Treatment of Alzheimer’s disease
Top 20 Articles

Crest Premedia Solutions (P) Ltd
# Table of contents

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Section Titles</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Query</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>List of Data Sources and screening details for top 20 articles</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Search Strategies Used and List of key words</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>Rationale for selection of top 20 articles</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>Top 20 Articles</td>
<td>7-17</td>
</tr>
</tbody>
</table>
1. Query

Treatment of Alzheimer's disease

Databases searched: PubMed Central, SpringerLink, ScienceDirect
Limit: Human
Timeline: 2008 to 2012
2. List of Data Sources and screening details for top 20 articles:

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Data sources</th>
<th>Number of query related articles screened</th>
<th>Number of articles included in top 20 (selected from screened results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PubMed Central</td>
<td>222</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>SpringerLink</td>
<td>339</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>ScienceDirect</td>
<td>500</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>1061</strong></td>
<td><strong>20</strong></td>
</tr>
</tbody>
</table>
3. Search Strategies Used and List of key words

- Comprehensive understanding of all fundamental aspects related to the query viz., Alzheimer’s disease – mechanism, diagnosis and treatment
- After completion of this preliminary analysis based on the important facets recognized, query related keywords were identified
- Based on the combination of keywords selected data mining was carried out using authentic data resources
- Boolean search strings were used to search the articles

The list of combination of keywords that were used to answer the query is given below:

<table>
<thead>
<tr>
<th>Keywords</th>
<th>Acetyl Cholinesterase</th>
<th>Amyloid β-Plaque</th>
<th>immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s Disease</td>
<td>Beta Amyloid Deposition</td>
<td>Metal complex</td>
<td></td>
</tr>
<tr>
<td>Aggregation inhibitors</td>
<td>Biomarkers</td>
<td>Oxidative stress</td>
<td></td>
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<tr>
<td>Amyloid peptide precursors</td>
<td>Complication</td>
<td>Secretase Inhibitors</td>
<td></td>
</tr>
<tr>
<td>Amyloid β-Protein</td>
<td>Chelating agents</td>
<td>Tau protein</td>
<td></td>
</tr>
<tr>
<td>A beta Fibrilisation</td>
<td>Diagnosis</td>
<td>Treatment</td>
<td></td>
</tr>
</tbody>
</table>
4. Rationale for selection of top 20 articles

As per the focus of query topics are mainly divided into four segments: Disease Basic research, Mechanism, Diagnosis, and Treatment. Wherein, priority is given to recent information relevant to Alzheimer's disease treatment and amyloid Beta protein involved. The articles within each section of each segment have been arranged on the basis of year of publication (latest to oldest):

1. Disease Basic Research: Article 1 and 2 gives an overview on recent discoveries unleashing the factors responsible for cause of disease.
2. Mechanism: articles 3rd-6th, focuses on recent advancement in understanding of disease mechanism.
3. Diagnosis: 7th-10th articles provide insights on recent diagnostic tools invented to improve the detection process.
4. Treatment: Articles from 11th-20th focusing on treatment of AD in association with A Beta protein utilising combination therapy, metal chelators, immunotherapy, and nano-technology

All the papers selected were considered in order to have a complete and recent most information about the treatment of Alzheimer's disease.
1. Title: Non-coding RNAs in Alzheimer's Disease
   **Author(s):** Lin Tan, Jin-Tai Yu, Nan Hu, Lan Tan
   **Journal:** Molecular Neurobiology
   **Journal Details:** Molecular Neurobiology, 2012
   **Reference link:** [link.springer.com/article/10.1007/s12035-012-8359-5](http://link.springer.com/article/10.1007/s12035-012-8359-5)
   **Abstract:** Alzheimer's disease (AD) is a complex neurodegenerative disorder and the most common dementia among the elderly. Accumulating research indicates that noncoding RNAs (ncRNAs), especially microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), are increasingly being implicated in AD. MiRNAs are conserved small ncRNAs that control gene expression post-transcriptionally while IncRNAs function in many ways. Recent profiling research in human or mouse models suggests that miRNAs are aberrantly expressed in AD, and these have been implicated in the regulation of amyloid-β (Aβ) peptide, tau, inflammation, cell death, and other aspects which are the main pathomechanisms of AD. In addition, regulation of miRNAs varies in blood, and cerebral spinal fluid may indicate alterations in AD. Together with brain-specific miRNAs, these miRNAs could be potential AD biomarkers. All the above may provide the basis for new approaches for AD. Here, we review current findings regarding ncRNA research in human and mouse models to provide a strong basis for future study aiming at promising contributions of ncRNA in AD.
   **Data Source:** SpringerLink

2. Title: Subcellular and metabolic examination of amyloid-β peptides in Alzheimer disease pathogenesis: Evidence for Aβ
   **Author(s):** Yury G. Kaminskya, Michael W Marlattb, Mark A. Smithc, Elena A. Kosenkoa
   **Journal:** Experimental Neurology
   **Journal Details:** Experimental Neurology, Volume 221, Issue 1, January 2010, Pages 26–37
   **Abstract:** Amyloid-β peptide (Aβ) is a central player in the pathogenesis and diagnosis of Alzheimer disease. It aggregates to form the core of Alzheimer disease-associated plaques found in coordination with tau deposits in diseased individuals. Despite this clinical relevance, no single hypothesis satisfies and explicates the role of Aβ in toxicity and progression of the disease. To explore this area, investigators have focused on mechanisms of cellular dysfunction, aggregation, and maladaptive responses. Extensive research has been conducted using various methodologies to investigate Aβ peptides and oligomers, and these multiple facets have provided a wealth of data from specific models. Notably, the utility of each experiment must be considered in regards to the brain environment. The use of Aβ_{25-35} in studies of cellular dysfunction has provided data indicating that the peptide is indeed responsible for multiple disturbances to cellular integrity. We will review how Aβ peptide induces oxidative stress and calcium homeostasis, and how multiple enzymes are deleteriously impacted by Aβ_{25-35}. Understanding and discussing the origin and properties of Aβ peptides is essential to evaluating their effects on various intracellular metabolic
processes. Attention will also be specifically directed to metabolic compartmentation in affected brain cells, including mitochondrial, cytosolic, nuclear, and lysosomal enzymes.

**Data Source:** ScienceDirect

3. **Title:** Small amphipathic molecules modulate secondary structure and amyloid fibril-forming kinetics of Alzheimer disease peptide Aβ (1-42)

**Author(s):** Ryan TM, Friedhuber A, Lind M, Howlett GJ, Masters C, Roberts BR

**Journal:** J Biol Chem.


**Abstract:** Amyloid fibril formation is associated with a number of debilitating systemic and neurodegenerative diseases. One of the most prominent is Alzheimer disease in which aggregation and deposition of the Aβ peptide occur. Aβ is widely considered to mediate the extensive neuronal loss observed in this disease through the formation of soluble oligomeric species, with the final fibrillar end product of the aggregation process being relatively inert. Factors that influence the aggregation of these amyloid-forming proteins are therefore very important. We have screened a library of 96 amphipathic molecules for effects on Aβ(1-42) aggregation and self-association. We find, using thioflavin T fluorescence and electron microscopy assays, that 30 of the molecules inhibit the aggregation process, whereas 36 activate fibril formation. Several activators and inhibitors were subjected to further analysis using analytical ultracentrifugation and circular dichroism. Activators typically display a 1:10 peptide:detergent stoichiometry for maximal activation, whereas the inhibitors are effective at a 1:1 stoichiometry. Analytical ultracentrifugation and circular dichroism experiments show that activators promote a mixture of unfolded and β-sheet structures and rapidly form large aggregates, whereas inhibitors induce α-helical structures that form stable dimeric/trimeric oligomers. The results suggest that Aβ(1-42) contains at least one small molecule binding site, which modulates the secondary structure and aggregation processes. Further studies of the binding of these compounds to Aβ may provide insight for developing therapeutic strategies aimed at stabilizing Aβ in a favorable conformation.

**Data Source:** PubMed Central

4. **Title:** Development of bifunctional stilbene derivatives for targeting and modulating metal-amyloid-β species


**Journal:** Inorg. Chem.


Abstract: Amyloid-β (Aβ) peptides and their metal-associated aggregated states have been implicated in the pathogenesis of Alzheimer's disease (AD). Although the etiology of AD remains uncertain, understanding the role of metal-Aβ species could provide insights into the onset and development of the disease. To unravel this, bifunctional small molecules that can specifically target and modulate metal-Aβ species have been developed, which could serve as suitable chemical tools for investigating metal-Aβ-associated events in AD. Through a rational structure-based design principle involving the incorporation of a metal binding site into the structure of an Aβ interacting molecule, we devised stilbene derivatives (L1-a and L1-b) and demonstrated their reactivity toward metal-Aβ species. In particular, the dual functions of compounds with different structural features (e.g., with or without a dimethylamino group) were explored by UV-vis, X-ray crystallography, high-resolution 2D NMR, and docking studies. Enhanced bifunctionality of compounds provided greater effects on metal-induced Aβ aggregation and neurotoxicity in vitro and in living cells. Mechanistic investigations of the reaction of L1-a and L1-b with Zn(2+)-Aβ species by UV-vis and 2D NMR suggest that metal chelation with ligand and/or metal-ligand interaction with the Aβ peptide may be driving factors for the observed modulation of metal-Aβ aggregation pathways. Overall, the studies presented herein demonstrate the importance of a structure-interaction-reactivity relationship for designing small molecules to target metal-Aβ species allowing for the modulation of metal-induced Aβ reactivity and neurotoxicity.

Data Source: PubMed Central

5. Title: YAP accelerates Aβ25–35-induced apoptosis through upregulation of Bax expression by interaction with p73
Author(s): Heng Zhang, Shengnan Wu, Da Xing
Journal: Apoptosis
Journal Details: Apoptosis, August 2011, Volume 16, Issue 8, pp 808-821

Abstract: Accumulation of amyloid-β-peptide (Aβ) in the brain is considered as a pathological hallmark of Alzheimer’s disease (AD). Previous studies show that p73 is vital for mediating the pathogenic process of AD. Yes-associated protein (YAP) has been shown to positively regulate p73 in promoting apoptosis induced by anti-cancer agents. However, the functional role of YAP and potential relationship between YAP and p73 in AD are unknown. In the present study, we found that YAP accelerated apoptosis in response to Aβ25–35 and the nuclear translocation of YAP was involved in cellular signals that regulated the apoptosis. Aβ25–35 induced YAP translocation from cytoplasm to nucleus accompanied with the increased phosphorylation on Y357, resulting in the enhancement of interaction between YAP and p73. Moreover, inhibition of YAP expression by small hairpin RNA (shRNA) suppressed apoptosis induced by Aβ25–35. More importantly, p73-mediated induction of Bax expression and activation were in a YAP-dependent manner. Overexpression of YAP accelerated Bax translocation, upregulated Bax expression and promoted caspase-3 activation. Taken together, our findings first demonstrated that YAP accelerated Aβ-induced apoptosis through nucleus translocation, leading to the induction of Bax expression and activation. Our results provided a potential therapeutic strategy for the treatment of AD through inhibiting YAP/p73/Bax pathway.

Data Source: SpringerLink
6. Title: Importance of dynamical processes in the coordination chemistry and redox conversion of copper amyloid-beta complexes
Author(s): Hureau C, Balland V, Coppel Y, Solari PL, Fonda E, Faller P.
Abstract: Interaction of Cu ions with the amyloid-beta (Abeta) peptide is linked to the development of Alzheimer's disease; hence, determining the coordination of Cu(I) and Cu(II) ions to Abeta and the pathway of the Cu(I)(Abeta)/Cu(II)(Abeta) redox conversion is of great interest. In the present report, we use the room temperature X-ray absorption near edge structure to show that the binding sites of the Cu(I) and Cu(II) complexes are similar to those previously determined from frozen-solution studies. More precisely, the Cu(I) is coordinated by the imidazole groups of two histidine residues in a linear fashion. However, an NMR study unravels the involvement of all three histidine residues in the Cu(I) binding due to dynamical exchange between several set of ligands. The presence of an equilibrium is also responsible for the complex redox process observed by cyclic voltammetry and evidenced by a concentration-dependent electrochemical response.
Data Source: PubMed Central

7. Title: Metals in Alzheimer's disease: a systemic perspective
Author(s): Squitti R.
Journal Details: Front Biosci. 2012, Jan 1; 17:451-72
Abstract: Many results from in vitro and animal studies have highlighted the important role played by specific metals, such as copper, iron and zinc, in the diverse toxic pathways on which Alzheimer's disease (AD) develops. Metals seem to mediate the aggregation and neurotoxicity of amyloid-beta (ABeta), the main constituent of the amyloid plaques, commonly seen in AD (1). The link between metals and AD has been mostly investigated with a focus on their local accumulation in defined areas of the brain critical for AD. In the present review, I have instead approached the issue from the different perspective of a systemic, rather than local, alteration of copper and iron status. This view is supported by the results of a series of in vivo studies demonstrating that abnormalities of metals homeostasis correlate with the main deficits and specific markers of AD, such as ABeta and Tau proteins in the cerebrospinal fluid. These findings clearly suggest that local metals accumulation in brain areas critical for AD should be viewed within a wider framework of metals systemic alteration.
Data Source: PubMed Central

8. Title: Sensing amyloid-β aggregation using luminescent dipyridophenazine ruthenium(II) complexes
Author(s): Cook NP, Torres V, Jain D, Martí AA.
Abstract: The aggregation of amyloid-β (Aβ) peptides has been associated with the onset of Alzheimer's disease. Here, we report the use of a luminescent dipyridophenazine ruthenium(II) complex to monitor Aβ fibrillization. This complex is not photoluminescent in aqueous solution nor in the presence of monomeric Aβ, but it presents a strong photoluminescence in the presence of Aβ fibril aggregates. One of the advantages of this metal complex is its large Stokes shift (180 nm). Furthermore, the long-lived photoluminescence lifetime of this ruthenium complex allows its use for the detection of fibrillar proteins in the presence of short-lived fluorescent backgrounds, using time-gating technology. We will present evidence of the advantages of dipyridophenazine ruthenium(II) complexes for monitoring protein fibrillization in highly fluorescent media.

Data Source: PubMed Central

9. Title: Critical issues for successful immunotherapy in Alzheimer's disease: development of biomarkers and methods for early detection and intervention
Author(s): Tarawneh R, Holtzman DM.
Journal: CNS Neurol. Disord. Drug Targets
Journal Details: CNS Neurol. Disord. Drug Targets, 2009 Apr; 8(2):144-59
Abstract: Over the last 10 years, promising data has emerged from both animal and human studies that both active immunization with amyloid-beta (Abeta) as well as passive immunization with anti-Abeta antibodies offer promise as therapies for Alzheimer's disease (AD). Data from animal models suggests that antibodies to Abeta through several mechanisms can decrease Abeta deposition, decrease Abeta -associated damage such as dystrophic neurite formation, and improve behavioral performance. Data from human studies suggests that active immunization can result in plaque clearance and that passive immunotherapy might result in slowing of cognitive decline. Despite this, a recent analysis from a phase I trial that involved active immunization with Abeta42, while not powered to determine efficacy, suggested no large effect of active immunization despite the fact that plaque clearance was very prominent in some subjects. An important issue to consider is when active or passive immunization targeting Abeta has the chance to be most effective. Clinico-pathological and biomarker studies have shown that in terms of the time course of AD, Abeta deposition probably begins about 10-15 years prior to symptom onset (preclinical AD) and that tau aggregation in tangles and in neurites does not begin to accelerate and build up in larger amounts in the neocortex until just prior to symptom onset. By the time the earliest clinical signs of AD emerge, Abeta deposition may be close to reaching its peak and tangle formation and neuronal cell loss is substantial though still not at its maximal extent. Since immunization targeting Abeta does not appear to have major effects on tangle pathology, for immunization to have the most chance for success, performing clinical trials in individuals who are cognitively only very mildly impaired or even in those with preclinical AD would likely offer a much better chance for success. Current work with AD biomarkers suggests that such individuals can now be identified and it seems likely that targeting this population with immunization strategies targeting Abeta would offer the best chance of success.
Data Source: PubMed Central
10. Title: Preventing beta-amyloid fibrillization and deposition: beta-sheet breakers and pathological chaperone inhibitors  
Author(s): Wisniewski T, Sadowski M.  
Journal Details: BMC Neurosci. 2008 Dec 3;9 Suppl 2:S5  
Abstract: Central to the pathogenesis of Alzheimer's disease (AD) is the conversion of normal, soluble beta-amyloid (sAbeta) to oligomeric, fibrillar Abeta. This process of conformational conversion can be influenced by interactions with other proteins that can stabilize the disease-associated state; these proteins have been termed 'pathological chaperones'. In a number of AD models, intervention that block soluble Abeta aggregation, including beta-sheet breakers, and compounds that block interactions with pathological chaperones, have been shown to be highly effective. When combined with early pathology detection, these therapeutic strategies hold great promise as effective and relatively toxicity free methods of preventing AD related pathology.  
Data Source: PubMed Central

11. Title: From BACE1 inhibitor to multifunctionality of tryptoline and tryptamine triazole derivatives for Alzheimer's disease  
Author(s): Jiaranaikulwanitch J, Govitrapong P, Fokin VV, Vajragupta O  
Journal: Molecules  
Journal Details: Molecules, 2012 Jul 10; 17(7):8312-33  
Abstract: Efforts to discover new drugs for Alzheimer's disease emphasizing multiple targets was conducted seeking to inhibit amyloid oligomer formation and to prevent radical formation. The tryptoline and tryptamine cores of BACE1 inhibitors previously identified by virtual screening were modified in silico for additional modes of action. These core structures were readily linked to different side chains using 1, 2, 3-triazole rings as bridges by copper catalyzed azide-alkyne cycloaddition reactions. Three compounds among the sixteen designed compounds exerted multifunctional activities including β-secretase inhibitory action, anti-amyloid aggregation, metal chelating and antioxidant effects at micromolar levels. The neuroprotective effects of the multifunctional compounds 6h, 12c and 12h on Aβ₁₋₄₂ induced neuronal cell death at 1 μM were significantly greater than those of the potent single target compound, BACE1 inhibitor IV and were comparable to curcumin. The observed synergistic effect resulting from the reduction of the Aβ₁₋₄₂ neurotoxicity cascade substantiates the validity of our multifunctional strategy in drug discovery for Alzheimer's disease.  
Data Source: PubMed Central

12. Title: Histidine-rich branched peptides as Cu(II) and Zn(II) chelators with potential therapeutic application in Alzheimer's disease  
Author(s): Lakatos A, Gyurcsik B, Nagy NV, Csendes Z, Wéber E, Fülöp L, Kiss T  
Journal: Dalton Trans  
Abstract: Two histidine-rich branched peptides with one lysine as a branching unit have been designed and synthesized by solid-phase peptide synthesis. Their complex formation
with Cu(II) and Zn(II) as well as their ability to attenuate the metal-ion induced amyloid aggregation has been characterized. Both peptides can keep Cu(II) and Zn(II) in complexed forms at pH 7.4 and can bind two equivalents of metal ions in solutions with excess metal. The stoichiometry, stability and structure of the complexes formed have been determined by pH potentiometry, UV-Vis spectrophotometry, circular dichroism, EPR and NMR spectroscopy and ESI-MS. Both mono- and bimetallic species have been detected over the whole pH range studied. The basic binding mode is either a tridentate (N(amine), N(amide), N(im)) or a histamine-type of coordination which is complemented by the binding of far imidazole or amino groups leading to macrochelate formation. The peptides were able to prevent Cu(II)-induced Aβ(1-40) aggregation but could not effectively compete for Zn(II) in vitro. Our results suggest that branched peptides containing potential metal-binding sites may be suitable metal chelators for reducing the risk of amyloid plaque formation in Alzheimer's disease.

Data Source: PubMed Central

13. Title: Gantenerumab for the treatment of Alzheimer's disease
Author(s): Delrieu J, Ousset PJ, Vellas B
Abstract:
IMPORTANCE OF THE FIELD: Alzheimer's disease is the leading cause of dementia in the elderly, and there is no disease-modifying therapy yet available. Immunotherapy directed against the β-amyloid peptide may be capable of slowing the rate of disease progression. Gantenerumab is the first fully human anti-β-amyloid monoclonal antibody.
AREAS COVERED: To review the efficacy and safety of immunotherapy drugs and in particular gantenerumab, we used the database MEDLINE. The primary literature on gantenerumab is reviewed in its entirety. We also reviewed the English-language, pre-clinical and clinical trials designed to evaluate the efficacy or/safety of immunotherapy drugs, from 1999 through 2011. Other Alzheimer's disease-passive immunotherapeutics currently in development, according to www.clinicaltrials.gov, are also discussed.
EXPERT OPINION: Gantenerumab appears capable of reducing the cerebral β-amyloid peptide burden in patients with Alzheimer's disease. Its ability to slow disease progression remains uncertain because no clinical data are available at present. The next step will be to investigate whether removal of brain amyloid translates into clinical benefit for patients at doses of gantenerumab that reduce brain amyloid and are well tolerated.
Data Source: PubMed Central

14. Title: Bryostatin-1 vs. TPPB: Dose-Dependent APP Processing and PKC-α, -δ, and -ε Isoform Activation in SH-SY5Y Neuronal Cells
Author(s): P. Yi, L. Schrott, T. P. Castor, and J. S. Alexander
Journal: Journal of Molecular Neuroscience
Journal Details: Journal of Molecular Neuroscience, September 2012, Volume 48, Issue 1, pp 234-244
Abstract: Activation of the α-secretase processing pathway of amyloid precursor protein (APP) is recognized as an important mechanism which diverts APP processing from production of beta-amyloid (Aβ) to non toxic sAPPα, decreasing Alzheimer’s disease (AD)
plaque formation and AD-associated cognitive deficits. Two potent classes of PKC modulators can activate the α-secretase pathway, the benzo/indolactams and bryostatin/bryoalogues. While both modulate PKC-dependent APP processing, no direct comparisons of their relative pharmacological potencies have been accomplished which could assist in the development of AD therapies. In this study, we measured the activation of α-secretase APP processing and PKC-α, -δ, and -ε induced by the benzolactam-APP modulator TPPB and bryostatin-1 in the neuroblastoma cell line SH-SY5Y which expresses APP and α- and β-secretase processing mechanisms. Bryostatin-1 produced a more rapid, potent, and sustained activation of α-secretase APP processing than TPPB and selectively activated PKC-δ and PKC-ε. Although TPPB also activated α-secretase, its potency was approximately 10- to 100-fold lower, possibly reflecting lower PKC-δ and -ε activation. Because bryostatin-1 is a highly potent PKC-δ and -ε activator which activates α-secretase APP processing, further characterization of bryostatin-1/bryoalogues may help refine their use as important tools for the clinical management of AD.

**Data Source:** SpringerLink

15. **Title:** Biomarkers in Alzheimer's disease drug development  
**Author(s):** Jeffrey L. Cummings  
**Journal:** Alzheimer's & Dementia: The Journal of the Alzheimer's Association  

**Abstract:** Developing new therapies for Alzheimer's disease (AD) is critically important to avoid the impending public health disaster imposed by this common disorder. Means must be found to prevent, delay the onset, or slow the progression of AD. These goals will be achieved by identifying disease-modifying therapies and testing them in clinical trials. Biomarkers play an increasingly important role in AD drug development. In preclinical testing, they assist in decisions to develop an agent. Biomarkers in phase I provide insights into toxic responses and drug metabolism and in Phase II proof-of-concept trials they facilitate go/no-go decisions and dose finding. Biomarkers can play a role in identifying presymptomatic patients or specific patient subgroups. They can provide evidence of target engagement before clinical changes can be expected. Brain imaging can serve as a primary outcome in Phase II trials and as a key secondary outcome in Phase III trials. Magnetic resonance imaging is currently best positioned for use in large multicenter clinical trials. Cerebrospinal fluid (CSF) measures of amyloid beta protein (Aβ), tau protein, and hyperphosphorylated tau (p-tau) protein are sensitive and specific to the diagnosis of AD and may serve as inclusion criteria and possibly as outcomes in clinical trials targeting relevant pathways. Plasma measures of Aβ are of limited diagnostic value but may provide important information as a measure of treatment response. A wide variety of measures of detectable products of cellular processes are being developed as possible biomarkers accessible in the cerebrospinal fluid and plasma or serum. Surrogate markers that can function as outcomes in pivotal trials and reliably predict clinical outcomes are needed to facilitate primary prevention trials of asymptomatic persons where clinical measures may be of limited value. Fit-for-purpose biomarkers are increasingly available to guide AD drug development decisions.  
**Data Source:** Sciencedirect
16. Title: Modified immunotherapies against Alzheimer's disease: toward safer and effective amyloid clearance
Author(s): Wang YJ, Zhou HD, Zhou XF
Abstract: Alzheimer's disease (AD) is characterized by the deposition of amyloid plaques, loss of neurons, neuritic degeneration, accumulation of fibrillary tangles in neurons, and a progressive loss of cognitive function. Amyloid-β peptide (Aβ) appears to play a pivotal role in the development of AD. Clearance of Aβ from the brain represents an important therapeutic strategy for prevention and treatment of AD. Immunotherapy targeting Aβ is effective to remove the peptide from the brain. However, it is associated with detrimental adverse effects, such as autoimmune meningoencephalitis and microhemorrhage. These are presumably the results of brain infiltration of provoked autoimmune T lymphocytes in response to Aβ vaccination and release of proinflammatory cytokines from microglia activated by the immune complex of Aβ and antibodies. An improvement of the safety of the immunotherapy is a major goal of the immunotherapy study. Here, we review the mechanisms involved in modified immunological strategies, as well as their adverse effects. We discuss the following: the development of B epitope vaccines to avoid activation of autoimmune T lymphocytes; DNA vaccines containing appropriate immunostimulatory and immunomodulatory sequences to induce the desired humoral immune responses; antibody modifications to avoid activation of microglia and subsequent release of proinflammatory cytokines; single chain antibody-based gene therapy; immunotherapy targeting Aβ oligomers; modulation of antibody delivery approach and dose; and application of autoantibodies against Aβ. These ultimately represent future directions of therapeutic approaches toward safer and effective Aβ clearance.
Data Source: PubMed Central

17. Title: Site-Activated Chelators Derived from Anti-Parkinson Drug Rasagiline as a Potential Safer and More Effective Approach to the Treatment of Alzheimer’s Disease
Author(s): Hailin Zheng, Mati Fridkin, Moussa B. H. Youdim
Journal: Neurochemical Research
Reference Link: http://link.springer.com/article/10.1007/s11064-010-0293-1
Abstract: Chelators can modulate β-amyloid accumulation, protect against tau hyperphosphorylation, and block metal-related oxidative stress, and thereby hold considerable promise as effective anti-AD drugs. At present, a growing interest is focusing on increasing the efficacy and targeting of chelators through drug design. To this end, we have developed a new class of multifunctional prochelators from three FDA-approved drugs rasagiline, rivastigmine, and donepezil or tacrine. HLA20 A was designed by merging the important pharmacophores of rasagiline, rivastigmine, and donepezil into our newly developed multifunctional chelator HLA20. M30D was constructed using the key pharmacophoric moieties from rasagiline, rivastigmine, and tacrine. Experiments showed that both compounds possess potent anti-acetylcholinesterase (AChE) activity in vitro with weak inhibition of butyrylcholinesterase (BuChE), and without significant metal-binding
activity. M30D was found also to be a highly potent MAO A inhibitor with moderate inhibition of MAO B in vitro. Both HLA20 and M30D can be activated by inhibition of AChE to release active chelators HLA20 and M30, respectively. HLA20 and M30 have been shown to be able to modulate amyloid precursor protein regulation and beta-amyloid reduction, suppress oxidative stress, and passivate excess metal ions (Fe, Cu, and Zn). Compared with the activated chelator HLA20 or M30, both HLA20A and M30D exhibited lower cytotoxicity in SH-SY5Y neuroblastoma cells, substantiating the prochelator strategy for minimizing toxicity associated with poor targeted chelators.

Data Source: SpringerLink

18. Title: Nanoparticle-chelator conjugates as inhibitors of amyloid-beta aggregation and neurotoxicity: a novel therapeutic approach for Alzheimer disease

Author(s): Liu G, Men P, Kudo W, Perry G, Smith MA

Abstract: Oxidative stress and amyloid-beta are considered major etiological and pathological factors in the initiation and promotion of neurodegeneration in Alzheimer disease (AD). Insomuch as causes of such oxidative stress, transition metals, such as iron and copper, which are found in high concentrations in the brains of AD patients and accumulate specifically in the pathological lesions, are viewed as key contributors to the altered redox state. Likewise, the aggregation and toxicity of amyloid-beta is dependent upon transition metals. As such, chelating agents that selectively bind to and remove and/or "redox silence" transition metals have long been considered as attractive therapies for AD. However, the blood-brain barrier and neurotoxicity of many traditional metal chelators has limited their utility in AD or other neurodegenerative disorders. To circumvent this, we previously suggested that nanoparticles conjugated to iron chelators may have the potential to deliver chelators into the brain and overcome such issues as chelator bioavailability and toxic side-effects. In this study, we synthesized a prototype nanoparticle-chelator conjugate (Nano-N2PY) and demonstrated its ability to protect human cortical neurons from amyloid-beta-associated oxidative toxicity. Furthermore, Nano-N2PY nanoparticle-chelator conjugates effectively inhibited amyloid-beta aggregate formation. Overall, this study indicates that Nano-N2PY, or other nanoparticles conjugated to metal chelators, may provide a novel therapeutic strategy for AD and other neurodegenerative diseases associated with excess transition metals.

Data Source: PubMed Central

19. Title: Rationale for peptide and DNA based epitope vaccines for Alzheimer's disease immunotherapy

Author(s): Ghochikyan A
Journal: CNS Neurol. Disord. Drug Targets

Abstract: Amyloid-beta (Abeta) immunotherapy has received considerable attention as a promising approach for reducing the level of Abeta in the CNS of Alzheimer's disease patients. However, the first Phase II clinical trial, for the immune therapy AN1792, was halted when a subset of those immunized with Abeta(42) developed adverse events in the central nervous system. In addition, data from the trial indicated that there was a low percentage of
responders and generally low to moderate titers in the patients that received the vaccine. Generated antibodies reduced beta-amyloid deposits in the parenchyma of patients’ brains, but no reduction in soluble Abeta or significant improvements in cognitive function of patients were observed. These data and data from pre-clinical studies suggest that reduction in the most toxic oligomeric forms of Abeta is important for prevention or slowing down of the progression of cognitive decline, and that vaccination should be started prior to irreversible accumulation of the oligomeric Abeta, at the early stages of AD. Protective immunotherapy requires a development of safe and effective strategy for Abeta immunotherapy. In this review, the rationale for developing epitope vaccines for the treatment of AD will be discussed. We believe that an epitope vaccine will induce an adequate anti-Abeta antibody response in the absence of potentially adverse self T cell-mediated events, making it possible to start immunization at the early stages of AD.

Data Source: PubMed Central

20. Title: Autoantibody-catalyzed hydrolysis of amyloid beta peptide
Journal: J. Biol. Chem.
Abstract: We describe IgM class human autoantibodies that hydrolyze amyloid beta peptide 1-40 (Abeta40). A monoclonal IgM from a patient with Waldenström's macroglobulinemia hydrolyzed Abeta40 at the Lys-28-Gly-29 bond and Lys-16-Ala-17 bonds. The catalytic activity was inhibited stoichiometrically by an electrophilic serine protease inhibitor. Treatment with the catalytic IgM blocked the aggregation and toxicity of Abeta40 in neuronal cell cultures. IgMs purified from the sera of patients with Alzheimer disease (AD) hydrolyzed Abeta40 at rates superior to IgMs from age-matched humans without dementia. IgMs from non-elderly humans expressed the least catalytic activity. The reaction rate was sufficient to afford appreciable degradation at physiological Abeta and IgM concentrations found in peripheral circulation. Increased Abeta concentrations in the AD brain are thought to induce neurodegenerative effects. Peripheral administration of Abeta binding antibodies has been suggested as a potential treatment of AD. Our results suggest that catalytic IgM autoantibodies can help clear Abeta, and they open the possibility of using catalytic Abs for AD immunotherapy.
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