splice variants of the receptor for advanced glycation end-products expressed in human vascular endothelial cells and pericytes, and their putative roles in diabetes-induced vascular injury. Biochemical Journal. 2003;370(3):1097-1109.
[17] Yeh C, Sturgis L, Haidacher J, Zhang X, Sherwood S, Bjercke R et al. Requirement for p38 and p44/p42 Mitogen-Activated Protein Kinases in RAGE-Mediated Nuclear Factor-κB Transcriptional Activation and Cytokine Secretion. Diabetes. 2001;50(6):1495-1504.
[18] Li J, Wang W, Huang X, Oldfield M, Schmidt A, Cooper M et al. Advanced Glycation End Products Induce Tubular Epithelial-Myofibroblast Transition through the RAGE-ERK1/2 MAP Kinase Signaling Pathway. The American Journal of Pathology. 2004;164(4):1389-1397.
[19] Dukic-Stefanovic S, Gasic-Milenkovic J, Deuther-Conrad W, Münch G. Signal transduction pathways in mouse microglia N-11 cells activated by advanced glycation endproducts (AGEs). Journal of Neurochemistry. 2003;87(1):44-55.
[20] Haslbeck K, Bierhaus A, Erwin S, Kirchner A, Nawroth P, Schlötzer U et al. Receptor for advanced glycation endproduct (RAGE)-mediated nuclear factor-κB activation in vasculitic neuropathy. Muscle & Nerve. 2004;29(6):853-860.
[21] Habib S. Alterations in tubular epithelial cells in diabetic nephropathy. Journal of Nephrology. 2013;26(5):865-869.
[22] Mohamed A, Bierhaus A, Schiekofer S, Tritschler H, Ziegler R, Nawroth P. The role of oxidative stress and NF-κB activation in late diabetic complications. BioFactors. 1999;10(2-3):157-167.
[23] Yu S, Wong C, Szeto C, Li E, Cai Z, Tam L. Members of the receptor for advanced glycation end products axis as potential therapeutic targets in patients with lupus nephritis. Lupus. 2014;24(7):675-686.
[24] Chaney M, Stine W, Kokjohn T, Kuo Y, Esh C, Rahman A et al. RAGE and amyloid beta interactions: Atomic force microscopy and molecular modeling. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2005;1741(1-2):199-205.
[25] Yan S, Chen X, Fu J, Chen M, Zhu H, Roher A et al. RAGE and amyloid-β peptide neurotoxicity in Alzheimer's disease. Nature. 1996;382(6593):685-691
[26] Lue L, Walker D, Brachova L, Beach T, Rogers J, Schmidt A et al. Involvement of Microglial Receptor for Advanced Glycation Endproducts (RAGE) in Alzheimer's Disease: Identification of a Cellular Activation Mechanism. Experimental Neurology. 2001;171(1):29-45.
[27] Du Yan S, Zhu H, Fu J, Yan S, Roher A, Tourtellotte W et al. Amyloid- peptide-Receptor for Advanced Glycation Endproduct interaction elicits neuronal expression of macrophage-colony stimulating factor: A proinflammatory pathway in Alzheimer disease. Proceedings of the National Academy of Sciences. 1997;94(10):5296-5301.
[28] Schmidt A, Yan S, Yan S, Stern D. The biology of the receptor for advanced glycation end products and its ligands. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research. 2000;1498(2-3):99-111.
[29] Schmidt A, Yan S, Yan S, Stern D. The multiligand receptor RAGE as a progression factor amplifying immune and inflammatory responses. Journal of Clinical Investigation. 2001;108(7):949-955.
[30] Bucciarelli L, Wendt T, Rong L, Lalla E, Hofmann M, Goova M et al. RAGE is a multiligand receptor of the immunoglobulin superfamily: implications for homeostasis and chronic disease. Cellular and Molecular Life Sciences (CMLS). 2002;59(7):1117-1128.
[31] Ray R, Juranek J, Rai V. RAGE axis in neuroinflammation, neurodegeneration and its emerging role in the pathogenesis of amyotrophic lateral sclerosis. Neuroscience & Biobehavioral Reviews. 2016;62: 48-55.
[32] Emanuele E, D'Angelo A, Tomaino C, Binetti G, Ghidoni R, Politi P et al. Circulating Levels of Soluble Receptor for Advanced Glycation End Products in Alzheimer Disease and Vascular Dementia. Archives of Neurology. 2005;62(11):1734.
[33] Teissier T, Boulanger É. The receptor for advanced glycation end-products (RAGE) is an important pattern recognition receptor (PRR) for inflammaging. Biogerontology. 2019;20(3):279-301.
[34] Xie J, Reverdatto S, Frolov A, Hoffmann R, Burz D, Shekhtman A. Structural Basis for Pattern Recognition by the Receptor for Advanced Glycation End Products (RAGE). Journal of Biological Chemistry. 2008;283(40):27255-27269.
[35] Koch M, Chitayat S, Dattilo B, Schiefner A, Diez J, Chazin W et al. Structural Basis for Ligand Recognition and Activation of RAGE. Structure. 2010;18(10):1342-1352.
[36] khter F, Akhter A, Kesari K, Javed R, Ruokolainen J, Vuorinen T. RAGE Exacerbate Amyloid Beta (Aβ) Induced Alzheimer Pathology: A Systemic Overview. 2021.
[37] Liu R, Wu C, Zhou D, Yang F, Tian S, Zhang L et al. Pinocembrin protects against β-amyloid-induced toxicity in neurons through inhibiting receptor for advanced glycation end products (RAGE)-independent signaling pathways and regulating mitochondrion-mediated apoptosis. BMC Medicine. 2012;10(1).
[38] Luth H. Age- and Stage-dependent Accumulation of Advanced Glycation End Products in Intracellular Deposits in Normal and Alzheimer's Disease Brains. Cerebral Cortex. 2004;15(2):211-220.
[39] Choi B, Cho W, Kim J, Lee H, Chung C, Jeon W et al. Increased expression of the receptor for advanced glycation end products in neurons and astrocytes in a triple transgenic mouse model of Alzheimer's disease. Experimental & Molecular Medicine. 2014;46(2):e75-e75.
[40] Cho H, Son S, Jin S, Hong H, Shin D, Kim S et al. RAGE regulates BACE1 and Aβ generation via NFAT1

activation in Alzheimer's disease animal model. The FASEB Journal. 2009;23(8):2639-2649.
[41] Loske C, Gerdemann A, Schepl W, Wycislo M, Schinzel R, Palm D et al. Transition metal-mediated glycoxidation accelerates cross-linking of β-amyloid peptide. European Journal of Biochemistry. 2000;267(13):4171-4178.
[42] Derk J, MacLean M, Juranek J, Schmidt A. The Receptor for Advanced Glycation Endproducts (RAGE) and Mediation of Inflammatory Neurodegeneration. Journal of Alzheimer's Disease & Parkinsonism. 2018;08(01).
[43] Kuhla B, Boeck K, Schmidt A, Ogunlade V, Arendt T, Münch G et al. Age- and stage-dependent glyoxalase I expression and its activity in normal and Alzheimer's disease brains. Neurobiology of Aging. 2007;28(1):29-41.
[44] More S, Vartak A, Vince R. Restoration of Glyoxalase Enzyme Activity Precludes Cognitive Dysfunction in a Mouse Model of Alzheimer's Disease. ACS Chemical Neuroscience. 2012;4(2):330-338.
[45] Li X, Xie J, Jiang X, Lv B, Cheng X, Du L et al. Methylglyoxal Induces Tau Hyperphosphorylation via Promoting AGEs Formation. NeuroMolecular Medicine. 2012;14(4):338-348.
[46] Cunnane S, Nugent S, Roy M, Courchesne-Loyer A, Croteau E, Tremblay S et al. Brain fuel metabolism, aging, and Alzheimer's disease. Nutrition. 2011;27(1):3-20.
[47] Rapoport S, Hatanpää K, Brady D, Chandrasekaran K. Brain Energy Metabolism, Cognitive Function and Down-regulated Oxidative Phosphorylation in Alzheimer Disease. Neurodegeneration. 1996;5(4):473-476.
[48] Yan S. RAGE is a key cellular target for A -induced perturbation in Alzheimer s disease. Frontiers in Bioscience. 2012; S4(1):240-250.
[49] Chaney M, Stine W, Kokjohn T, Kuo Y, Esh C, Rahman A et al. RAGE and amyloid beta interactions: Atomic force microscopy and molecular modeling. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2005;1741(1-2):199-205.
[50] Zong H, Madden A, Ward M, Mooney M, Elliott C, Stitt A. Homodimerization Is Essential for the Receptor for Advanced Glycation End Products (RAGE)-mediated Signal Transduction. Journal of Biological Chemistry. 2010;285(30):23137-23146.
[51] Son S, Jung E, Shin H, Byun J, Mook-Jung I. Aβ-induced formation of autophagosomes is mediated by RAGE-CaMKKβ-AMPK signaling. Neurobiology of Aging. 2012;33(5): 1006.e11-1006.e23.
[52] Marksteiner J, Imarhiagbe D, Defrancesco M, Deisenhammer E, Kemmler G, Humpel C. Analysis of 27 vascular-related proteins reveals that NT-proBNP is a potential biomarker for Alzheimer's disease and mild cognitive impairment: A pilot-study. Experimental Gerontology. 2014;50: 114-121.
[53] Watson R, Prabhala R, Plezia P, Alberts D. Effect of β-carotene on lymphocyte subpopulations in elderly humans: evidence for a dose-response relationship. The American Journal of Clinical Nutrition. 1991;53(1):90-94.
[54] Wan W, Chen H, Li Y. The potential mechanisms of Aβ-receptor for advanced glycation end-products interaction disrupting tight junctions of the blood-brain barrier in Alzheimer's disease. International Journal of Neuroscience. 2013;124(2):75-81.
[55] Kook S, Seok Hong H, Moon M, Mook-Jung I. Disruption of blood-brain barrier in Alzheimer disease pathogenesis. Tissue Barriers. 2013;1(2):e23993.
[56] Qosa H, LeVine H, Keller J, Kaddoumi A. Mixed oligomers and monomeric amyloid-β disrupts endothelial cells integrity and reduces monomeric amyloid-β transport across hCMEC/D3 cell line as an in vitro blood–brain barrier model. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2014;1842(9):1806-1815.
[57] Jiang JM, Wang Z, Li DD. Effects of AGEs on oxidation stress and antioxidation abilities in cultured astrocytes. Biomed Environ Sci. 2004;17(1):79-86.
[58] Durany N, Münch G, Michel T, Riederer P. Investigations on oxidative stress and therapeutical implications in dementia. European Archives of Psychiatry and Clinical Neurosciences. 1999;249(S3):S68-S73.
[59] Ramasamy R, Vannucci S, Yan S, Herold K, Yan S, Schmidt A. Advanced glycation end products and RAGE: a common thread in aging, diabetes, neurodegeneration, and inflammation. Glycobiology. 2005;15(7):16R-28R.
[60] Fernández J, Rojo L, Kuljis R, Maccioni R. The Damage Signals Hypothesis of Alzheimer's Disease Pathogenesis. Journal of Alzheimer's Disease. 2008;14(3):329-333.
[61] Salminen A, Kaarniranta K, Haapasalo A, Soininen H, Hiltunen M. AMP-activated protein kinase: a potential player in Alzheimer's disease. Journal of Neurochemistry. 2011;118(4):460-474.
[62] Webster B, Hansen L, Adame A, Crews L, Torrance M, Thal L et al. Astroglial Activation of Extracellular-Regulated Kinase in Early Stages of Alzheimer Disease. Journal of Neuropathology and Experimental Neurology. 2006;65(2):142-151.
[63] Slowik A, Merres J, Elfgen A, Jansen S, Mohr F, Wruck C et al. Involvement of formyl peptide receptors in receptor for advanced glycation end products (RAGE) - and amyloid beta 1-42-induced signal transduction in glial cells. Molecular Neurodegeneration. 2012;7(1):55.
[64] Barroso E, del Valle J, Porquet D, Vieira Santos A, Salvadó L, Rodríguez-Rodríguez R et al. Tau hyperphosphorylation and increased BACE1 and RAGE levels in the cortex of PPARβ/δ-null mice. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2013;1832(8):1241-1248.
[65] Li X, Lv B, Xie J, Liu J, Zhou X, Wang J. AGEs induce Alzheimer-like tau pathology and memory deficit via RAGE-mediated GSK-3 activation. Neurobiology of Aging. 2012;33(7):1400-1410.
[66] Wang C, Xie J, Xu Y, Wang T, Cai J, Wang X et al. Trientine Reduces BACE1 Activity and Mitigates Amyloidosisviathe AGE/RAGE/NF-κB Pathway in a

Transgenic Mouse Model of Alzheimer's Disease. Antioxidants & Redox Signaling. 2013;19(17):2024-2039.
[67] Wang X, Yu S, Hu J, Wang C, Wang Y, Liu H et al. Streptozotocin-induced diabetes increases amyloid plaque deposition in AD transgenic mice through modulating AGEs/RAGE/NF-κB pathway. International Journal of Neuroscience. 2013;124(8):601-608.
[68] Lukiw W. NF-κB-regulated, proinflammatory miRNAs in Alzheimer's disease. Alzheimer's Research & Therapy. 2012;4(6):47.
[69] Hudson B, Stickland M, Grant P. Identification of polymorphisms in the receptor for advanced glycation end products (RAGE) gene: prevalence in type 2 diabetes and ethnic groups. Diabetes. 1998;47(7):1155-1157.
[70] Prevost G, Fajardy I, Fontaine P, Danze P, Besmond C. Human RAGE GLY82SER dimorphism and HLA class II DRB1-DQA1-DQB1 haplotypes in type 1 diabetes. European Journal of Immunogenetics. 1999;26(5):343-348.
[71] Rani P. G82S RAGE polymorphism is associated with Alzheimer rsquo s disease. Frontiers in Bioscience. 2020;12(1):150-161.
[72] Hofmann M, Drury S, Hudson B, Gleason M, Qu W, Lu Y et al. RAGE and arthritis: the G82S polymorphism amplifies the inflammatory response. Genes & Immunity. 2002;3(3):123-135.
[73] Park L, Raman K, Lee K, Lu Y, Ferran L, Chow W et al. Suppression of accelerated diabetic atherosclerosis by the soluble receptor for advanced glycation endproducts. Nature Medicine. 1998;4(9):1025-1031.
[74] Wear-Maggitti K, Lee J, Conejero A, Schmidt A, Grant R, Breitbart A. Use of Topical sRAGE in Diabetic Wounds Increases Neovascularization and Granulation Tissue Formation. Annals of Plastic Surgery. 2004;52(5):519-521.
[75] LaRue B, Hogg E, Sagare A, Jovanovic S, Maness L, Maurer C et al. Method for measurement of the blood–brain barrier permeability in the perfused mouse brain: application to amyloid-β peptide in wild type and Alzheimer's Tg2576 mice. Journal of Neuroscience Methods. 2004;138(1-2):233-242.
[76] Li X, Du L, Cheng X, Jiang X, Zhang Y, Lv B et al. Glycation exacerbates the neuronal toxicity of β-amyloid. Cell Death & Disease. 2013;4(6): e673-e673.
[77] Quade-Lyssy P, Kanarek A, Baiersdörfer M, Postina R, Kojro E. Statins stimulate the production of a soluble form of the receptor for advanced glycation end products. Journal of Lipid Research. 2013;54(11):3052-3061.
[78] Yamagishi S. Soluble form of a receptor for advanced glycation end products sRAGE as a biomarker. Frontiers in Bioscience. 2010; E2(4):1184-1195.
[79] Sugihara T, Munesue S, Yamamoto Y, Sakurai S, Akhter N, Kitamura Y et al. Endogenous Secretory Receptor for Advanced Glycation End-Products Inhibits Amyloid-β1-42 Uptake into Mouse Brain. Journal of Alzheimer's Disease. 2012;28(3):709-720.
[80] Huang W, Chen W, Jiang L, Yang Y, Yao L, Li K. Influence of ADAM10 Polymorphisms on Plasma Level of Soluble Receptor for Advanced Glycation End Products and The Association with Alzheimer's Disease Risk. Frontiers in Genetics. 2018;9.
[81] Bongarzone S, Savickas V, Luzi F, Gee A. Targeting the Receptor for Advanced Glycation Endproducts (RAGE): A Medicinal Chemistry Perspective. Journal of Medicinal Chemistry. 2017;60(17):7213-7232.
[82] Matsumoto H, Matsumoto N, Shimazaki J, Nakagawa J, Imamura Y, Yamakawa K et al. Therapeutic Effectiveness of Anti-RAGE Antibody Administration in a Rat Model of Crush Injury. Scientific Reports. 2017;7(1): 12255.
[83] Kozyrev N, Albers S, Yang J, Prado V, Prado M, Fonseca G et al. Infiltrating Hematogenous Macrophages Aggregate Around β-Amyloid Plaques in an Age- and Sex-Dependent Manner in a Mouse Model of Alzheimer Disease. Journal of Neuropathology & Experimental Neurology. 2020;79(11):1147-1162.
[84] Galasko D, Bell J, Mancuso J, Kupiec J, Sabbagh M, van Dyck C et al. Clinical trial of an inhibitor of RAGE-A interactions in Alzheimer disease. Neurology. 2014;82(17):1536-1542.
[85] Burstein A, Grimes I, Galasko D, Aisen P, Sabbagh M, Mjalli A. Effect of TTP488 in patients with mild to moderate Alzheimer's disease. BMC Neurology. 2014;14(1).
[86] Diseases A, derivatives a, derivatives a, derivatives g, derivatives i, compositions p et al. WO2011041198A1 - Substituted imidazole derivatives for treatment of alzheimers disease - Google Patents [Internet]. Patents.google.com. 2021 [cited 25 January 2021]. Available from: https://patents.google.com/patent/WO2011041198A1/en
[87] Sabbagh M, Agro A, Bell J, Aisen P, Schweizer E, Galasko D. PF-04494700, an Oral Inhibitor of Receptor for Advanced Glycation End Products (RAGE), in Alzheimer Disease. Alzheimer Disease & Associated Disorders. 2011;25(3):206-212.
[88] Lee Y, Kim H, Kim Y, Roh E, Han H, Shin K. Synthesis and structure–activity relationships of tri-substituted thiazoles as RAGE antagonists for the treatment of Alzheimer's disease. Bioorganic & Medicinal Chemistry Letters. 2012;22(24):7555-7561.
[89] Han Y, Choi G, Son D, Kim N, Yun H, Lee S et al. Ligand-Based Design, Synthesis, and Biological Evaluation of 2-Aminopyrimidines, a Novel Series of Receptor for Advanced Glycation End Products (RAGE) Inhibitors. Journal of Medicinal Chemistry. 2012;55(21):9120-9135.
[90] Kim S, Han Y. Design, synthesis, and biological evaluation of pyrimidine-2-carboxamide analogs: investigation for novel RAGE inhibitors with reduced hydrophobicity and toxicity. Archives of Pharmacal Research. 2015;38(11):1952-1962.
[91] Han Y, Kim K, Choi G, An H, Son D, Kim H et al. Pyrazole-5-carboxamides, novel inhibitors of receptor for advanced glycation end products (RAGE). European Journal of Medicinal Chemistry. 2014;79: 128-142.
[92] Han Y, Kim K, Son D, An H, Kim H, Lee J et al. Fine tuning of 4,6-bisphenyl-2-(3-alkoxyanilino) pyrimidine focusing on the activity-sensitive aminoalkoxy moiety for a

therapeutically useful inhibitor of receptor for advanced glycation end products (RAGE). Bioorganic & Medicinal Chemistry. 2015;23(3):579-587.
[93] Choi K, Lim K, Shin J, Kim S, Suh Y, Hong H et al. 6-Phenoxy-2-phenylbenzoxazoles, novel inhibitors of receptor for advanced glycation end products (RAGE). Bioorganic & Medicinal Chemistry. 2015;23(15):4919-4935.
[94] Deane R, Singh I, Sagare A, Bell R, Ross N, LaRue B et al. A multimodal RAGE-specific inhibitor reduces amyloid β–mediated brain disorder in a mouse model of Alzheimer disease. Journal of Clinical Investigation. 2012;122(4):1377-1392.
[95] Hong Y, Shen C, Yin Q, Sun M, Ma Y, Liu X. Effects of RAGE-Specific Inhibitor FPS-ZM1 on Amyloid-β Metabolism and AGEs-Induced Inflammation and Oxidative Stress in Rat Hippocampus. Neurochemical Research. 2016;41(5):1192-1199.
[96] Cary B, Brooks A, Fawaz M, Drake L, Desmond T, Sherman P et al. Synthesis and Evaluation of [18F] RAGER: A First Generation Small-Molecule PET Radioligand Targeting the Receptor for Advanced Glycation Endproducts. ACS Chemical Neuroscience. 2016;7(3):391-398.
[97] Cui L, Cai Y, Cheng W, Liu G, Zhao J, Cao H et al. A Novel, Multi-Target Natural Drug Candidate, Matrine, Improves Cognitive Dessficits in Alzheimer's Disease Transgenic Mice by Inhibiting Aβ Aggregation and Blocking the RAGE/Aβ Axis. Molecular Neurobiology. 2016;54(3):1939-1952.
[98] Lee A, Harris J, Khanna K, Hong J. A Comprehensive Review on Current Advances in Peptide Drug Development and Design. International Journal of Molecular Sciences. 2019;20(10):2383.