TOPICS IN
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02

Volume Editors Lit-Fui Lau · Michael A. Brodney

Alzheimer's Disease

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Topics in Medicinal Chemistry

Alzheimer's Disease

Volume Editors: Lit-Fui Lau · Michael A. Brodney

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Preface to the Series

Medicinal chemistry is both science and art. The science of medicinal chemistry offers mankind one of its best hopes for improving the quality of life. The art of medicinal chemistry continues to challenge its practitioners with the need for both intuition and experience to discover new drugs. Hence sharing the experience of drug discovery is uniquely beneficial to the field of medicinal chemistry.

The series *Topics in Medicinal Chemistry* is designed to help both novice and experienced medicinal chemists share insights from the drug discovery process. For the novice, the introductory chapter to each volume provides background and valuable perspective on a field of medicinal chemistry not available elsewhere. Succeeding chapters then provide examples of successful drug discovery efforts that describe the most up-to-date work from this field.

The editors have chosen topics from both important therapeutic areas and from work that advances the discipline of medicinal chemistry. For example, cancer, metabolic syndrome and Alzheimer's disease are fields in which academia and industry are heavily invested to discover new drugs because of their considerable unmet medical need. The editors have therefore prioritized covering new developments in medicinal chemistry in these fields. In addition, important advances in the discipline, such as fragment-based drug design and other aspects of new lead-seeking approaches, are also planned for early volumes in this series. Each volume thus offers a unique opportunity to capture the most up-to-date perspective in an area of medicinal chemistry.

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Preface to Volume 2

It was one hundred and one years ago that Alois Alzheimer presented at a scientific meeting a case of progressive dementia in a 51-year-old patient Auguste D. Postmortem analysis revealed two pathologies, namely, senile plaques and neurofibrillary tangles. These findings were published the following year in 1907. In 1910 Emil Kraepelin, Alzheimer's mentor, named this disease after its discoverer. The two initial pathological findings remain the postmortem diagnostic features of Alzheimer's disease (AD) today. At the time, however, Kraepelin made the distinction between AD and senile dementia (> 65 years old) despite their similarities in pathologies and clinical symptoms [1, 2]. In 1976 Robert Katzman argued in an editorial in the April issue of *Archives of Neurology* that this distinction be removed. AD has thus morphed from a rare orphan disease to one with a much bigger socioeconomic threat. This nosological shift has brought AD into the lime light and exponentially—and thankfully—hastened the pace of research. Enormous strides have been made in understanding the root causes and risk factors of the disease. Analogous to the discovery of new cancer treatments over the past 20 years (see Volume 1), advances in understanding the underlying molecular biology are providing novel drug targets for future research. These efforts have resulted in greater than 500 ongoing clinical trials focused on novel mechanisms and intervention points in the disease. These trials will hopefully lead to the first approval of a disease-modifying agent for AD and pave the way for an arsenal of new medications.

October, 2007, Groton Connecticut, USA

Lit-Fui Lau and Michael A. Brodney

1. Ballenger JF (2006) J Alzheimers Dis 9:5
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Therapeutic Approaches for the Treatment of Alzheimer's Disease: An Overview

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Abstract Alzheimer's disease (AD) is a neurodegenerative disease that robs the minds of our elderly population. Approximately one in every eight adults over the age of 65 and nearly half of those over 85 are afflicted with this disease. Aging and other risk factors (e.g. cardiovascular diseases, obesity and diabetes) in developed societies will impose an ever increasing socioeconomic threat in the future. Current medicines for AD patients are mainly symptomatic treatments and a huge unmet medical need exists to slow, stop or reverse the progression of this disease. A great deal of research has been dedicated to understanding the pathogenesis of AD from which come many ideas for intervening in its progression. They can be grossly categorized into those targeting the amyloid pathology, tau pathology, microgliosis (neuroinflammation) and functional deficits. Some of these ideas have been fast-tracked to clinical trials due to the availability of medicines with proven clinical efficacies for other diseases while others represent novel chemical entities. Our continued commitment in searching for efficacious treatments together with a healthier lifestyle will be important in fighting against the growing threat of this deteriorating disease.

Keywords Aβ · Alzheimer's disease · Amyloid · Microgliosis · Neurodegeneration · tau

Abbreviations

AD	Alzheimer's disease
apoE	apolipoprotein E
APP	amyloid precursor protein
Aβ	β-amyloid
BACE	β-site APP-cleaving enzyme
CCL2	chemokine (C–C) motif ligand-2
CCR2	chemokine (C–C) motif receptor-2
Cdk5	cyclin-dependent kinase 5
CK-1	casein kinase-1
ECE	endothelin converting enzyme
ERK	extracellular signal-regulated kinase
FDA	Food and Drug Administration
FTDP-17	frontotemporal dementia and parkinsonism linked to chromosome 17
GAB2	GRB associated binding protein 2
HTS	high throughput screening
IDE	insulin degrading enzyme
LRP	lipoprotein receptor-related protein
LTP	long term potentiation
MARK	Microtubule-affinity regulating kinase
MCI	mild cognitive impairment
NFT	neurofibrillary tangle
NMDA	*N*-methyl-D-aspartate
NSAIDs	non-steroidal anti-inflammatory drugs
PPAR-γ	Peroxisome proliferator-activated receptor-γ
PS1	presenilin-1
PS2	presenilin-2
RAGE	receptor for advanced glycation end products

1 Introduction

Since the first report describing Alzheimer's disease (AD) in 1906 by Alois Alzheimer, AD has become the most common form of dementia, accounting for 50–70% of all cases. According to a 2007 report from the Alzheimer's Association (http://www.alz.org/national/documents/Report_2007FactsAndFigures.pdf) there are currently 5.1 million people in the U.S. and over 30 million worldwide afflicted with the disease. Every one in eight people over the age of 65 and every nearly half of those over 85 have AD. With its aging population, the number of AD patients in the U.S. will climb to 16 million by 2050. Combination of direct and indirect cost in the treatment and care of AD patients is already a staggering $138 billion dollars each year. It is hoped that a better understanding of the symptoms, pathologies and etiology of AD can slow, stop, reverse or even prevent the disease. Even the slightest intervention could have an enormous impact. It has been estimated that by simply postponing the onset of AD five years can reduce the number of AD patients by 50 percent by 2050 [1].

2
AD Symptoms and Neutodegeneration

AD is a chronic progressive neurodegenerative disease. The progression of symptoms varies from patient to patient but can be roughly divided into three stages: mild, moderate and severe (Mayo Clinic, http://www.mayoclinic.com/health/alzheimers-stages/AZ00041). The progression of symptoms can be ascribed to the sequential and progressive loss of neuronal functions and synaptic connections, and neuronal cell death in different regions of the brain. In the mild stage AD is first manifested with loss of memory as neurons in the region for memory formation, the hippocampus, are first affected. Patients may forget words and names with increasing frequency and get lost even in familiar places. Some believe that these incipient cases of AD are equivalent to a clinical condition known as mild cognitive impairment (MCI). Not all MCI patients will convert to AD; a 36 month study shows that the conversion rate from amnestic MCI to AD is about 16% per year [2]. In the moderate stage cortical regions responsible for reasoning become affected and AD patients may begin to lose their logical thinking and experience confusion. They may need help putting on proper clothing appropriate for the season. They may have difficulty recognizing and identifying family members. Changes in personality may also occur, e.g., making accusations of theft and fidelity, cursing, and inappropriate kicking and screaming. In the severe stage additional brain regions are damaged resulting in loss of control of many normal physiological functions and responses to the external environment. AD patients are unable to take care of their daily living and lose their ability to speak coherently. They may need help with feeding, toilet use and walking. Once diagnosed, the median survival time is 4 to 6 years [3] although some individuals can live up to 20 years. The cause of death comes from deterioration of the brain's control of vital physiological functions resulting in deadly complications including pneumonia, urinary tract infections or a physical fall.

3
Pathological Features of AD

3.1
Amyloid Pathologies

Neurodegeneration is an important but not a unique characteristic feature of AD. What distinguishes AD from other neurodegenerative diseases is the presence of its telltale pathologies in the brains of these patients: amyloid plaques and neurofibrillary tangles (NFTs). Amyloid plaques consist of mainly extracellular β-amyloid (Aβ) peptide while neurofibrillary tangles are

mainly composed of intracellular hyperphosphorylated tau in the form of paired helical filaments. A great deal of research has been done to understand the relevance of these pathologies to AD. According to the amyloid cascade hypothesis [4, 5], Aβ is the main culprit triggering a whole cascade of events, including formation of NFTs, eventually leading to neurodegeneration and loss of brain function in AD patients. The key argument for this hypothesis is that familial mutations causing AD with a 100% penetrance are found on genes that all encode proteins involved in regulating Aβ levels. These include mutations on the amyloid precursor protein (APP, substrate for Aβ production), and presenilin 1 and 2 (components of the γ-secretase complex that cleaves APP to Aβ). AD pathologies are invariably detected in Downs syndrome which is caused by having an additional copy of chromosome 21 where the APP gene is located. The major genetic risk factor for AD, apoE4 [6], has also been found to affect amyloid plaque deposition in mice [7–9]. One of the main criticisms on the amyloid cascade hypothesis is the inability of high levels of Aβ in animal models to recapitulate the other key AD pathologies (e.g. NFTs and neuronal cell loss). This shortfall has been addressed by a number of studies showing that Aβ is able to augment formation of NFTs [10–12] and that removal of Aβ subsequently reduces an early tau pathological marker [13]. What is still missing is evidence that Aβ can induce, not simply augment, tau pathologies. Despite the lack of neuronal cell loss in APP transgenic mice, Aβ peptides have been shown to impair hippocampal long term potentiation (LTP) – a cellular process believed to be the basis of learning and memory – both in vitro and in vivo [14]. The amyloid cascade hypothesis has been the foundation of many drug discovery efforts towards a treatment for AD.

3.2 Tau Pathologies

Although believed to be downstream of Aβ, tau pathologies may play an important role in the deterioration of neuronal health in AD. NFTs have been classified into six stages (I–VI) by Braak and Braak [15]. The different stages describe the progression of tau pathologies from the transentorhinal region (I–II) to the limbic region (III–IV) and finally to the cerebral cortex (V–VI). During stages I–II the affected subject remains clinically silent. Stages III–IV pathologies are found in incipient AD when there is loss of cognitive functions and subtle personality changes. In the final stages of V–VI patients have fully developed AD. The sequential evolution of tau pathologies and its correlation with neurodegeneration and clinical manifestations suggests that tau pathologies, although not the ultimate trigger of AD, may play a prominent role in the demise of neurons. In fact, genetic mutations on tau have been shown to be sufficient to cause neurodegeneration in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) [16]. A recent

study showed that genetic polymorphism of GRB associated binding protein 2 (GAB2) was associated with a higher risk of developing AD [17]. In the same study interference of GAB2 expression was shown to increase the amount of hyperphosphorylated tau – a key component of the NFTs. Finally, cognitive deficits in APP transgenic animals [18] and toxic effects of Aβ [19] can be dramatically reduced by eliminating tau expression. In PS1 $\times$ APP $\times$ tau triple transgenic mice, reduction of Aβ alone by Aβ immunization is insufficient to rescue cognitive deficits but reduction of both amyloid and tau pathologies are necessary [13]. These studies suggest that tau plays an important role in the manifestation of Aβ-induced deficits.

There are at least two schools of thoughts on how tau pathologies may cause neurodegeneration: loss of essential functions and gain of toxic functions [20]. As mentioned earlier, NFTs consist mainly of hyperphosphorylated tau. Tau is a microtubule stabilizing protein. When tau is hyperphosphorylated, it dissociates from microtubules causing their disassembly (loss of essential functions). The disintegration of microtubules then leads to disruption of axonal transport, atrophy of distal neurites and eventually neuronal cell death. In addition to loss of microtubule stabilizing activity, hyperphosphorylated tau tends to aggregate and sequester additional normal tau from binding microtubules. The aggregated tau continues to form paired helical filaments and straight filaments approximately 10 and 15 nm in diameter, respectively. The former constitutes about 95% and the latter about 5% of the tau filaments found in AD brains. The gain of toxic functions school proposes that these abnormally aggregated tau species (not limited to NFTs) may be toxic to neurons. In fact, a number of transgenic animals overexpressing FTDP-17 tau have been able to recapitulate formation of tau filaments and NFTs. These animals, unlike APP transgenic mice, display clear signs of neuronal cell loss. A recent study in conditional transgenic mice overexpressing a mutant form of tau suggests that NFTs are not sufficient for causing neurodegeneration and cognitive deficits [21]. Nevertheless, tau phosphorylation appears to be responsible for the toxic functions of tau as elimination of all the proline-directed phosphorylation sites in tau drastically reduces toxicities [22]. The exact mechanisms by which tau overexpression induces degeneration and dysfunctions of neurons remains to be elucidated. Reduction of tau pathologies and/or tau toxicities is certainly an important area in the fight against AD.

3.3 Microgliosis

Surrounding the amyloid plaques in AD brains are clusters of reactive microglia, a phenomenon known as microgliosis. Microglia are immune cells of the brain derived from bone marrow. They are equivalent to macrophages in blood whose function is to cleanse by phagocytosis. Activation of microglia, however, could be a double-edged sword. On one hand, activated

microglia can release a variety of toxic substances detrimental to neurons, e.g., proinflammatory cytokines, reactive oxygen species, proteases and complements [23–27]. On the other hand, activated microglia may be one of the defense mechanisms to clean up amyloid plaque deposits. *In vitro* it has been shown that microglial cells can scavenge deposited amyloid [28–30]. Recent studies have provided strong evidence that microglia can remove amyloid plaques *in vivo* as well. In fact, it is the bone marrow-derived microglia – not resident microglia – that are critical in eliminating brain amyloid deposits [31]. Attraction of blood microglia cells to the brain depends on the microglial surface chemokine (C–C) motif receptor, CCR2, in response to its ligand, chemokine (C–C) motif ligand 2 (CCL2). Mice deficient in CCR2 crossed with APP transgenic mice display a dramatic reduction in the number of microglial cells in the brain, a concomitant elevation of amyloid plaques and increased mortality [32]. Interestingly, overexpression of the ligand CCL2 in APP transgenic mice appears to lead to inactivation or desensitization of microglia and exacerbates plaque deposition [33]. Finally, recent success in using Aβ immunotherapy to reduce amyloid plaque deposition in mice has been shown to depend at least in part on the activation of microglial cells [34].

4 Etiology and Environmental Risk Factors for AD

The etiology of AD remains largely elusive. A small percentage (5–10%) of all AD cases can be ascribed to genetic mutations and has an early onset age (< 65). The large majority (90–95%), however, is considered sporadic and has a late onset. Thus, aging is the biggest risk factor for AD. A myriad of environmental factors that increase with age may play an important role in AD. It is unclear if these factors can be converged to one common underlying mechanism or if they are independent events leading to a heterogeneous disease. Preclinical experiments exposing animals to some of the risk factors have shown an increase in AD pathologies. Understanding the causal relationship between these associations may not only provide clues to treat AD but also prevent it.

Environmental risk factors linked to AD include, but are not limited to, cardiovascular risk factors, metabolic and energy disorders and traumatic brain injury. Problems with the cardiovascular system can lead to reduced cerebral blood flow – an important feature of the AD brain. It is possible that a compromised delivery of nutrients and oxygen to the brain may in turn cause impairment of neuronal functions. Mid-life hypercholesterolemia has been shown to increase the risk of AD by about three fold [35, 36]. The cholesterol transport protein, apoE4, is the single most reliable genetic risk factor for late onset AD [6]. Usage of cholesterol lowering agents has been associated with a reduced incidence [37, 38] and progression [39] but the causal relationship between statin usage and AD risk has been debated [40–42]. How

mid-life hypercholesterolemia is linked to the development of AD a decade or more later is not completely understood. Preclinical studies have shown that cholesterol is an important component of lipid rafts where APP processing and production of Aβ peptides occur. Animals fed on high cholesterol diets develop more amyloid plaques [43] whereas statin treatment can reduce brain Aβ levels [44]. Hypertension is another cardiovascular factor known to elevate the risk of AD [45]. Hyperhomocysteinaemia, associated with an increased risk of cardiovascular diseases, is also linked to an increase in AD risk [46–50].

Type 2 diabetes has been associated with cognitive impairment and AD [51–55]. Since diabetes usually precedes AD, it is believed that conditions in diabetics are conducive to the development of AD but the mechanism(s) by which this occurs is/are poorly understood. First, diabetics are more likely to suffer from cardiovascular diseases that may enhance the occurrence of AD as discussed above. Second, type 2 diabetes is characterized by insulin resistance. The reduced ability of neurons to respond to insulin and metabolize glucose could lead to neuronal functional impairment [56]. Indeed, disruption of insulin signal transduction in rat brains by intracerebroventricular injection of streptozotocin has been shown to recapitulate many pathological features reminiscent of AD [57–59]. Third, insulin insensitivity can cause hyperinsulinemia as the body is trying to compensate. Insulin is brain permeable and degraded by the insulin degrading enzyme (IDE). It happens that IDE is one of the enzymes responsible for the clearance of Aβ peptides [60]. A high insulin level may reduce clearance of Aβ peptides by competing for IDE. Administration of insulin in peripheral circulation has been shown to increase Aβ peptides in the cerebrospinal fluid [61]. Accumulation of brain Aβ will, according to the amyloid cascade hypothesis discussed above, lead to other AD pathologies and eventually manifestation of AD symptoms. Since obesity may increase the likelihood of developing diabetes and cardiovascular diseases, it is not surprising to find that obesity is another risk factor for AD [62]. According to the Centers for Disease Control and Prevention, in 2006 only four states in the U.S. have a prevalence rate of obesity of less than 20%. Twenty two states have a prevalence rate of equal to or greater than 25%; in two of these states almost one in three adults has obesity. The increasing trend of obesity in the U.S. will pose an extra burden to the already gargantuan task of controlling AD in light of an aging population.

In addition to aberrant internal metabolism, external insult such as traumatic brain injury can increase the risk of AD [63–65]. The mechanisms by which head trauma may augment the risk of AD is unknown. Repetitive head trauma experienced by professional boxers may lead to "punch drunk" syndrome or dementia pugilistica later in life [66]. This syndrome is characterized by progressive dementia and parkinsonism and the presence of senile plaques and neurofibrillary tangles [67, 68]. Aβ deposition has been detected in the brains of victims of even a single head injury [69]. In preclinical models head trauma can exacerbate the formation of plaques or tangles, induce neu-

ronal cell death, and impair cognitive functions [70–73]. However, under certain experimental conditions, it has been shown that traumatic brain injury may actually cause regression of amyloid plaques [74].

In addition to the risk factors, epidemiological studies have revealed protective factors associated with AD. An engagement in physical, mental and social activities has been shown to reduce the risk of developing AD. The mechanisms for the associations are not well understood. Physical exercise or caloric restriction may indirectly curb the risk for AD by reducing one's risk for cardiovascular diseases, obesity and diabetes. It has been postulated that mental activities can build cognitive "reserve" so that some cognitive decline will not adversely affect normal functions. Interestingly, recent preclinical studies have suggested that these protective factors may have a more direct role in AD pathologies. For instance, exercise in APP transgenic mice can enhance cognition and ameliorate amyloid plaque deposition [75]. Caloric restriction [76] or learning in the Morris water maze [77] not only can improve cognitive functions but also dampen development of amyloid and/or tau pathologies. Enrichment of housing has been shown to reduce amyloid pathologies [77] and improve cognition [78]. Interestingly, the improvement in cognition in the latter study is associated with increased amyloid plaque deposition.

5
Therapeutic Strategies and Approaches for the Treatment of AD

5.1
General Strategies

Our improved understanding of AD has generated a number of potential therapeutic approaches for this disease. Some of the approaches are symptomatic while others are believed to be disease modifying, i.e., being able to slow, halt or reverse the progression of AD. In general, the strategy to treat the disease aims either at ameliorating the pathologies or compensating for the functional deficits to restore normal functions. Current therapeutic approaches can be classified into those targeting amyloid pathology, tau pathology, microgliosis (or neuroinflammation), metabolic aberrations and neurodegeneration in AD. Distinction among these approaches is often not clear cut, however, as different pathologies may be interwoven with each other through complicated and murky signal transduction pathways. This can be exemplified by an Aβ vaccine that not only reduces amyloid but also tau pathologies in the PS1 $\times$ APP $\times$ tau triple transgenic mice [13].

There are at least two approaches from which therapeutic agents are discovered that fuel the AD clinical trial pipeline. They are the "bottom up" and "top down" approaches. The "bottom up" approach is the traditional approach adopted by pharmaceutical companies. A drug target is first identi-

fied followed by high throughput screening (HTS) of their chemical libraries. The HTS hits are optimized to give potent and selected leads, which have to demonstrate both efficacy and safety in appropriate animal models (see Chapter 5). This approach enables the pharmaceutical companies to pursue novel targets with no existing chemical matter but can be an arduous and time consuming process. The "top down" approach takes advantage of epidemiological findings, anecdotal evidence or preclinical studies that suggest that an FDA approved compound on the market can be beneficial for AD. Since these medicines developed for other indications have proven safety profiles in humans, they can often be fast tracked to clinical trials in AD patients (see Chapters 2 and 3). The advantage of this approach is its speed – it can potentially cut precious years typically required for research and development in the "bottom up" approach. Epidemiological and anecdotal association ,however, is not necessarily causative. Clinical trials may fail due to the lack of a causal relationship. The available medicines that could be used for AD as an alternative indication may also be limited. Their properties, designed for their original indication, may not be appropriate for AD (e.g. brain permeability). Nevertheless, there is increasing interest in tapping these opportunities. The candidates for the "top down" approach may not be limited to marketed drugs but may include those in ongoing clinical trials and those terminated for lack of efficacy for other indications.

5.2 Specific Approaches

Below we will highlight some of the therapeutic approaches in research and development. Due to the vast amount of literature and information available, this is by no means intended to be a comprehensive review but it will highlight key areas under investigation, especially those that have entered clinical trials.

5.2.1 Targeting Symptoms

It is known that symptoms in AD patients fluctuate. The rapid fluctuation cannot be accounted for by changes in structural damage. It suggests that surviving neurons in an AD brain, under the right circumstances, still retain the ability to carry out the once lost brain functions. In fact, preserving and maintaining functional balance of the surviving neuronal systems has been shown to provide benefits for AD patients. However, the full potential of symptomatic relief remains to be elucidated. To date the FDA has approved five drugs for the symptomatic relief of AD: four cholinesterase inhibitors and an *N*-methlyl-D-aspartate (NMDA) receptor antagonist. The four approved cholinesterase inhibitors are tacrine (Cognex), donepezil (Aricept), ri-

Table 1 Selected compounds in Phase III trials for the treatment of AD Sources: http://www.alzforum.org/ & http://www.clinicaltrials.gov/

Drug(s)	Mechanism of action	Sponsor
Neramexane	NMDA receptor antagonist	Forest Laboratories
Xaliproden[a]	Nerve growth factor agonist/ 5HT1A receptor agonist	Sanofi-Aventis
AAB-001	Humanized monoclonal anti-Aβ antibody	Wyeth/Elan
R-flurbriprofen (Flurizan)	γ-modulator; Nonsteroidal anti-inflammatory durg (NSAID)	Myriad Genetics
Tramiprosate[a] (Alzhemed)	Inhibit Aβ oligomerization by binding and reducing soluble Aβ	Neurochem
Simvastatin (Zocor)	HMG-CoA reductase inhibitor	Merck/NIA
Atorvastatin (Lipitor)	HMG-CoA reductase inhibitor	Pfizer
Rosiglitazone (Avandia)	PPAR-γ agonist	GlaxoSmithKline
AIT-082 (NeoTrofin)	Neurotrophic agent	NeoTherapeutics
Cerebrolysin	Neuroprotection, neurotrophic agent	Ebewe

[a] Recent results show that both xaliproden and tramiprosate have failed to demonstrate significant efficacy in AD patients

Table 2 Selected compounds in Phase II trials for the treatment of AD Sources: http://www.alzforum.org/ & http://www.clinicaltrials.gov/

Drug(s)	Mechanism of action	Sponsor
Huperzine A	Acetylcholinesterase inhibitor	Alzheimer's Disease Cooperative Study Group, Neuro-Hitech
Sabcomeline	Muscarinic M1 receptor agonist	GlaxoSmithKline
CX516	AMPAkines	Cortex
Lecozotan	5HT1A receptor antagonist	Wyeth
Paliroden	5HT4 receptor agonist	Sanofi-Aventis
MEM 1003	Neuronal L-type calcium channel modulator	Memory
SGS-742	GABA receptor agonist	Saegis/Novartis
Phenserine	Acetylcholinesterase inhibitor/ beta amyloid precursor protein inhibitor	TorreyPines
Bapineuzumab	Antibody to Aβ	Elan/Wyeth
AN-1792	Antibody to Aβ	Elan/Wyeth
LY-450139	γ-secretase inhibitor	Eli Lilly
PBT-2	Inhibits Aβ oligomer formation, disaggregates plaques	Prana Biotechnology