**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 47402

**Manuscript type:** MINIREVIEWS

**New treatment modalities in Alzheimer's disease**

Koseoglu E.New treatments in AD

Emel Koseoglu

**Emel Koseoglu,** Department of Neurology, Faculty of Medicine, Erciyes University, Kayseri 38039, Turkey

**ORCID number:** Emel Koseoglu (0000-0001-9620-9949).

**Author contributions:** Koseoglu E designed and wrote this review.

**Conflict-of-interest statement:** The author declares no conflict of interest.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Corresponding author:** **Emel Koseoglu, MD, Professor,** Department of Neurology, Faculty of Medicine, Erciyes University, Kayseri 38039, Turkey. emelk@erciyes.edu.tr

**Telephone:** +90-352-2076666/21755

**Fax:** +90-352-4374931

**Received:** March 21, 2019

**Peer-review started:** March 23, 2019

**First decision:** April 18, 2019

**Revised:** May 18, 2019

**Accepted:** June 10, 2019

**Article in press:** June 10, 2019

**Published online:** July 26, 2019

**Abstract**

Alzheimer’s disease (AD) is still a major public health challenge without an effective treatment to prevent or stop it. Routinely used acetylcholinesterase inhibitors and memantine seem to slow disease progression only to a limited exten. Therefore, many investigations on new drugs and other treatment modalities are ongoing in close association with increasing knowledge of the pathophysiology of the disease. Here, we review the studies about the new treatment modalities in AD with a classification based on their main targets, specifically pathologic structures of the disease, amyloid and tau, neural network dysfunction with special interest to the regulation of gamma oscillations, and attempts for the restoration of neural tissue via regenerative medicine. Additionally, we describe the evolving modalities related to gut microbiota, modulation, microglial function, and glucose metabolism.

**Key words**:Alzheimer’s disease treatment; Anti-amyloid; Anti-tau; Gamma oscillations; Stem cell therapy

**© The Author(s) 2019.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** This review discusses various new treatment modalities in Alzheimer’s disease (AD) based on the classification of their mechanism of action. New anti-amyloid, anti-tau, and treatments targeting network dysfunction with particular attention to deep brain stimulation to modulate gamma oscillations in the brain are evaluated. Moreover exciting developments in stem cell therapy especially combined with tissue engineering techniques are presented. Lastly some other modalities including microglial function modulators, gut microbiome transplantation, modulation of vagus nerve and metabolic arrangements are mentioned. It seems that new treatments in AD will involve each of them individually or in combination.

**Citation:** Koseoglu E. New treatment modalities in Alzheimer's disease.*World J Clin Cases* 2019; 7(14): 1764-1774

**URL:** https://www.wjgnet.com/2307-8960/full/v7/i14/1764.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v7.i14.1764

**INTRODUCTION**

Alzheimer’s disease (AD) is a major public health challenge in the 21st century. For this reason, near to 500 clinical trials have been conducted and huge amounts of money have been spent in an effort to handle the disease[1]. At present, cholinesterase inhibitors donepezil, rivastigmine, and galantamine and, memantine, which acts as a N-methyl D-aspartate receptor antagonist and also as a dopamine antagonist, are approved as symptomatic treatments for use in AD[2,3]. Other alternative treatments and measures include nutraceutical huperzine A, correction of Vitamin D deficiency, use of non-steroidal anti-inflammatory drugs, omega 3 fatty acid supplements, management of cardiovascular risk factors, and aerobic physical exercise[4-8]. The benefits of these options are limited to slowing the disease, not matching the expectation of stopping it.

With advances in molecular biology and pharmacology, some new treatment modalities related to the pathognomonic pathological features of the disease have come onto the scene. Additionally, new therapeutic neurophysiological interventions have aimed to resolve the neural network dysfunction that emerge through progression of the disease, and trials of stem cell therapy have been initiated. Early therapeutic intervention is an important factor for the success of treatment. Moreover, some environmental regulations can be considered as measures of prevention, especially in persons who are at high risk of developing AD.

Here, we review investigations on the new treatment modalities in AD with a classification based on their main targets, specifically pathologic structures of the disease (*i.e.*, amyloid and tau), neural network dysfunction with special attention to the regulation of gamma oscillations and attempts for the restoration of neural tissue *via* regenerative medicine. Additionally, we describe the evolving modalities related to gut microbiota, modulation, microglial function, and glucose metabolism.

**ANTI-AMYLOID**

Amyloid plaques are the earliest manifestation of AD, and can be detected 20 years prior to the onset of symptoms[9]. The most direct action in anti-Amyloid treatment is to reduce Amyloid-β (Aβ) production from its precursor, Amyloid precursor protein (APP), by targeting β and γ-secretases, but some safety problems exist for these drugs. For γ-secretase inhibitors, unwanted side effects are unavoidable due to its physiological substrates, which are essential in normal biological processes, such as the Notch signaling protein[10]. β-Amyloid secretase inhibitors (β-site APP cleaving enzyme 1: BACE1) have some challenges such as the large catalytic pocket and adverse side effects including blindness[11]. Additionally, there are some handicaps with the use of these drugs, because the majority of AD patients do not have over-produced APP and some Aβ isoforms can increase neurotransmitter release at hippocampal synapses by some regulatory mechanims [12].

Though early investigations of BACE1 inhibitors failed to show meaningful results in human subjects, a recent study declared that the novel medication verubecestat caused a decrease in Aβ levels at a level of more than 40 fold in animals and showed good safety profile in early human trials[13] (Table 1).

Another approach for decreasing Aβ plaque deposition is immunotherapy. Although active Aβ-immunotherapeutic agents showed some beneficial clinical effects, the studies were suspended due to serious side effects such as meningoencephalitis[14-16]. Monoclonal antibodies initially developed as passive immunotherapy agents removed plaques from the brains of patients, but did not improve cognitive scores in patients with mild to moderate disease[17-25]. These results have led investigators to believe that these agents may be beneficial solely in the early phases of mild cognitive impairment. Solanezumab did not yield beneficial clinical effects in patients with few symptoms, despite some improvements in amyloid PET imaging and in assessments of Mini Mental State Examination[21,22,26-30]. Another agent named aducanumab is currently under investigation (EARLY study) for its clinical effects in elderly persons with positive biomarkers or family history of AD, and has promising initial results[21,22,26-30].

To overcome the failures with monoclonal antibodies, multiple functional subregions of Aβ may be targeted[31]. Moreover, combination therapy with a monoclonal antibody and BACE1 inhibitor may be more promising, because it has been shown to reduce the amount of amyloid plaques in mice significantly[32]. Despite many problems, immunotherapy is still a promising approach to modify the exten of neurodegeneration in AD[33].

**ANTI-TAU**

Since the anti-amyloid treatment measures have not been as successful as expected so far, some other targets are starting to being investigated. Tau-targeted trials are the major new interest for this aim, since biomarker studies propose that tau pathology is closely correlated to the clinical follow up of AD[34]. Initially, inhibitors of kinases and tau aggregation or stabilizators of microtubules were tried as potential anti-tau therapies. However, most of these approaches have failed because of their toxicity and/or lack of efficacy. Recently, most of the anti-tau clinical investigations are based on immunotherapeutic approaches. There are 8 ongoing clinical trials, (in Phase I, Phase II) and several preclinical studies on tau immunotherapies. TRx0237 as a tau aggregation blocker failed to yield beneficial treatment effects in a phase III trial[35]. Intravenous immunoglobulin, the passive immunotherapy among Phase III clinical trials, did not fulfill primary end points in mild to moderate AD[36]. AADvac1 as a tau vaccine showed good results in terms of both safety and immunological response in Alzheimer patients. Further studies are needed to prove its clinical efficacy[37] (Table 1).

Goldstein *et al*[38] reported that cholesterol esters (CE), the storage form of excess cholesterol within cells, regulate tau activity. Moreover, they found that the anti-HIV drug efavirenz decreased CE by activating the neuronal enzyme “CYP46A1” and thereby reduced phosphorylated tau within neurons of patients with AD. Furthermore, they observed that CE promotes formation of tau even in the absence of Aβ, indicating that simply removing Aβ from the brain, which was the target of many candidate drugs for AD treatment, would not be adequate to halt the disease. They thought that the CYP46A1-CE-tau axis was a target and a potential mechanism against which new drugs could be developed in the treatment of early AD. The researchers also confirmed previous reports declaring that reducing CE prevented amyloid formation additionally. They stated that CE were upstream of both Aβ and tau, presenting a way to prevent abnormal deposition of these proteins.

Key opinion leaders believe that the research field of tau therapies is still premature and trials may face the similar difficulties as in amyloid therapies[1]. However, if these trials become successful, they may cause enrichment in the alternative choices including combination therapies against accumulation of pathologic amyloid and tau proteins, in the early stages of the disease.

**TARGETING NEURAL NETWORK DYSFUNCTION**

In recent years, it has been discovered that alterations at the genetic and cellular levels initiate neural network dysfunction which causes further deterioriation in cognition. Additionally, a novel hypothesis has been proposed, stating that AD patients are able to encode memories but unable to retrieve them[39]. Therefore, in addition to treatments targeting the pathological structures, strategies restoring neural network connectivity may be directly useful in reversing memory loss[40-45]. These therapeutic drugs and interventions also have positive feedback effects on molecular processes to re-establish cellular health[46].

Deep brain stimulation techniques used in Phase 1 studies to directly target the activity of brain networks ended with positive results[47,48]. Stimulation of the fornix in animal models changed protein expression and in turn restored cellular health and network function[49]. Likewise, increased histone acetylation using inhibitors of histone deacetylases in a mouse model caused the sprouting of dendrites and increased number of synapses, thereby inducing repair of neural networks and leading to recovery of learning behaviour and access to long-term memories[50]. Excitation of hippocampal engram cells using optogenetic techniques in a transgenic mouse model of early AD increased the number of dendritic cells and recovered learning and memory[39]. Arrangement of gamma oscillations in the hippocampus is also a new technique that has been shown to have positive effects on cognitive activity by restoring interneuron activity and by some non-neuronal effects[42].

Gamma oscillations are rthymic fluctuations of brain waves in local field potentials with a wide range of high frequencies (approximately 25-100 Hz) and are associated with inter-neuronal communication in virtually all brain networks. These oscillations may actually be two functionally distinct rhythms, slow (approximately 25-50 Hz) and fast (approximately 55-100 Hz) gamma[51]. Although slow and fast gamma waves are found to be generated locally, gamma oscillators with similar frequencies in various brain regions can be synchronized through anatomical connections[51]. There is growing evidence that gamma rhythms are important for hippocampal memory processing, as fast gamma stimulates new memory encoding by conveying current sensory information to the hippocampus [52,53] and slow gamma plays a role in memory retrieval by facilitating hippocampal CA3 inputs to CA1[51,52,54,55]. Sharp wave-ripples (SWRs)[54] are also important in memory retrieval, because slow gamma power and harmony between CA3 and CA1 increases during them[56,57] .

A decrease in SWR-associated slow gamma was demonstrated in AD mouse models. The rescue of slow gamma rhythms resulted in alleviation of deficits in learning-memory and mitigation of AD pathology by the modulation of gamma oscillations[40-43]. Hippocampal fast-spiking parvalbumin-positive interneurons were excited optogenetically by using a non-invasive 40 Hz photic stimulator. This technique also decreased Aβ production and stimulated its attenuation by increasing microglial engulfment[42].

**RESTORATION OF NEURAL TISSUE *VIA* REGENERATIVE MEDICINE**

Elimination or blocking of amyloid or hyperphosphorylated tau protein cannot restore or replace the degenerated neurons in AD. Stem cell therapy seems to be a convenient candidate for repopulation and regeneration of degenerating neuronal networks in the disease. The designs of stem cell therapies target two theoretical aims. One of these is designed to induce endogenous repair by upregulating resident brain-derived neural stem cell (NSC) niches within the adult brain and stimulating adult hippocampal neurogenesis, which is particularly important in the early stages of the disease. Nevertheless, this approach failed in clinical trials probably due to the ineffectiveness of the procedure to functionally compensate for the lost hippocampal neurons or because the method does not adequately address other features of the disease[58-60].

The other design is exogenous cell therapy, aiming to restore the neuronal networks using native or induced production of neuroprotective growth factors as contributers, based on the fact that the production of neurotrophins, which are factors supporting the growth and survival of neurons, is low in AD patients. Moreover, differentiation and participation of the stem cells in repopulating regions of degenerated neurons can lead to therapeutic restoration[58].

The types of stem cells used in cell therapy are highly important from the points of providing unique distinctive cells required and for their different abilities to promote neurotrophic factors. In general two major stem cell types exist. One type is pluripotent stem cells including embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). The other type is adult stem cells which comprise NSCs, hematopoietic stem cells (HSC), mesenchymal stem cells (MSCs), and olfactory ensheathing cells (OECs)[61].

ESCs are capable of unlimited self-renewal. They are a perfect choice for cell replacement therapy, when their pluiropotency is precisely arranged into necessary neuronal types. Nevertheless their use is largely limited due to ethical concerns. Induced PSCs produced from fully differentiated somatic cells provide an opportunity to deliver patients specific pluiropotent cells suitable for autologous transplantation[62]. There have been successful trials with iPSC-derived cholinergic neuronal precursors, iPSC-derived macrophage-like cells, and iPSC-derived NSCs[63-65]. It seems that the niche of stem cell is very important in stimulating the differentiation of transplanted cells toward a special type from the point that some beneficial immunological or biochemical effects become possible. Use of neurotrophins leading to a shift from proinflammatory to anti-inflammatory cytokine reactions and use of proteins causing apotransferrin release from the cells are good examples of this phenomenon[64,66]. Both adult NSCs and adult MSCs can be affected and expanded with extrinsic chemical agents and growth factors[61,67]. Both are effective through replacement of degenerated cells and release of neurotrophic factors enhancing neurogenesis, such as vascular endothelial growth factor, brain-derived neurotrophic factor (BDNF), insulin growth factor-1, nerve growth factor (NGF), and fibroblast factor 2. In addition to enhancing neurogenesis, these secreted neurotrophic factors promote Aβ clearance, reduce tau hyperphoshorylation, enhance synaptogenesis, modify innate and adaptive immune cell responses by upregulating neuroprotective cytokines and decreasing proinflammatory cytokines, increase microglial phagocytic activity, enhance neovascularization, and modulate autophagy pathways[68-74]. Both NSCs and MSCs can be genetically improved to increase the success of transplantation and to enable delivery of more efficient therapeutic and neurotrophic factors[75,76]. Several investigations have clearly shown that exogenous transplanted NSCs migrate precisely and may differentiate into various types nerve cells [61]. MSCs can be derived from a variety of adult tissues and organs, comprising peripheral blood, bone marrow, umbilical cord, amniotic fluid, Wharton jelly, fetal liver, muscle, lung and adipose tissue[77]. MSCs have been a good option in practice due to their high potency of proliferation, anti-inflammatory features, easy accessibility, high capability of propagation *in vitro*, secretion of a extensive range of cytokines, and absence of ethical problems. They can be administered intravenously, which is the least invasive method making multiple injections possible[61]. Additionally, MSC-extracellular vesicles (MSC-EVs), especially genetically modified ones, may be a new horizon in the treatment of AD. EVs are membrane vesicles that are secreted by various mammalian cell types, and have been demonstrated to deliver biologically effective molecules to neighbouring diseased or harmed cells, stimulating immune modulation, angiogenesis, neurogenesis, and synaptogenesis. They also modulate physiological or pathological processes by echoing the genetic profile of their parent cell to recipient cells[78]. MSCs can be genetically modified to secret EVs supplied with therapeutic agents like growth factors and small interfering RNA (siRNAs) that target useful enzymes to the brain[79,80]. OECs are another source of multipotent stem cells found in the lamina propria, generally supporting neurons in structural, metabolic, and trophic aspects through secretion of neurotrophic growth factors (*e.g.*, NGF, BDNF) along with extracellular matrix molecules like fibronectin. By this way, OECs causes a synergistic effect for other transplanted stem cells. Genetically modified olfactory bulb-NSC/NPCs expressing hNGF showed beneficial effects on cognitive decline caused by ibotenic acid-induced lesions[81].

To increase the efficacy of stem cells and to protect them from the hostile microenvironment in AD, transplanting self-assembling proteins as three dimensional scaffolds or optimising structures for encapsulating stem cells using the techniques of tissue engineering and nanotechnology are highly recommended for the treatment of AD. Likewise there are some successful trials of these methods in animals and humans[82-89].

There are several phase 1 or phase 1/1b clinical trial studies with positive results using various methods such as transplantation of microencapsulated implants of genetically modified retinal pigment epithelial cells and autologous fibroblasts genetically programmed to produce NGF[86,87,90]. A recent study performed with human umbilical cord blood (hUCB)- derived MSCs on nine mild-moderate AD patients showed no adverse effects no significant clinical efficacy or neuroprotective effect[91]. Currently, several phase 1 or 2 studies in humans are ongoing (Table 2). Stem cell treatment seems promising especially with the possible use of genetically modified stem cells and application of different tissue enginering techniques.

**ADDITIONAL MODALITIES ON THE WAY**

With the increase in knowledge about the fundamental mechanisms of gut microbiota affecting the brain through the immune system, endocrine system, vagus nerve, and bacteria-derived metabolites, some newer therapeutic approaches such as microbiome transplant can be developed[92-94]. Modulation of the vagus nerve, being in close contact with the gastrointestinal tract, has the ability to regulate mood and the immune system andmay be another possible therapeutic modality[95,96].

Microglia-related pathways are also found to be related to the pathogenesis of AD based on emerging genetic and transcriptomic studies[97-101]. In the very early stages of the disease, microglia are active in synaptic pruning and in the regulation of neuroplasticity[102,103]. In the advanced stages, reactive microglia and astrocytes engulf amyloid plaques and secrete some pro-inflammatory cytokines. The recent observations that the blockade of PD-1 immune checkpoint decreases the pathology of AD and improves memory in mouse models of AD are promising and inspiring for the future [104-106]. New opportunities in the treatment of AD will arise with more studies, leading to better understanding of the role of microglial dysfunction as related to immunity, synaptic prunning, and neuroplasticity[104-109].

The early studies targeting mitochondria and bioenergetics as related to glucose hypometabolism of the brain in AD have shown promise in preclinical stages, but have not been successful in clinical trials[110,111]. However, this is still an important area of investigation aiming to develop new treatment measures.

**CONCLUSION**

It is accepted that there is need for new treatment modalities and effective combinations of these modalities. A foundation for effective approaches seems to be only possible with better understanding of the pathophysiology in relation to the stages of the disease and accurate follow-up of the disease with sensitive and comprehensive biomarkers. Using different biomarkers related to different aspects and stages of the disease will foster more plausible therapeutic strategies and assessment of outcomes.

While performing trials based on different therapeutic modalities, it will continue to be important to give careful attention to the relationships among cells within the brain and to the relationships between the brain and other organ systems.

**ACKNOWLEDGEMENT**

I specially thank Dr. Jeffrey Ehmsen, MD, PhD, a postdoctoral fellow at Johns Hopkins University, for his careful language editing.

**REFERENCES**

1 The industry shift to anti-tau therapies to treat Alzheimer’s. Available from: https://www.pharmaceutical-technology.com/comment/anti-tau-immunotherapies-to-treat-alzheimers/

2 **Howard R**, McShane R, Lindesay J, Ritchie C, Baldwin A, Barber R, Burns A, Dening T, Findlay D, Holmes C, Hughes A, Jacoby R, Jones R, Jones R, McKeith I, Macharouthu A, O'Brien J, Passmore P, Sheehan B, Juszczak E, Katona C, Hills R, Knapp M, Ballard C, Brown R, Banerjee S, Onions C, Griffin M, Adams J, Gray R, Johnson T, Bentham P, Phillips P. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med* 2012; **366**: 893-903 [PMID: 22397651 DOI: 10.1056/NEJMoa1106668]

3 **Grossberg GT**, Manes F, Allegri RF, Gutiérrez-Robledo LM, Gloger S, Xie L, Jia XD, Pejović V, Miller ML, Perhach JL, Graham SM. The safety, tolerability, and efficacy of once-daily memantine (28 mg): a multinational, randomized, double-blind, placebo-controlled trial in patients with moderate-to-severe Alzheimer's disease taking cholinesterase inhibitors. *CNS Drugs* 2013; **27**: 469-478 [PMID: 23733403 DOI: 10.1007/s40263-013-0077-7]

4 **Xing SH**, Zhu CX, Zhang R, An L. Huperzine a in the treatment of Alzheimer's disease and vascular dementia: a meta-analysis. *Evid Based Complement Alternat Med* 2014; **2014**: 363985 [PMID: 24639880 DOI: 10.1155/2014/363985]

5 **Littlejohns TJ**, Henley WE, Lang IA, Annweiler C, Beauchet O, Chaves PH, Fried L, Kestenbaum BR, Kuller LH, Langa KM, Lopez OL, Kos K, Soni M, Llewellyn DJ. Vitamin D and the risk of dementia and Alzheimer disease. *Neurology* 2014; **83**: 920-928 [PMID: 25098535 DOI: 10.1212/WNL.0000000000000755]

6 **Gupta PP**, Pandey RD, Jha D, Shrivastav V, Kumar S. Role of traditional nonsteroidal anti-inflammatory drugs in Alzheimer's disease: a meta-analysis of randomized clinical trials. *Am J Alzheimers Dis Other Demen* 2015; **30**: 178-182 [PMID: 25024454 DOI: 10.1177/1533317514542644]

7 **Lee LK**, Shahar S, Chin AV, Yusoff NA. Docosahexaenoic acid-concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI): a 12-month randomised, double-blind, placebo-controlled trial. *Psychopharmacology (Berl)* 2013; **225**: 605-612 [PMID: 22932777 DOI: 10.1007/s00213-012-2848-0]

8 **Bo Y**, Zhang X, Wang Y, You J, Cui H, Zhu Y, Pang W, Liu W, Jiang Y, Lu Q. The n-3 Polyunsaturated Fatty Acids Supplementation Improved the Cognitive Function in the Chinese Elderly with Mild Cognitive Impairment: A Double-Blind Randomized Controlled Trial. *Nutrients* 2017; **9** [PMID: 28075381 DOI: 10.3390/nu9010054]

9 **Bateman RJ**, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, Marcus DS, Cairns NJ, Xie X, Blazey TM, Holtzman DM, Santacruz A, Buckles V, Oliver A, Moulder K, Aisen PS, Ghetti B, Klunk WE, McDade E, Martins RN, Masters CL, Mayeux R, Ringman JM, Rossor MN, Schofield PR, Sperling RA, Salloway S, Morris JC; Dominantly Inherited Alzheimer Network. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med* 2012; **367**: 795-804 [PMID: 22784036 DOI: 10.1056/NEJMoa1202753]

10 **Tarassishin L**, Yin YI, Bassit B, Li YM. Processing of Notch and amyloid precursor protein by gamma-secretase is spatially distinct. *Proc Natl Acad Sci U S A* 2004; **101**: 17050-17055 [PMID: 15563588 DOI: 10.1073/pnas.0408007101]

11 **Klaver DW**, Wilce MC, Cui H, Hung AC, Gasperini R, Foa L, Small DH. Is BACE1 a suitable therapeutic target for the treatment of Alzheimer's disease? Current strategies and future directions. *Biol Chem* 2010; **391**: 849-859 [PMID: 20731541 DOI: 10.1515/BC.2010.089]

12 **Abramov E**, Dolev I, Fogel H, Ciccotosto GD, Ruff E, Slutsky I. Amyloid-beta as a positive endogenous regulator of release probability at hippocampal synapses. *Nat Neurosci* 2009; **12**: 1567-1576 [PMID: 19935655 DOI: 10.1038/nn.2433]

13 **Kennedy ME**, Stamford AW, Chen X, Cox K, Cumming JN, Dockendorf MF, Egan M, Ereshefsky L, Hodgson RA, Hyde LA, Jhee S, Kleijn HJ, Kuvelkar R, Li W, Mattson BA, Mei H, Palcza J, Scott JD, Tanen M, Troyer MD, Tseng JL, Stone JA, Parker EM, Forman MS. The BACE1 inhibitor verubecestat (MK-8931) reduces CNS β-amyloid in animal models and in Alzheimer's disease patients. *Sci Transl Med* 2016; **8**: 363ra150 [PMID: 27807285 DOI: 10.1126/scitranslmed.aad9704]

14 **Gilman S**, Koller M, Black RS, Jenkins L, Griffith SG, Fox NC, Eisner L, Kirby L, Rovira MB, Forette F, Orgogozo JM; AN1792(QS-21)-201 Study Team. Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. *Neurology* 2005; **64**: 1553-1562 [PMID: 15883316 DOI: 10.1212/01.WNL.0000159740.16984.3C]

15 **Bayer AJ**, Bullock R, Jones RW, Wilkinson D, Paterson KR, Jenkins L, Millais SB, Donoghue S. Evaluation of the safety and immunogenicity of synthetic Abeta42 (AN1792) in patients with AD. *Neurology* 2005; **64**: 94-101 [PMID: 15642910 DOI: 10.1212/01.WNL.0000148604.77591.67]

16 **Holmes C**, Boche D, Wilkinson D, Yadegarfar G, Hopkins V, Bayer A, Jones RW, Bullock R, Love S, Neal JW, Zotova E, Nicoll JA. Long-term effects of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial. *Lancet* 2008; **372**: 216-223 [PMID: 18640458 DOI: 10.1016/S0140-6736(08)61075-2]

17 **Laskowitz DT**, Kolls BJ. A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. *Neurology* 2010; **74**: 2026; author reply 2026-2026; author reply 2027 [PMID: 20548049 DOI: 10.1212/WNL.0b013e3181e03844]

18 **Salloway S**, Sperling R, Gilman S, Fox NC, Blennow K, Raskind M, Sabbagh M, Honig LS, Doody R, van Dyck CH, Mulnard R, Barakos J, Gregg KM, Liu E, Lieberburg I, Schenk D, Black R, Grundman M; Bapineuzumab 201 Clinical Trial Investigators. A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. *Neurology* 2009; **73**: 2061-2070 [PMID: 19923550 DOI: 10.1212/WNL.0b013e3181c67808]

19 **Ultsch M**, Li B, Maurer T, Mathieu M, Adolfsson O, Muhs A, Pfeifer A, Pihlgren M, Bainbridge TW, Reichelt M, Ernst JA, Eigenbrot C, Fuh G, Atwal JK, Watts RJ, Wang W. Structure of Crenezumab Complex with Aβ Shows Loss of β-Hairpin. *Sci Rep* 2016; **6**: 39374 [PMID: 27996029 DOI: 10.1038/srep39374]

20 **Bouter Y**, Lopez Noguerola JS, Tucholla P, Crespi GA, Parker MW, Wiltfang J, Miles LA, Bayer TA. Abeta targets of the biosimilar antibodies of Bapineuzumab, Crenezumab, Solanezumab in comparison to an antibody against N‑truncated Abeta in sporadic Alzheimer disease cases and mouse models. *Acta Neuropathol* 2015; **130**: 713-729 [PMID: 26467270 DOI: 10.1007/s00401-015-1489-x]

21 **The Lancet Neurology**. Solanezumab: too late in mild Alzheimer's disease? *Lancet Neurol* 2017; **16**: 97 [PMID: 28102152 DOI: 10.1016/S1474-4422(16)30395-7]

22 **Gandy S**, Sano M. Alzheimer disease: Solanezumab-prospects for meaningful interventions in AD? *Nat Rev Neurol* 2015; **11**: 669-670 [PMID: 26526537 DOI: 10.1038/nrneurol.2015.218]

23 **Landen JW**, Zhao Q, Cohen S, Borrie M, Woodward M, Billing CB Jr, Bales K, Alvey C, McCush F, Yang J, Kupiec JW, Bednar MM. Safety and pharmacology of a single intravenous dose of ponezumab in subjects with mild-to-moderate Alzheimer disease: a phase I, randomized, placebo-controlled, double-blind, dose-escalation study. *Clin Neuropharmacol* 2013; **36**: 14-23 [PMID: 23334070 DOI: 10.1097/WNF.0b013e31827db49b]

24 **Burstein AH**, Zhao Q, Ross J, Styren S, Landen JW, Ma WW, McCush F, Alvey C, Kupiec JW, Bednar MM. Safety and pharmacology of ponezumab (PF-04360365) after a single 10-minute intravenous infusion in subjects with mild to moderate Alzheimer disease. *Clin Neuropharmacol* 2013; **36**: 8-13 [PMID: 23334069 DOI: 10.1097/WNF.0b013e318279bcfa]

25 **La Porte SL**, Bollini SS, Lanz TA, Abdiche YN, Rusnak AS, Ho WH, Kobayashi D, Harrabi O, Pappas D, Mina EW, Milici AJ, Kawabe TT, Bales K, Lin JC, Pons J. Structural basis of C-terminal β-amyloid peptide binding by the antibody ponezumab for the treatment of Alzheimer's disease. *J Mol Biol* 2012; **421**: 525-536 [PMID: 22197375 DOI: 10.1016/j.jmb.2011.11.047]

26 **Sevigny J**, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, Dunstan R, Salloway S, Chen T, Ling Y, O'Gorman J, Qian F, Arastu M, Li M, Chollate S, Brennan MS, Quintero-Monzon O, Scannevin RH, Arnold HM, Engber T, Rhodes K, Ferrero J, Hang Y, Mikulskis A, Grimm J, Hock C, Nitsch RM, Sandrock A. Addendum: The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature* 2017; **546**: 564 [PMID: 28640269 DOI: 10.1038/nature22809]

27 **Sevigny J**, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, Dunstan R, Salloway S, Chen T, Ling Y, O'Gorman J, Qian F, Arastu M, Li M, Chollate S, Brennan MS, Quintero-Monzon O, Scannevin RH, Arnold HM, Engber T, Rhodes K, Ferrero J, Hang Y, Mikulskis A, Grimm J, Hock C, Nitsch RM, Sandrock A. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature* 2016; **537**: 50-56 [PMID: 27582220 DOI: 10.1038/nature19323]

28 **Patel KR**. Biogen's aducanumab raises hope that Alzheimer's can be treated at its source. *Manag Care* 2015; **24**: 19 [PMID: 26182718]

29 **Karran E**. Recent trial shows that solanezumab has disease modifying effects. *BMJ* 2015; **351**: h4528 [PMID: 26318507 DOI: 10.1136/bmj.h4528]

30 **Siemers ER**, Sundell KL, Carlson C, Case M, Sethuraman G, Liu-Seifert H, Dowsett SA, Pontecorvo MJ, Dean RA, Demattos R. Phase 3 solanezumab trials: Secondary outcomes in mild Alzheimer's disease patients. *Alzheimers Dement* 2016; **12**: 110-120 [PMID: 26238576 DOI: 10.1016/j.jalz.2015.06.1893]

31 **Karran E**, Mercken M, De Strooper B. The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. *Nat Rev Drug Discov* 2011; **10**: 698-712 [PMID: 21852788 DOI: 10.1038/nrd3505]

32 **Jacobsen H**, Ozmen L, Caruso A, Narquizian R, Hilpert H, Jacobsen B, Terwel D, Tanghe A, Bohrmann B. Combined treatment with a BACE inhibitor and anti-Aβ antibody gantenerumab enhances amyloid reduction in APPLondon mice. *J Neurosci* 2014; **34**: 11621-11630 [PMID: 25164658 DOI: 10.1523/JNEUROSCI.1405-14.2014]

33 **Barrera-Ocampo A**, Lopera F. Amyloid-beta immunotherapy: the hope for Alzheimer disease? *Colomb Med (Cali)* 2016; **47**: 203-212 [PMID: 28293044]

34 **Brier MR**, Gordon B, Friedrichsen K, McCarthy J, Stern A, Christensen J, Owen C, Aldea P, Su Y, Hassenstab J, Cairns NJ, Holtzman DM, Fagan AM, Morris JC, Benzinger TL, Ances BM. Tau and Aβ imaging, CSF measures, and cognition in Alzheimer's disease. *Sci Transl Med* 2016; **8**: 338ra66 [PMID: 27169802 DOI: 10.1126/scitranslmed.aaf2362]

35 **Gauthier S**, Feldman HH, Schneider LS, Wilcock GK, Frisoni GB, Hardlund JH, Moebius HJ, Bentham P, Kook KA, Wischik DJ, Schelter BO, Davis CS, Staff RT, Bracoud L, Shamsi K, Storey JM, Harrington CR, Wischik CM. Efficacy and safety of tau-aggregation inhibitor therapy in patients with mild or moderate Alzheimer's disease: a randomised, controlled, double-blind, parallel-arm, phase 3 trial. *Lancet* 2016; **388**: 2873-2884 [PMID: 27863809 DOI: 10.1016/S0140-6736(16)31275-2]

36 **Li C**, Götz J. Tau-based therapies in neurodegeneration: opportunities and challenges. *Nat Rev Drug Discov* 2017; **16**: 863-883 [PMID: 28983098 DOI: 10.1038/nrd.2017.155]

37 **Novak P**, Schmidt R, Kontsekova E, Zilka N, Kovacech B, Skrabana R, Vince-Kazmerova Z, Katina S, Fialova L, Prcina M, Parrak V, Dal-Bianco P, Brunner M, Staffen W, Rainer M, Ondrus M, Ropele S, Smisek M, Sivak R, Winblad B, Novak M. Safety and immunogenicity of the tau vaccine AADvac1 in patients with Alzheimer's disease: a randomised, double-blind, placebo-controlled, phase 1 trial. *Lancet Neurol* 2017; **16**: 123-134 [PMID: 27955995 DOI: 10.1016/S1474-4422(16)30331-3]

38 **van der Kant R**, Langness VF, Herrera CM, Williams DA, Fong LK, Leestemaker Y, Steenvoorden E, Rynearson KD, Brouwers JF, Helms JB, Ovaa H, Giera M, Wagner SL, Bang AG, Goldstein LSB. Cholesterol Metabolism Is a Druggable Axis that Independently Regulates Tau and Amyloid-β in iPSC-Derived Alzheimer's Disease Neurons. *Cell Stem Cell* 2019; **24**: 363-375.e9 [PMID: 30686764 DOI: 10.1016/j.stem.2018.12.013]

39 **Roy DS**, Arons A, Mitchell TI, Pignatelli M, Ryan TJ, Tonegawa S. Memory retrieval by activating engram cells in mouse models of early Alzheimer's disease. *Nature* 2016; **531**: 508-512 [PMID: 26982728 DOI: 10.1038/nature17172]

40 **Gillespie AK**, Jones EA, Lin YH, Karlsson MP, Kay K, Yoon SY, Tong LM, Nova P, Carr JS, Frank LM, Huang Y. Apolipoprotein E4 Causes Age-Dependent Disruption of Slow Gamma Oscillations during Hippocampal Sharp-Wave Ripples. *Neuron* 2016; **90**: 740-751 [PMID: 27161522 DOI: 10.1016/j.neuron.2016.04.009]

41 **Knoferle J**, Yoon SY, Walker D, Leung L, Gillespie AK, Tong LM, Bien-Ly N, Huang Y. Apolipoprotein E4 produced in GABAergic interneurons causes learning and memory deficits in mice. *J Neurosci* 2014; **34**: 14069-14078 [PMID: 25319703 DOI: 10.1523/JNEUROSCI.2281-14.2014]

42 **Iaccarino HF**, Singer AC, Martorell AJ, Rudenko A, Gao F, Gillingham TZ, Mathys H, Seo J, Kritskiy O, Abdurrob F, Adaikkan C, Canter RG, Rueda R, Brown EN, Boyden ES, Tsai LH. Gamma frequency entrainment attenuates amyloid load and modifies microglia. *Nature* 2016; **540**: 230-235 [PMID: 27929004 DOI: 10.1038/nature20587]

43 **Oakley H**, Cole SL, Logan S, Maus E, Shao P, Craft J, Guillozet-Bongaarts A, Ohno M, Disterhoft J, Van Eldik L, Berry R, Vassar R. Intraneuronal beta-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: potential factors in amyloid plaque formation. *J Neurosci* 2006; **26**: 10129-10140 [PMID: 17021169 DOI: 10.1523/JNEUROSCI.1202-06.2006]

44 **Tong LM**, Djukic B, Arnold C, Gillespie AK, Yoon SY, Wang MM, Zhang O, Knoferle J, Rubenstein JL, Alvarez-Buylla A, Huang Y. Inhibitory interneuron progenitor transplantation restores normal learning and memory in ApoE4 knock-in mice without or with Aβ accumulation. *J Neurosci* 2014; **34**: 9506-9515 [PMID: 25031394 DOI: 10.1523/JNEUROSCI.0693-14.2014]

45 **Martinez-Losa M**, Tracy TE, Ma K, Verret L, Clemente-Perez A, Khan AS, Cobos I, Ho K, Gan L, Mucke L, Alvarez-Dolado M, Palop JJ. Nav1.1-Overexpressing Interneuron Transplants Restore Brain Rhythms and Cognition in a Mouse Model of Alzheimer's Disease. *Neuron* 2018; **98**: 75-89.e5 [PMID: 29551491 DOI: 10.1016/j.neuron.2018.02.029]

46 **Canter RG**, Penney J, Tsai LH. The road to restoring neural circuits for the treatment of Alzheimer's disease. *Nature* 2016; **539**: 187-196 [PMID: 27830780 DOI: 10.1038/nature20412]

47 **Kuhn J**, Hardenacke K, Lenartz D, Gruendler T, Ullsperger M, Bartsch C, Mai JK, Zilles K, Bauer A, Matusch A, Schulz RJ, Noreik M, Bührle CP, Maintz D, Woopen C, Häussermann P, Hellmich M, Klosterkötter J, Wiltfang J, Maarouf M, Freund HJ, Sturm V. Deep brain stimulation of the nucleus basalis of Meynert in Alzheimer's dementia. *Mol Psychiatry* 2015; **20**: 353-360 [PMID: 24798585 DOI: 10.1038/mp.2014.32]

48 **Laxton AW**, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, Wherrett J, Naglie G, Hamani C, Smith GS, Lozano AM. A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. *Ann Neurol* 2010; **68**: 521-534 [PMID: 20687206 DOI: 10.1002/ana.22089]

49 **Sankar T**, Chakravarty MM, Bescos A, Lara M, Obuchi T, Laxton AW, McAndrews MP, Tang-Wai DF, Workman CI, Smith GS, Lozano AM. Deep Brain Stimulation Influences Brain Structure in Alzheimer's Disease. *Brain Stimul* 2015; **8**: 645-654 [PMID: 25814404 DOI: 10.1016/j.brs.2014.11.020]

50 **Fischer A**, Sananbenesi F, Wang X, Dobbin M, Tsai LH. Recovery of learning and memory is associated with chromatin remodelling. *Nature* 2007; **447**: 178-182 [PMID: 17468743 DOI: 10.1038/nature05772]

51 **Colgin LL**, Denninger T, Fyhn M, Hafting T, Bonnevie T, Jensen O, Moser MB, Moser EI. Frequency of gamma oscillations routes flow of information in the hippocampus. *Nature* 2009; **462**: 353-357 [PMID: 19924214 DOI: 10.1038/nature08573]

52 **Colgin LL**. Rhythms of the hippocampal network. *Nat Rev Neurosci* 2016; **17**: 239-249 [PMID: 26961163 DOI: 10.1038/nrn.2016.21]

53 **Zheng C**, Bieri KW, Hwaun E, Colgin LL. Fast Gamma Rhythms in the Hippocampus Promote Encoding of Novel Object-Place Pairings. *eNeuro* 2016; **3** [PMID: 27257621 DOI: 10.1523/ENEURO.0001-16.2016]

54 **Bieri KW**, Bobbitt KN, Colgin LL. Slow and fast γ rhythms coordinate different spatial coding modes in hippocampal place cells. *Neuron* 2014; **82**: 670-681 [PMID: 24746420 DOI: 10.1016/j.neuron.2014.03.013]

55 **Nakazawa K**, Quirk MC, Chitwood RA, Watanabe M, Yeckel MF, Sun LD, Kato A, Carr CA, Johnston D, Wilson MA, Tonegawa S. Requirement for hippocampal CA3 NMDA receptors in associative memory recall. *Science* 2002; **297**: 211-218 [PMID: 12040087 DOI: 10.1126/science.1071795]

56 **Carr MF**, Karlsson MP, Frank LM. Transient slow gamma synchrony underlies hippocampal memory replay. *Neuron* 2012; **75**: 700-713 [PMID: 22920260 DOI: 10.1016/j.neuron.2012.06.014]

57 **Buzsáki G**. Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory and planning. *Hippocampus* 2015; **25**: 1073-1188 [PMID: 26135716 DOI: 10.1002/hipo.22488]

58 **Duncan T**, Valenzuela M. Alzheimer's disease, dementia, and stem cell therapy. *Stem Cell Res Ther* 2017; **8**: 111 [PMID: 28494803 DOI: 10.1186/s13287-017-0567-5]

59 **Donovan MH**, Yazdani U, Norris RD, Games D, German DC, Eisch AJ. Decreased adult hippocampal neurogenesis in the PDAPP mouse model of Alzheimer's disease. *J Comp Neurol* 2006; **495**: 70-83 [PMID: 16432899 DOI: 10.1002/cne.20840]

60 **López-Toledano MA**, Shelanski ML. Increased neurogenesis in young transgenic mice overexpressing human APP(Sw, Ind). *J Alzheimers Dis* 2007; **12**: 229-240 [PMID: 18057556]

61 **Alipour M**, Nabavi SM, Arab L, Vosough M, Pakdaman H, Ehsani E, Shahpasand K. Stem cell therapy in Alzheimer's disease: possible benefits and limiting drawbacks. *Mol Biol Rep* 2019; **46**: 1425-1446 [PMID: 30565076 DOI: 10.1007/s11033-018-4499-7]

62 **Ross CA**, Akimov SS. Human-induced pluripotent stem cells: potential for neurodegenerative diseases. *Hum Mol Genet* 2014; **23**: R17-R26 [PMID: 24824217 DOI: 10.1093/hmg/ddu204]

63 **Fujioka K**, Hanada S, Inoue Y, Sato K, Hirakuri K, Shiraishi K, Kanaya F, Ikeda K, Usui R, Yamamoto K, Kim SU, Manome Y. Effects of silica and titanium oxide particles on a human neural stem cell line: morphology, mitochondrial activity, and gene expression of differentiation markers. *Int J Mol Sci* 2014; **15**: 11742-11759 [PMID: 24992594 DOI: 10.3390/ijms150711742]

64 **Eckert A**, Huang L, Gonzalez R, Kim HS, Hamblin MH, Lee JP. Bystander Effect Fuels Human Induced Pluripotent Stem Cell-Derived Neural Stem Cells to Quickly Attenuate Early Stage Neurological Deficits After Stroke. *Stem Cells Transl Med* 2015; **4**: 841-851 [PMID: 26025980 DOI: 10.5966/sctm.2014-0184]

65 **Takamatsu K**, Ikeda T, Haruta M, Matsumura K, Ogi Y, Nakagata N, Uchino M, Ando Y, Nishimura Y, Senju S. Degradation of amyloid beta by human induced pluripotent stem cell-derived macrophages expressing Neprilysin-2. *Stem Cell Res* 2014; **13**: 442-453 [PMID: 25460605 DOI: 10.1016/j.scr.2014.10.001]

66 **Cha MY**, Kwon YW, Ahn HS, Jeong H, Lee YY, Moon M, Baik SH, Kim DK, Song H, Yi EC, Hwang D, Kim HS, Mook-Jung I. Protein-Induced Pluripotent Stem Cells Ameliorate Cognitive Dysfunction and Reduce Aβ Deposition in a Mouse Model of Alzheimer's Disease. *Stem Cells Transl Med* 2017; **6**: 293-305 [PMID: 28170178 DOI: 10.5966/sctm.2016-0081]

67 **Bali P**, Lahiri DK, Banik A, Nehru B, Anand A. Potential for Stem Cells Therapy in Alzheimer's Disease: Do Neurotrophic Factors Play Critical Role? *Curr Alzheimer Res* 2017; **14**: 208-220 [PMID: 26971940]

68 **Cui Y**, Ma S, Zhang C, Cao W, Liu M, Li D, Lv P, Xing Q, Qu R, Yao N, Yang B, Guan F. Human umbilical cord mesenchymal stem cells transplantation improves cognitive function in Alzheimer's disease mice by decreasing oxidative stress and promoting hippocampal neurogenesis. *Behav Brain Res* 2017; **320**: 291-301 [PMID: 28007537 DOI: 10.1016/j.bbr.2016.12.021]

69 **Garcia KO**, Ornellas FL, Martin PK, Patti CL, Mello LE, Frussa-Filho R, Han SW, Longo BM. Therapeutic effects of the transplantation of VEGF overexpressing bone marrow mesenchymal stem cells in the hippocampus of murine model of Alzheimer's disease. *Front Aging Neurosci* 2014; **6**: 30 [PMID: 24639647 DOI: 10.3389/fnagi.2014.00030]

70 **Kim S**, Chang KA, Kim Ja, Park HG, Ra JC, Kim HS, Suh YH. The preventive and therapeutic effects of intravenous human adipose-derived stem cells in Alzheimer's disease mice. *PLoS One* 2012; **7**: e45757 [PMID: 23049854 DOI: 10.1371/journal.pone.0045757]

71 **Kim KS**, Kim HS, Park JM, Kim HW, Park MK, Lee HS, Lim DS, Lee TH, Chopp M, Moon J. Long-term immunomodulatory effect of amniotic stem cells in an Alzheimer's disease model. *Neurobiol Aging* 2013; **34**: 2408-2420 [PMID: 23623603 DOI: 10.1016/j.neurobiolaging.2013.03.029]

72 **Kim DH**, Lee D, Chang EH, Kim JH, Hwang JW, Kim JY, Kyung JW, Kim SH, Oh JS, Shim SM, Na DL, Oh W, Chang JW. GDF-15 secreted from human umbilical cord blood mesenchymal stem cells delivered through the cerebrospinal fluid promotes hippocampal neurogenesis and synaptic activity in an Alzheimer's disease model. *Stem Cells Dev* 2015; **24**: 2378-2390 [PMID: 26154268 DOI: 10.1089/scd.2014.0487]

73 **Lee HJ**, Lee JK, Lee H, Carter JE, Chang JW, Oh W, Yang YS, Suh JG, Lee BH, Jin HK, Bae JS. Human umbilical cord blood-derived mesenchymal stem cells improve neuropathology and cognitive impairment in an Alzheimer's disease mouse model through modulation of neuroinflammation. *Neurobiol Aging* 2012; **33**: 588-602 [PMID: 20471717 DOI: 10.1016/j.neurobiolaging.2010.03.024]

74 **Li W**, Li K, Gao J, Yang Z. Autophagy is required for human umbilical cord mesenchymal stem cells to improve spatial working memory in APP/PS1 transgenic mouse model. *Stem Cell Res Ther* 2018; **9**: 9 [PMID: 29335016 DOI: 10.1186/s13287-017-0756-2]

75 **Burke RM**, Norman TA, Haydar TF, Slack BE, Leeman SE, Blusztajn JK, Mellott TJ. BMP9 ameliorates amyloidosis and the cholinergic defect in a mouse model of Alzheimer's disease. *Proc Natl Acad Sci U S A* 2013; **110**: 19567-19572 [PMID: 24218590 DOI: 10.1073/pnas.1319297110]

76 **Njie eG**, Kantorovich S, Astary GW, Green C, Zheng T, Semple-Rowland SL, Steindler DA, Sarntinoranont M, Streit WJ, Borchelt DR. A preclinical assessment of neural stem cells as delivery vehicles for anti-amyloid therapeutics. *PLoS One* 2012; **7**: e34097 [PMID: 22496779 DOI: 10.1371/journal.pone.0034097]

77 **Bianco P**, Robey PG, Simmons PJ. Mesenchymal stem cells: revisiting history, concepts, and assays. *Cell Stem Cell* 2008; **2**: 313-319 [PMID: 18397751 DOI: 10.1016/j.stem.2008.03.002]

78 **Alvarez-Erviti L**, Seow Y, Yin H, Betts C, Lakhal S, Wood MJ. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. *Nat Biotechnol* 2011; **29**: 341-345 [PMID: 21423189 DOI: 10.1038/nbt.1807]

79 **Cassar P,** Blundell R. The use of umbilical stem cells. *OJPathology* 2016; **6**: 41 [DOI: 10.4236/ojpathology.2016.61007]

80 **Xin H**, Li Y, Buller B, Katakowski M, Zhang Y, Wang X, Shang X, Zhang ZG, Chopp M. Exosome-mediated transfer of miR-133b from multipotent mesenchymal stromal cells to neural cells contributes to neurite outgrowth. *Stem Cells* 2012; **30**: 1556-1564 [PMID: 22605481 DOI: 10.1002/stem.1129]

81 **Marei HE**, Casalbore P, Althani A, Coccè V, Cenciarelli C, Alessandri G, Brini AT, Parati E, Bondiolotti G, Pessina A. Human Olfactory Bulb Neural Stem Cells (Hu-OBNSCs) Can Be Loaded with Paclitaxel and Used to Inhibit Glioblastoma Cell Growth. *Pharmaceutics* 2019; **11** [PMID: 30669623 DOI: 10.3390/pharmaceutics11010045]

82 **Guan J**, Zhu Z, Zhao RC, Xiao Z, Wu C, Han Q, Chen L, Tong W, Zhang J, Han Q, Gao J, Feng M, Bao X, Dai J, Wang R. Transplantation of human mesenchymal stem cells loaded on collagen scaffolds for the treatment of traumatic brain injury in rats. *Biomaterials* 2013; **34**: 5937-5946 [PMID: 23664090 DOI: 10.1016/j.biomaterials.2013.04.047]

83 **Carlson AL**, Bennett NK, Francis NL, Halikere A, Clarke S, Moore JC, Hart RP, Paradiso K, Wernig M, Kohn J, Pang ZP, Moghe PV. Generation and transplantation of reprogrammed human neurons in the brain using 3D microtopographic scaffolds. *Nat Commun* 2016; **7**: 10862 [PMID: 26983594 DOI: 10.1038/ncomms10862]

84 **Spuch C**, Antequera D, Portero A, Orive G, Hernández RM, Molina JA, Bermejo-Pareja F, Pedraz JL, Carro E. The effect of encapsulated VEGF-secreting cells on brain amyloid load and behavioral impairment in a mouse model of Alzheimer's disease. *Biomaterials* 2010; **31**: 5608-5618 [PMID: 20430437 DOI: 10.1016/j.biomaterials.2010.03.042]

85 **Garcia P**, Youssef I, Utvik JK, Florent-Béchard S, Barthélémy V, Malaplate-Armand C, Kriem B, Stenger C, Koziel V, Olivier JL, Escanye MC, Hanse M, Allouche A, Desbène C, Yen FT, Bjerkvig R, Oster T, Niclou SP, Pillot T. Ciliary neurotrophic factor cell-based delivery prevents synaptic impairment and improves memory in mouse models of Alzheimer's disease. *J Neurosci* 2010; **30**: 7516-7527 [PMID: 20519526 DOI: 10.1523/JNEUROSCI.4182-09.2010]

86 **Eriksdotter-Jönhagen M**, Linderoth B, Lind G, Aladellie L, Almkvist O, Andreasen N, Blennow K, Bogdanovic N, Jelic V, Kadir A, Nordberg A, Sundström E, Wahlund LO, Wall A, Wiberg M, Winblad B, Seiger A, Almqvist P, Wahlberg L. Encapsulated cell biodelivery of nerve growth factor to the Basal forebrain in patients with Alzheimer's disease. *Dement Geriatr Cogn Disord* 2012; **33**: 18-28 [PMID: 22377499 DOI: 10.1159/000336051]

87 **Eyjolfsdottir H**, Eriksdotter M, Linderoth B, Lind G, Juliusson B, Kusk P, Almkvist O, Andreasen N, Blennow K, Ferreira D, Westman E, Nennesmo I, Karami A, Darreh-Shori T, Kadir A, Nordberg A, Sundström E, Wahlund LO, Wall A, Wiberg M, Winblad B, Seiger Å, Wahlberg L, Almqvist P. Targeted delivery of nerve growth factor to the cholinergic basal forebrain of Alzheimer's disease patients: application of a second-generation encapsulated cell biodelivery device. *Alzheimers Res Ther* 2016; **8**: 30 [PMID: 27389402 DOI: 10.1186/s13195-016-0195-9]

88 **Gu G**, Zhang W, Li M, Ni J, Wang P. Transplantation of NSC-derived cholinergic neuron-like cells improves cognitive function in APP/PS1 transgenic mice. *Neuroscience* 2015; **291**: 81-92 [PMID: 25681520 DOI: 10.1016/j.neuroscience.2015.01.073]

89 **Liedmann A**, Frech S, Morgan PJ, Rolfs A, Frech MJ. Differentiation of human neural progenitor cells in functionalized hydrogel matrices. *Biores Open Access* 2012; **1**: 16-24 [PMID: 23515105 DOI: 10.1089/biores.2012.0209]

90 **Tuszynski MH**, Yang JH, Barba D, U HS, Bakay RA, Pay MM, Masliah E, Conner JM, Kobalka P, Roy S, Nagahara AH. Nerve Growth Factor Gene Therapy: Activation of Neuronal Responses in Alzheimer Disease. *JAMA Neurol* 2015; **72**: 1139-1147 [PMID: 26302439 DOI: 10.1001/jamaneurol.2015.1807]

91 **Kim HJ**, Seo SW, Chang JW, Lee JI, Kim CH, Chin J, Choi SJ, Kwon H, Yun HJ, Lee JM, Kim ST, Choe YS, Lee KH, Na DL. Stereotactic brain injection of human umbilical cord blood mesenchymal stem cells in patients with Alzheimer's disease dementia: A phase 1 clinical trial. *Alzheimers Dement (N Y)* 2015; **1**: 95-102 [PMID: 29854930 DOI: 10.1016/j.trci.2015.06.007]

92 **Du X**, Wang X, Geng M. Alzheimer's disease hypothesis and related therapies. *Transl Neurodegener* 2018; **7**: 2 [PMID: 29423193 DOI: 10.1186/s40035-018-0107-y]

93 **Mitchell RW**, On NH, Del Bigio MR, Miller DW, Hatch GM. Fatty acid transport protein expression in human brain and potential role in fatty acid transport across human brain microvessel endothelial cells. *J Neurochem* 2011; **117**: 735-746 [PMID: 21395585 DOI: 10.1111/j.1471-4159.2011.07245.x]

94 **Cattaneo A**, Cattane N, Galluzzi S, Provasi S, Lopizzo N, Festari C, Ferrari C, Guerra UP, Paghera B, Muscio C, Bianchetti A, Volta GD, Turla M, Cotelli MS, Gennuso M, Prelle A, Zanetti O, Lussignoli G, Mirabile D, Bellandi D, Gentile S, Belotti G, Villani D, Harach T, Bolmont T, Padovani A, Boccardi M, Frisoni GB; INDIA-FBP Group. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. *Neurobiol Aging* 2017; **49**: 60-68 [PMID: 27776263 DOI: 10.1016/j.neurobiolaging.2016.08.019]

95 **Das UN**. Vagus nerve stimulation, depression, and inflammation. *Neuropsychopharmacology* 2007; **32**: 2053-2054 [PMID: 17700515 DOI: 10.1038/sj.npp.1301286]

96 **Browning KN**, Verheijden S, Boeckxstaens GE. The Vagus Nerve in Appetite Regulation, Mood, and Intestinal Inflammation. *Gastroenterology* 2017; **152**: 730-744 [PMID: 27988382 DOI: 10.1053/j.gastro.2016.10.046]

97 **Zhang B**, Gaiteri C, Bodea LG, Wang Z, McElwee J, Podtelezhnikov AA, Zhang C, Xie T, Tran L, Dobrin R, Fluder E, Clurman B, Melquist S, Narayanan M, Suver C, Shah H, Mahajan M, Gillis T, Mysore J, MacDonald ME, Lamb JR, Bennett DA, Molony C, Stone DJ, Gudnason V, Myers AJ, Schadt EE, Neumann H, Zhu J, Emilsson V. Integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease. *Cell* 2013; **153**: 707-720 [PMID: 23622250 DOI: 10.1016/j.cell.2013.03.030]

98 **Guerreiro R**, Wojtas A, Bras J, Carrasquillo M, Rogaeva E, Majounie E, Cruchaga C, Sassi C, Kauwe JS, Younkin S, Hazrati L, Collinge J, Pocock J, Lashley T, Williams J, Lambert JC, Amouyel P, Goate A, Rademakers R, Morgan K, Powell J, St George-Hyslop P, Singleton A, Hardy J; Alzheimer Genetic Analysis Group. TREM2 variants in Alzheimer's disease. *N Engl J Med* 2013; **368**: 117-127 [PMID: 23150934 DOI: 10.1056/NEJMoa1211851]

99 **Song W**, Hooli B, Mullin K, Jin SC, Cella M, Ulland TK, Wang Y, Tanzi RE, Colonna M. Alzheimer's disease-associated TREM2 variants exhibit either decreased or increased ligand-dependent activation. *Alzheimers Dement* 2017; **13**: 381-387 [PMID: 27520774 DOI: 10.1016/j.jalz.2016.07.004]

100 **Colonna M**, Wang Y. TREM2 variants: new keys to decipher Alzheimer disease pathogenesis. *Nat Rev Neurosci* 2016; **17**: 201-207 [PMID: 26911435 DOI: 10.1038/nrn.2016.7]

101 **Bolós M**, Perea JR, Avila J. Alzheimer's disease as an inflammatory disease. *Biomol Concepts* 2017; **8**: 37-43 [PMID: 28231054 DOI: 10.1515/bmc-2016-0029]

102 **Hong S**, Dissing-Olesen L, Stevens B. New insights on the role of microglia in synaptic pruning in health and disease. *Curr Opin Neurobiol* 2016; **36**: 128-134 [PMID: 26745839 DOI: 10.1016/j.conb.2015.12.004]

103 **Paolicelli RC**, Bolasco G, Pagani F, Maggi L, Scianni M, Panzanelli P, Giustetto M, Ferreira TA, Guiducci E, Dumas L, Ragozzino D, Gross CT. Synaptic pruning by microglia is necessary for normal brain development. *Science* 2011; **333**: 1456-1458 [PMID: 21778362 DOI: 10.1126/science.1202529]

104 **Baruch K**, Deczkowska A, Rosenzweig N, Tsitsou-Kampeli A, Sharif AM, Matcovitch-Natan O, Kertser A, David E, Amit I, Schwartz M. PD-1 immune checkpoint blockade reduces pathology and improves memory in mouse models of Alzheimer's disease. *Nat Med* 2016; **22**: 135-137 [PMID: 26779813 DOI: 10.1038/nm.4022]

105 **Saresella M**, Calabrese E, Marventano I, Piancone F, Gatti A, Farina E, Alberoni M, Clerici M. A potential role for the PD1/PD-L1 pathway in the neuroinflammation of Alzheimer's disease. *Neurobiol Aging* 2012; **33**: 624.e11-624.e22 [PMID: 21514692 DOI: 10.1016/j.neurobiolaging.2011.03.004]

106 **Saresella M**, Calabrese E, Marventano I, Piancone F, Gatti A, Calvo MG, Nemni R, Clerici M. PD1 negative and PD1 positive CD4+ T regulatory cells in mild cognitive impairment and Alzheimer's disease. *J Alzheimers Dis* 2010; **21**: 927-938 [PMID: 20634592 DOI: 10.3233/JAD-2010-091696]

107 **Jevtic S**, Sengar AS, Salter MW, McLaurin J. The role of the immune system in Alzheimer disease: Etiology and treatment. *Ageing Res Rev* 2017; **40**: 84-94 [PMID: 28941639 DOI: 10.1016/j.arr.2017.08.005]

108 **McGeer PL**, McGeer EG. Targeting microglia for the treatment of Alzheimer's disease. *Expert Opin Ther Targets* 2015; **19**: 497-506 [PMID: 25435348 DOI: 10.1517/14728222.2014.988707]

109 **Salter MW**, Stevens B. Microglia emerge as central players in brain disease. *Nat Med* 2017; **23**: 1018-1027 [PMID: 28886007 DOI: 10.1038/nm.4397]

110 **Caldwell CC**, Yao J, Brinton RD. Targeting the prodromal stage of Alzheimer's disease: bioenergetic and mitochondrial opportunities. *Neurotherapeutics* 2015; **12**: 66-80 [PMID: 25534394 DOI: 10.1007/s13311-014-0324-8]

111 **Daulatzai MA**. Cerebral hypoperfusion and glucose hypometabolism: Key pathophysiological modulators promote neurodegeneration, cognitive impairment, and Alzheimer's disease. *J Neurosci Res* 2017; **95**: 943-972 [PMID: 27350397 DOI: 10.1002/jnr.23777]

**P-Reviewer:** Kim YB **S-Editor:** Dou Y **L-Editor:** A **E-Editor:** Wang J

**Specialty type:** Medicine, Research and Experimental

**Country of origin:** Turkey

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

Table 1 Potential treatments related to BACE1 and p-tau undergoing clinical trials

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Target** | **Drug** | **Study phase** | **Expected completion date** | **Results** |
| BACE1 | Lanabecestat | 2 | September 2019 |  |
|  | JNJ-54861911 | 2 | October 2022 |  |
|  | Elenbecestat | 3 | December 2020 |  |
|  | Verubecestat | 3 | March 2021 |  |
|  | LY450139 | 3 | Completed April 2011 | Not effective |
| P-tau | IONIS-MAPTRx | 1, 2 | February 2020 |  |
|  | JNJ-63733657 | 1 | February 2019 |  |
|  | RO7105705 | 2 | September 2022 |  |
|  | ABBV-8E12 | 2 | June 2021 |  |
|  | AADvac 1 | 2 | June 2019 |  |
|  | BIIB-092 | 2 | September 2020 |  |
|  | BIIB-080 | 1 | February 2020 |  |
|  | TPI-287 | 1 | Completed May 2017 |  |
|  | TRx0237 | 3 | February 2019 |  |
|  | LY3303560 | 1 | June 2019 |  |
|  | MTAU9937A | 2 | (-) Continuing |  |
|  | E2814 | 1 | (-) Continuing |  |

BACE1: β-site amyloid precursor protein cleaving enzyme 1; p-tau: hyperphosphorylated tau peptide.

Table 2 Current clinical trials on stem cells

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Clinical Trials. Gov identifier** | **Type of stem cell transplantation**  | **Study phase** | **Estimated number of participants** | **Status** |
| NCT02054208 | Intraventricular administration of hUCB-MSCs | 1/2a | 45 | Recruiting |
| NCT02672306 | UCMSCs | 1/2a | 16 | Active, not recruiting |
| NCT02833792 | Allogeneic hMSCs | 2a | 40 | Recruiting |
| NCT02600130 | Allogeneic hMSCs | 1 | 30 | Recruiting |
| NCT03117738 | Autologous adipose tissue derived MSCs | 1/2 | 60 | Recruiting |

UCB-MSCs:Umbilical cord blood-derived mesenchymal stem cells**;** UCMSC: Umbilical cord mesenchymal stem cells.