Review

A History of Antidementic Drug Development in Japan

Masatoshi Takeda, M.D., Ph. D.[1*], *Shinji Tagami, M.D., Ph.D.*[2]

[1]*Osaka Kawasaki Rehabilitation University,* [2]*Department of Integrated Medicine, Division of Internal Medicine, Osaka University Graduate School of Medicine, Osaka, Japan*

Abstract

Objective: Japan is the top runner in the world in society aging, in which the number of patients with Alzheimer's disease has significantly increased and still keeps increasing. Many countries and societies are still struggling with people with dementia and the burden related to the high number of the elderly. In this study, both authors have been involved with research works on elucidating the pathological process of Alzheimer's disease and developing antidementic drugs for more than 30 years. **Methods:** Based on lifetime professional experiences in basic research and clinical work as well as our own contribution in the areas of expertise, we describe in this review the changes of the number of dementia patients and the concept of dementia, as well as the development of antidementic drugs in Japan. **Results:** In this review, we define the super-aged society first. Historical concept changes in Alzheimer's disease, perspectives of research on Alzheimer's disease and drug development, history of antidementic drug developments (for nootropics and drugs for improving brain metabolism and circulation, development of symptom-modifying drugs; hormones, neurotrophic factors, etc.; acetylcholinergic drugs; and glutamatergic drugs), and development of disease-modifying drugs (with amyloid cascade hypothesis, nonsteroidal anti-inflammatory drugs, and amyloid vaccine) have been outlined as review sections. Finally, we devote discussion in two review sections – failure of new drugs and development from the existing drugs as well as development of preemptive medicine. **Conclusion**: We hope that the whole society, including the elderly with and without cognitive decline, can resolve this issue in the near future.

Key words: Alzheimer's disease, acetylcholine esterase inhibitor, γ-secretase inhibitor, immunotherapy
Taiwanese Journal of Psychiatry **(Taipei) 2020; 34: 152-161**

Introduction

In 1994, the World Health Organization (WHO) and the International Association for Alzheimer's disease (ADI) designated the World Alzheimer's Day on September 21 every year as a day for Alzheimer's disease, and various efforts have been made around the world to promote and deepen the understanding of Alzheimer's disease and dementia. In Japan, September 21 has been a national holiday named "Respect for the Aged Day" to celebrate the elderly longer life since the ancient time. Every year, the Japanese Ministry of Health, Labor and Welfare publishes statistics on the elderly on Respect for the Aged Day. According to the White Paper on the Elderly, the proportion of elderly adults aged 65 years and over in 2019 was 28.4% of the population. The number of those senior citizens aged 100 years and over, the so-called centenarians, has an increase of 1,489 from the previous year to 71,274.

Such an increase in the number of the elderly leads to an increase in the number of patients with dementia. According to the WHO, the number of people with dementia was 50 million in 2015, and nearly 10 million new elder adults will have dementia every year [1]. According to the 2017 White Paper on the Elderly in Japan, the number of dementic patients was 4.6 million in 2012, which was 15% of the elderly population. The prevalence of dementia will become 20% in 2025, implying that 1 in 5 old adults aged 65 years and above will have dementia.

Received: Sep. 29, 2020 revised: Oct. 13, 2020 accepted: Oct. 20, 2020
date published: Dec. 17, 2020

Access this article online

Quick Response Code:

Website: www.e-tjp.org

DOI: 10.4103/TPSY.TPSY_33_20

[1]*Corresponding author. 158 Mizuma, Kaizuka City, Osaka 597-0104, Japan.
E-mail: Masatoshi Takeda <masatakeda@kawasakigakuen.ac.jp> or <prof2001@gmail.com>

How to cite this article: Takeda M, Tagami S. A history of antidementic drug development in japan. Taiwan J Psychiatry 2020;34:152-61.

Super-aged Society

The number of demented senior citizens has increased with the extension of life expectancy in humans. According to Gompertz's law [2], the average life expectancy of humans up to the 19th century was such that the number of surviving individuals decreased with age, but medicine has advanced with the goal of reducing the number of deceased individuals with age as much as possible. As a result, many people have survived and lived to their maximum lifespan, increasing the proportion of the elderly in the society. This is, of course, a brilliant achievement of modern medicine, but at the same time, it bears the burden of increasing number of the elderly with dementia.

Japan is the world's front-runner in society aging [3], which is demonstrated by the highest value parameters in the world, including the average life expectancy, the ratio of the elder adults, the ratio of the old adult citizens (meaning the people of 75 years of age and above), and the speed of social aging from the aging to the aged society. No models exist in Western countries including those in Europe and the USA for solving the problems of this super-aging society. Japan is required to take the lead in creating a new social system and building a society in which old adults with dementia can live in safe and peace [3]. It is not only a problem of developing therapeutic pharmaceuticals, but also a social problem imposed on humankind that should be considered within a larger framework. We must integrate the wisdom of all people from Japan and the world to build a society in which the elderly, including those with dementia, have a purposeful and respectful life, supporting each other until the end of their lives. With this perspective, we would like to add our experiences and review the history of the development of antidementic drugs.

Historical Changes in the Concept of Alzheimer's Disease

Since Alois Alzheimer presented the first case of the patient with Alzheimer's disease at the South German Psychiatric Association on November 3, 1906, the understanding and treatment of elderly dementia has changed significantly.

Auguste Deter, the first case of the patient with Alzheimer's disease, was a 51-year-old woman who was admitted to Fensteiner Feld Mental Hospital in Frankfurt in November 1901 [4]. When she was hospitalized, she could not live independently and could not recognize the face of her husband who was a clerk of the railway station. She kept talking about an incomprehensible thing. At this time, Alois Alzheimer, a 37-year-old *Nervenarzt*, became a doctor in charge and kept a detailed medical record on the patient. In 1903, Alzheimer was transferred to become the director of the Department of Psychiatry at the University of Munich, which was presided by Emil Kräpelin in those days. The patient died at the age of 55 years after a hospitalization for 4½ years, and the specimen of her brain from the autopsy was sent to Alzheimer in Munich. Then, at the 37th South German Psychiatric Association Meeting held in Tubingen on November 3, 1906, Alzheimer presented the neuropathological findings of this autopsy brain under the title of "Über eine eigenartige Erkrankung der Hirneinde" [4].

The name of Alzheimer's disease (*Morbus Alzheimer*) was described for the first time in the eighth edition of the textbook written by Emil Kräpelin, published in 1913 [4]. Kräpelin described Alzheimer's disease as follows: "Alzheimer describes a unique group of cases with very severe cell changes in the cerebrum… This is a very serious, slowly progressing disease with unclear symptoms due to an organic brain disease. After a few years, the patient gradually becomes mentally weak, loses memory, becomes poor in thought, becomes confused, and becomes vague. The patient misidentifies things and gives all belongings to someone. Then, the patient shows a restless state. Talking, muttering in the mouth, singing, laughing, wandering, messing with hands, rubbing, grabbing, dirtying. The language disorder is especially noticeable. The patient can still speak each word or sentence, but always falls into a meaningless chat. The chat is also lacking in intonation and repeats the same syllable many times. The significance of the clinical symptoms of Alzheimer's disease is currently unknown [4]."

Alzheimer's disease, initially coined by Kräpelin [4], was a rare type of dementia that presents with various psychological symptoms of senile onset and was a pathological condition that should be distinguished from cerebral arteriosclerosis and progressive paralysis, being classified into neurodegenerative disease. For a long time, Alzheimer's disease, along with Pick's disease, had been regarded as a presenile dementia with onset age of 65 years and younger. That is, Alzheimer's disease is originally a disease with presenile onset age and is distinguished from senile dementia which appears after the age of 65 years.

The concept of senile dementia itself has changed over time. The greatest risk factor for senile dementia is aging, and the prevalence of senile dementia is doubled every five years after the age of 65 years. Previously, forgetfulness due to aging and some worse cognitive function were regarded as the inevitable consequences of brain aging, and such aging changes of the brain have been referred to as "normal aging" [5]. Only when the degree of cognitive decline was so strong that the subject was regarded as "pathological," and given the diagnosis of senile dementia. This kind of understanding was also a valid view from the understanding of brain aging at that time. It is considered that the nerve cells in the brain do not regenerate and, therefore, the nerve cells in the brain are decreased due to aging. The decrease in brain volume due to aging is due to the loss of such nerve cells, recognized as the atrophy of the brain. This finding is because it was thought to cause functional decline. This understanding was due to the fact that the basic process of brain aging has not been clarified, but it was understood that the cognitive function necessarily is declined with aging of the brain up to 50 years.

Since the 1980s, neuropathological and biochemical studies on dementia have been significantly changed the above viewpoint. In both Alzheimer's disease and senile dementia,

the main pathological findings are neurofibrillary tangles and senile plaques, and the appearance of these pathological hallmarks has been considered to be a common pathological process in the nerve cells of the diseases and the aged brain. The pathological processes of both physiological and pathological brains are indistinguishable, and both are collectively referred to as senile dementia of Alzheimer type (SDAT) or dementia of the Alzheimer type (DAT) [6]. When the term Alzheimer's disease is spread in the lay public, the name of Alzheimer's disease has been widely accepted, including not only Alzheimer's disease but also SDAT and DAT. In those days, the concept of Alzheimer's disease was the one contrasting to vascular dementia [6], and all degenerative dementias other than vascular dementia were collectively called Alzheimer's disease.

Advances in dementia symptomology and brain imaging in the 1990s have made it possible to recognize that Alzheimer's disease includes a wide range of neuropathological conditions from typical to atypical cases. Then, some of the degenerative dementias that were once classified as Alzheimer's disease were regarded as independent diseases, that is, as non-Alzheimer's type dementia, Nowadays, Lewy body dementia, frontotemporal dementia, cortico-basal degeneration, and silver granulocytic dementia are regarded as different neurodegenerative dementia other than Alzheimer's disease. Alzheimer's disease itself is also classified into several subtypes – young-onset type (early onset) Alzheimer's disease and late-onset type (late onset) Alzheimer's disease according to onset age and familial Alzheimer's disease (familial Alzheimer's disease) or sporadic Alzheimer's disease depending on the presence or absence of genetic load of the disease.

In Japan, the term *chihou* (unwise + stupid) was used as a translation of the word dementia for a long term. But the term *chihou* was considered to have a discriminatory meaning and, in 2004, a new translation of dementia *ninchisho* was introduced, meaning cognitive impairment. The movement of reducing stigma for dementia can be observed in Europe and other Western countries [7]. Originally, the term dementia itself is a compound word of de (de) + mentia (mental), and there is an opinion that dementia contains negative nuances as if the entire mental function was lost. In 2013, *DSM-5* introduced the term neurocognitive disorder instead of dementia [8].

The authors think that the changes in the concept of Alzheimer's disease as described above may have been influenced in part by the development status of therapeutic drugs. As will be described later, when the first therapeutic drug for Alzheimer's disease was launched in the late 1990s (donepezil launched worldwide in 1996 and in Japan in 1999), a great expectation existed for such drug therapy, and the use of the drug has come to be recommended for many old adults with cognitive decline. An atmosphere would have existed where it was natural to use a drug if it was effective at all. Around this time, we also had many opportunities to give lectures on therapeutic agents for Alzheimer's disease in various places in Japan and at international conferences in Asian countries. Medical experts considered that forgetfulness of the elderly in the general public was an aging phenomenon, and the fact that cognitive decline in the elderly is caused by diseases is not shared by the general lay public. We often heard that it was a major issue in promoting drug therapy.

Recent advance in brain sciences has provided new insights on brain aging and cognitive decline. Although it was known that brain volume is decreased by 20%–30% with aging, the number of nerve cells in the brain does not decrease as expected from this volume decrease, and most of the decreased brain volume is due to a reduced neurites rather than a decreased number of neurons, and in part is explained by a decrease in large neurons and an increase in small neurons in the endoplasmic reticuli. The neurogenesis of human hippocampal dentate gyrus has also been identified in the elderly although the function of these newly generated neurons has not been fully understood. Thus, the idea that nerve cells in the central nervous system will not be newly produced, has been denied. Those findings suggest that preventing cognitive decline in the elderly is possible through promoting research on brain aging and finding ways to maximize the brain function of the elderly.

Nevertheless, the pathological process of Alzheimer's disease is closely related to the aging of the brain. Neurofibrillary tangles, senile plaques, and neuronal loss, which are considered the basic pathological findings of Alzheimer's disease, are observed in the brain of normal elderly adults, although to a lesser extent. As described above, the greatest risk factor for Alzheimer's disease is aging, but the prevalence of Alzheimer's disease exceeds 50% at the age of 100 years and over, implying that the cognitive function of less than half of the centenarians is normal. We would like to wait for future discussions as whether those kinds of nondementic centenarians are normal [5], or whether they are selected above the average, which should be called supernormal.

Historical Perspectives of Research on Alzheimer's Disease and Drug Development

Since Alois Alzheimer's description of neurofibrillary tangles and senile plaques, research on the pathogenesis of Alzheimer's disease had been centered on neuropathological research, trying to elucidate mainly the structural characteristics of pathological hallmarks without producing major progress for about 70 years. It was not the neuropathological research efforts but the introduction of biochemical research methods into Alzheimer research field that made great contribution to understanding the pathophysiology of Alzheimer's disease [9,10].

Neurofibrillary tangle is observed as a characteristic structure (paired helical filaments, PHF) in which two 10-nm diameter fibers are twisted together under an electron microscope [11]. In the early years of Alzheimer research, it was believed that normal fibrous protein is changed to form characteristic insoluble structures in the brain of Alzheimer's disease [12, 13], and we were engaged in research on the formation mechanism of neurofibrillary tangles. At that time,

it was at the dawn of research on cytoskeletal proteins, and cytoskeletal proteins are classified into microtubules (φ25 nm), intermediate fibers (φ10 nm), and microfilaments (φ8 nm) according to their length in diameters. Microtubules consist of tubulin and microtubule-associated proteins (MAPs) and tau, which is ubiquitously distributing in the cells of all organs. In the neuronal cells, intermediate fibers are named neurofilaments, which consist of three kinds of constituent proteins NF-L, NF-M, and NF-H. Intermediate fibers of glial cells are glial fibers consisting of glial fibrillary acidic protein (GFAP). We were involved with the experiments trying to produce experimental PHFs in experimental animals and human brain based on the fact that the shape of PHFs is to be a twisted form of two neurofilaments.

We were one of the first investigators who developed an animal model of experimental PHF using aluminum administration into rabbit brain [14, 15]. Aluminum administration-induced neurofilament hyperplasia also reproduced microtubule inhibitors such as colchicine and vinblastine intracerebral administration into the rabbit brain. In fact, when we examined the intermediate-sized fibers of Alzheimer's disease, we found that changes exist in GFAP in glial cells and in vimentin in epithelial cells. We reported that the administration of colchicine and vinblastine increases the amount of neurofilament in the experimental animal brain [14, 15]. We failed to verify our working hypothesis that PHFs might be composed of twisted two-strand neurofilaments in human brain. Looking back the failure of our experimental approach from now, we were overly dragged by the morphology of PHFs which looked like 10 nm double helical fibrils.

PHFs from the brain homogenate of Alzheimer's disease patients stained with thioflavin S were individually collected one by one using an aspirator under a fluorescence microscope, and several thousand PHFs were pooled and studied. When analyzed using sodium dodecyl sulfate electrophoresis, a smear band was detected at a position of 50,000–70,000 Da, but there were limited samples for immunostaining, and regrettably the band could not be identified by Western blotting. In 1986, it was revealed that the constituent protein of PHF is phosphorylated tau [13-15].

History of Antidementic Drug Developments

Based on neuropathological and biochemical research, development of Alzheimer's disease therapeutic agents has been progressed. Here, we would like to look at the history of drug development along with the progress of research on the pathology of Alzheimer's disease. Figure 1 shows the level of drug development in Japan in three levels. Level 1 is before the launch of drug acetylcholine (Ach) esterase inhibitors. Level 2 is the use of AchE inhibitors (donepezil, galantamine, and rivastigmine) and the *N*-methyl-D-aspartate (NMDA) antagonist (memantine), those are currently in the market as level 2. All drugs in level 2 are not powerful enough in therapeutic efficacy to reverse the pathogenetic

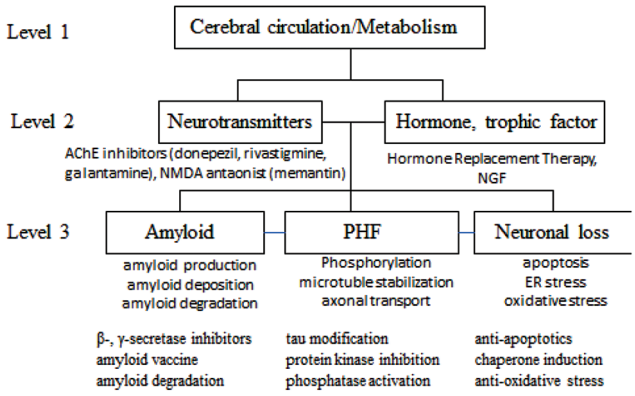

Figure 1. Development of antidementia drugs. Levels 1, 2, and 3 represent the past, now, and the future, respectively. NMDA, *N*-methyl-D-aspartate; NGF, nerve growth factor; PHF, paired helical fragments; AchE, acetylcholinesterase; ER, endoplasmic reticulum.

process of Alzheimer's disease, and further development of more effective drugs is expected as level 3. Based on the history of pathological research, the history of therapeutic drug development will be divided into three levels according to the schema (Figure 1).

History of nootropics and drugs for improving brain metabolism and circulation

In the 1980s, cognitive decline in the elderly with increasing lifespan attracted attention, leading to the proposal of the concept of age-associated memory impairment (AAMI) and age-associated cognitive decline (AACD). With the increased interest in the diet, various nutritional foods and supplements were tried with the aim at suppressing cognitive decline in the elderly. Omega-3 fatty acids – as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) – folic acid, vitamin B6, vitamin B12, and vitamin E are currently considered to have insufficient effects on cognitive decline [16, 17]. Ginseng (*Panax ginseng*) has many negative opinions [18], but Ginkgo biloba, which had been commercialized mainly in Europe since then, may still improve the cognitive function of the elderly. As expected, sufficient evidence is not obtained [19]. Regarding drugs, pramipexole, guanfacine, clonidine, and fexofenadine have been studied and all have been judged to be ineffective [20].

These facts are a retrospective evaluation based on the knowledge obtained by the time of writing in 2020, but at that time, many pharmaceutical companies were competing to develop drugs for the purpose of improving cognitive function for the elderly. Drugs developed to improve the cognitive function for the elderly are called "nootropics" [21], and Nishimura first introduced nootropics into Japan.

The nootropic drugs include cerebral metabolism-improving drugs and circulation-improving drugs and, in particular, drugs having a chemical structure known as racetams were expected to act as nootropic drugs. Racetams include piracetam [22], oxiracetam, phenylpiracetam, and aniracetam, and the mechanism of action of piracetam and aniracetam is a choline-

type mediated by the allosteric effect of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Basic laboratory data were reported and looked promising, but clinically sufficient effect was not shown in clinical trials [23]. Until the 1990s, many cerebral metabolism and circulatory agents had been frequently prescribed in Japan.

In 1999, as a result of re-evaluation by the Japanese Ministry of Health, Labor and Welfare, the usefulness of most cerebral metabolism-improving drugs was denied, including calcium popanthenate, which was a typical cerebral metabolism-improving drug. Because calcium popanthenate was used as the competitor in many clinical trials of nootropics in those days, authorization of the prescription of most cerebral metabolism and circulatory agents was invalidated. Thirty-one items approved as cerebral metabolism- and circulation-improving drugs were denied in 1999. The only survived drug was ifenprodil (Cellocral) [24-26], and nilvadipine (Nivazil), ibuzilast (Ketas), and vinpocetine (Caran) were not denied, but further clinical trial was required with placebo as comparison, and their effectiveness against placebo was not proven. Other drugs including tocopherols, calidinogenase, nicardipine, trapidil, and dihydroergotoxin were exempted from cerebral circulatory metabolism-improving drugs, but these drugs have other indications and are left on the health insurance coverage.

Pentoxifylline, lisuride, brovincamine, moxicilitocinnarizine, flunarizine, and cyclanderetate were banned from marketing due to approval cancellation. Five remaining drugsare are nicergoline (Sarmion), nilvadipine (Nivadir), ibudilast (Ketas), vinpocetine (Caran), and ifenprodil (Cellocral) [24-26], those were regarded as cerebral circulation-improving drugs and cerebral metabolism-improving drugs, were banned as cerebral metabolism-improving drugs. Only aniracetam (Dragannon) remained as a cerebral metabolism-improving drug. Of course, none of those drugs is a therapeutic drug for Alzheimer's disease, and is indicated for improving mental symptoms due to sequelae of cerebral infarction or cerebrovascular disorder, and is not effective for improving cognitive impairment.

Hormones, neurotrophic factors, etc.

In the 1980s, much information was collected on the abnormalities of hormones and neurotrophic factors in the brain of patients with Alzheimer's disease. It was thought that hormones such as estrogen and neurotrophic factors such as nerve growth factor (NGF) may improve cognitive function, and many studies have been conducted. Eventually, a large-scale clinical trial of administering estrogen as hormone replacement therapy was planned and carried out halfway, but the effect of estrogen as a dementia therapeutic drug is not confirmed. NGF was also experimentally administered to a small number of patients, but it was not developed as a therapeutic drug.

Acetylcholinergic drugs

The investigation of neurotransmitters in the brain has been energetically advanced, and it has been revealed that acetylcholine (ACh) significantly decreases mainly in the basal ganglia in the brain of patients with Alzheimer's disease [27]. All parameters regarding the ACh system are decreased in Alzheimer's disease brain, including the number of cells in the originated nuclei, Ach synthase (choline acetyltransferase [CAT]) activity, degrading Ach enzyme (AchE) activity, and ACh level. Not surprisingly, the choline replacement therapy, which is the source of ACh, was first considered. Lecithin, an ACh precursor, was tried, but it was abandoned because lecithin ingestion of several tens of grams was required to increase ACh in the brain. Then, ACh synthase activator, ACh degrading enzyme (acetylcholine esterase [AChE]) inhibitor, muscarinic ACh receptor agonist, nicotinic ACh receptor agonist, second messenger downstream of ACh receptor reinforcement agents were targets of cholinergic drug development against Alzheimer's disease.

It was tacrine with AChE inhibitory effect that first emerged from the drug development research based on the ACh hypothesis. The theoretical background of the effectiveness of AChE inhibitors is based on the fact that the ratio of synthase (CAT)/degrading enzyme (AchE) in Alzheimer's disease brain is significantly lower than that in healthy subjects, and higher degrading enzyme activity should be suppressed to normalize ACh metabolism [28, 29]. In 1993, tacrine was put on the market as the world's first drug for Alzheimer's disease. Good response was reported in some cases, but it was not widely used due to its limited efficacy and severe hepatotoxicity in many cases.

The drug against Alzheimer's disease that has become widely used in the world is donepezil. Donepezil is a long-acting ACh esterase inhibitor with low hepatotoxicity, which has high selectivity for ACh esterase compared with that of butyryl choline esterase. Phase I clinical trial of donepezil was completed in Japan in 1989, and Phase I in the USA in 1991 was successfully completed. Donepezil was approved by the US FDA in November 1996. Donepezil was marketed by Eisai and Pfizer and became the most popular drug for Alzheimer's disease in the world. It was approved in Japan in November 1999.

In 2011, three new drugs for Alzheimer's disease were introduced in Japan, namely, rivastigmine, galantamine, and memantine. Rivastigmine and galantamine had been used all over the world more than 10 years before, and they were finally launched after delayed development in Japan. Galantamine has an allosteric-potentiating effect on nicotinic receptors in addition to an ACh esterase inhibitory effect, and is also expected to have a neuronal protective effect. It was put on market in US and Europe by Janssen in 2000, and was launched in Japan in March 2011. It was jointly sold by Janssen Pharma and Takeda under the product name Reminyl®, which has been used around the world. Then, in June 2011, rivastigmine was put on the market. Rivastigmine is a drug that has a butyrylcholinesterase inhibitory action in addition to an ACh esterase inhibitory action, and is a drug developed by Novartis under the trade name Exelon® since 1997. In Japan, only the patch formulation was developed and was released by Novartis under the trade name Exelon® patch and by Ono Pharma as Rivastouch patch. In the brain of advanced

Alzheimer's disease, ACh esterase activity is assumed to be decreased and butyrylcholinesterase activity is relatively increased. In such a condition, butyrylcholinesterase inhibitory activity of rivastigmine is expected to show clinical use.

Glutamatergic drug

Though originally planned to be released in March 2011, Memantine was delayed in release due to the Great East Japan Earthquake in Japan, and put on the market by Daiichi Sankyo Co., Ltd. in June 2011 with the trade name of Memary®. Memantine is a drug having an NMDA receptor antagonistic action, and was originally developed by German pharmaceutical company Meltz and has been used worldwide since 2002 for patients with moderate-to-severe Alzheimer's disease. Initially, Suntory was involved in the development of memantine in Japan, and after the re-organization of the company, it once went to the hand of Azbiopharma and was finally put in the market by Daiichi Sankyo. Memantine has an antagonistic effect on the NMDA glutamate receptor, and acts protectively on nerve cells through controlling abnormal firing of the NMDA receptor and preventing calcium influx.

Development of Disease-modifying Drug

Currently, three types of ACh esterase inhibitors and one type of NMDA antagonist are widely used; none of those drugs modify the pathological process of Alzheimer's disease. Because cognitive decline progresses even if the drug is continued to be administered, all those drugs are for symptomatic treatments that improve cognitive function for a certain period of time. At this moment, no drug exists to improve the pathological process of Alzheimer's disease. Therefore, even if there is a temporary cognitive improvement effect at the beginning of the use of those drugs, cognitive function declines beyond the baseline after 48 weeks (Figure 2).

In this sense, an urgent need exists to develop Level 3 drugs (Figure 1), and researchers in this field have been working hard to develop disease-modifying drugs that modify the pathological process itself of Alzheimer's disease and suppress the progression of the pathological process. The candidates for disease-modifying drug are those based on the amyloid hypothesis, those related with neurofibrillary change formation, and those directly involved with neuronal apoptosis as shown in Level 3 of Figure 1.

Amyloid cascade hypothesis

Once the method was found to solubilize amyloid deposit in the core of senile plaques with formic acid, the amino acid sequence of amyloid protein has been soon completed, and the amyloid precursor protein (APP) gene has been identified based on the partial sequence information of amyloid protein. APP gene has been identified in chromosome 21 (21q21.3-q22.05) [30].

Once the causative gene of Alzheimer's disease was identified, missense mutations on APP gene were identified with familial Alzheimer's disease, and subsequent research has been progressed rapidly. The amyloid β protein deposited in the core of senile plaque and blood vessel wall has been found to be the excised peptide from APP through the action of β-secretase and γ-secretase. The processing mechanism of APP has been vigorously promoted to lead the amyloid cascade hypothesis of Alzheimer's disease.

As shown in Figure 3, various causes, including aging, gene mutations, intoxication, and others, the production of amyloid β protein from APP is enhanced, resulting in the phosphorylation of tau, and the formation of neurofibrillary tangles, which eventually results in the death of nerve cells, causing neural degeneration and clinical symptoms of dementia. This hypothesis has become widely accepted, and drug development based on the amyloid cascade hypothesis has been vigorously pursued with the aim of developing a therapeutic drug for Alzheimer's disease.

Nonsteroidal anti-inflammatory drugs

Amyloid β protein is cleaved from APP through β-secretase, and then γ-secretase. Presenilin-1 complex is identified as γ-secretase, and γ-secretase inhibitors or γ-secretase modulators have been studied as a candidate for disease-

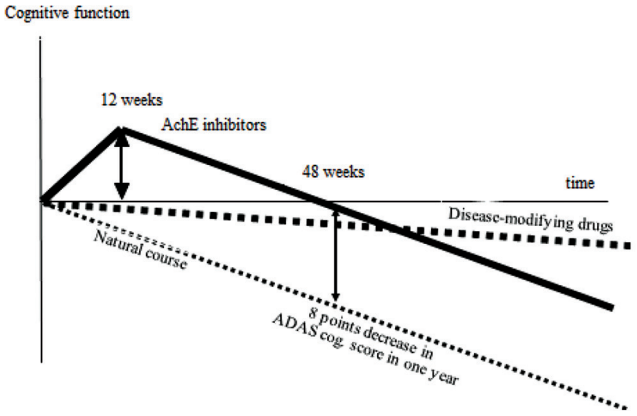

Figure 2. Symptomatic drug and disease-modifying drug against Alzheimer's disease. AchE, acetylcholinesterase; ADAS-Cog, Alzheimer's disease assessment scale-cognitive subscale.

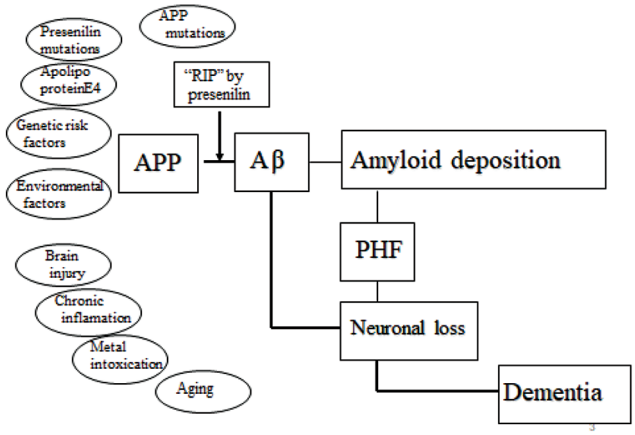

Figure 3. The amyloid cascade hypothesis. App, amyloid precursor protein; Aβ, amyloid beta-protein; PHF, paired helical filaments.

modifying drug. In fact, there are various amyloid *β* proteins with different length, including amyloid β-protein 42 (A*β*42) and A*β*40, which are produced by sequential action of γ-secretase. A*β*42 is regarded more toxic than A*β*40, and drugs which affect γ-secretase activity can be a candidate for disease-modifying drug.

Abundant data exist to show the relationship between Alzheimer's disease and chronic inflammation. In addition to epidemiological findings suggesting that the use of nonsteroid anti-inflammatory drug (NSAID) suppresses the onset of Alzheimer's disease, the γ-secretase modulator activity of NSAID has been studied. For example, flurbiprofen has a strong inhibitory effect on amyloid production, and tarenflurbil, an optical isomer (R enantiomer) of flurbiprofen, inhibits amyloid production without any cyclooxygenase (COX) inhibitory effect.

Based on these laboratory findings, clinical trials of flurbiprofen and tarenflurbil were conducted, but unfortunately the results of the trials have been unsatisfactory [31], and Myriad Genetics announced in June 2008 that it abandoned the development of tarenflurbil as a disease modifier for Alzheimer's disease. We have been involved with the research of γ-secretase inhibitors and γ-secretase modifiers under the purpose of developing disease-modifying drugs and our contribution was recently reviewed elsewhere [32].

The clinical effectiveness of tarenflurbil was so highly expected from the data of animal experiments and theoretical background that the impact of this trial failure was shocking to the academia and developer of the drug, realizing how difficult it is to develop a drug for treating Alzheimer's disease. As an extreme opinion, it is argued that despite the fact that tarenflurbil has sufficient power, there might be a problem with the method of clinical trial itself.

Amyloid vaccine

In Alzheimer's disease brain, Aβ42 is produced more than the non-Alzheimer brain, and of increased amount of Aβ42 is insolubilized to be deposited as amyloid fibrils. Although the mechanism of toxicity of brain amyloid remains unclear, amyloid β oligomers are thought to be more toxic than insoluble amyloid deposits, causing neurodegeneration in Alzheimer brain. The report that administration of aggregated Aβ42 to APP transgenic (APPTG) mice with large amount of amyloid plaques can reduce amyloid deposits in the brain was accepted as a big surprise because the central nervous system was thought to be isolated from the systemic immune system due to the blood–brain barrier, which inhibits the entry of antibody against Aβ into the brain. This report opened the way for immunotherapy to Alzheimer's disease [33]. In mice immunized with aggregated Aβ42, degenerated axons and astrogliosis are significantly reduced, indicating that amyloid vaccine improves short-term memory and spatial cognitive function in APPTG mice [34]. Furthermore, administration of monoclonal antibodies against Aβ to APPTG mice caused 80% reduction of amyloid plaques [35].

Based on the results of those animal experiments, the first clinical trial (AN-1792) of the amyloid β42 vaccine was started. Phase 1 was safely completed, and Phase 2 started in September 2000, confirming the antibody titer to Aβ in the serum of the administered patients [36]. The cognitive function of the vaccinated patients using mini-mental status examination (MMSE) was −6.3 ± 4.0 points in the untreated group and −1.4 ± 3.5 points in the anti-Aβ antibody-positive group after one year, showing significant differences between the groups [37]. But in March 2002, 19 study patients (5.2%) developed aseptic meningitis, and the clinical trial was discontinued [38].

In this way, the first amyloid vaccine (Elan, AN-1792) was unsuccessful, but it provided many findings, such as increased antibody titers to amyloid fibrils in patients who received several doses of the vaccine. Elan's clinical trial was vaccination with active immunization in which the whole amyloid β42 molecule was immunized with an adjuvant (QS-21).

Then, many research groups from Myeth, Myeth/Elan, Roche, MSD, GSK, and Pfizer conducted passive immunization. In addition, various antibodies against the *N*-terminal, the central portion, and the *C*-terminal of the amyloid peptide epitope were also studied. Such immunotherapy is expected to activate neurites that have been impaired due to the formation of senile plaques, to stimulate nerve regeneration, activate neurite outgrowth, and repair amyloid angiopathy. Side effects of amyloid vaccines such as aseptic meningoencephalitis, small bleeding, and angiogenic edema should be overcome.

Failure of New Drugs and Development from Existing Drugs

The development of disease-modifying drugs for Alzheimer's disease has progressed smoothly in most cases to the level of animal experiments. But many candidates for disease-modifying drug have failed repeatedly in clinical trials over 20 years. As described above, the development of both γ-flurbiprofen (Myriad) and semagacestat (LY450139 of Eli Lilly) had to be interrupted due to the failure in clinical trials.

As for amyloid vaccine, clinical trials of bapineuzumab and solanezumab were suspended, and high-dose globulin therapy (intravenous immunoglobulin) was also failed. As a result of the continued awareness of the difficulty of developing Alzheimer's disease therapeutic agents, some pharmaceutical companies are searching for Alzheimer's disease therapeutic agents focusing on the existing drugs to reduce the risk of development, which might be the last resort of some pharmaceutical companies to fulfill the unmet needs. Here is just one such example.

Dimebon (latrepirdine) is a nonspecific antihistamine that has long been used in Russia. Dimebon has been reported to have cholinesterase inhibitory action, NMDA receptor inhibitory action, and mitochondrial permeability inhibitory action, expecting to have some effect on Alzheimer's disease and Huntington's disease model animals, and clinical trials of Dimebon for Alzheimer's disease were conducted. Doody et al. reported the results of a randomized, double-blind trial of Dimebon with 183 patients of mild-to-moderate Alzheimer's disease with 11–24 MMSE at 11 centers in Russia [39].

The results of the trial are surprisingly clean. This trial was conducted in Russia, where the use of cholinesterase was not generally widespread, maximizing the advantage of trials without being affected by other drugs. To obtain scientific knowledge, patients with Alzheimer's disease need to be treated with placebo for a long period of six months or one year, but it is difficult with the current availability of other therapeutic agents asking for the participation into clinical trials with the option of not administering other therapeutic agents. Probably, such trials were possible only in Russia, considering ethical issues where administration of ACh esterase inhibitors has not yet been widely approved.

We think that the clinical trial report of Dimebon has two meanings. The US FDA as well as the Japanese Pharmaceutic and Medical Device Agency has the following two criteria for approval of drugs for Alzheimer's disease:

- Having psychological tests such as ADAS-cog to show improvement in cognitive function,
- Showing an actual improvement in activity in daily life and clinical symptoms in addition to having improvement in assessment test such as Clinician's Interview-based Impression of Change (CIBIC), indicating an actual improvement in activity in daily life and clinical symptoms.

While many candidate drugs have been forced to stop development because the second criterion was not fully proved, Dimebon's report showed that the drug can actually meet the two criteria of improving cognitive function and improving clinical symptoms. It was meaningful in showing the fact that there is a possibility of meeting both the criteria. Another meaning of Dimebon experience is the potential of already-developed drugs as anti-Alzheimer drug. Dimebon was originally intended to be developed as an antihistamine, but it was no longer used because a new, more specific antihistamine formulation was developed. This is because the development direction of seeking new indications for such known drugs can significantly reduce the development cost.

Based on this idea, the effectiveness of many existing drugs as therapeutic agents for Alzheimer's disease was examined including 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (atorvastatin, simvastatin), insulin-resistant diabetes drug (rosiglitazone), compound with both ChE inhibitory action and Aβ production inhibition (phenserine), Aβ polymerization inhibitory action (tramiprosate), and 5-HT1A agonist (xaliproden). Clinical trials of those existing drugs were conducted, but no efficacy has not been confirmed as of September 2020.

Development of Pre-emptive Medicine

The failure of amyloid immunotherapy has resulted in intense debates focusing how difficult it would be to develop a therapeutic drug for Alzheimer's disease. A typical argument is aimed at understanding what is the reason of the gap between animal studies and human clinical trials. For example, we discussed many questions whether removal of brain amyloid helps improve cognitive function in humans, whether the amyloid cascade hypothesis is valid, and whether the evaluation method in clinical trials of dementia is appropriate.

Those who received the amyloid vaccine demonstrated significantly reduced amount of amyloid in the brain, and the amount of amyloid reduction was well correlated with the serum antibody titer. But no improvement in cognitive function was observed in patients with marked amyloid reduction. Various discussions existed in the difference between animal experiments and clinical human trials, in which reduction of amyloid deposits in the animal brain is usually accompanied with improvement of memory function of the animals. The core question on this point is whether clinical cognitive improvement can be expected only by removing amyloid in the brain of patients with Alzheimer's disease.

So far, many researchers still believe in the validity of the amyloid cascade hypothesis. It is clearly demonstrated that the amyloid vaccine can suppress amyloid deposition in the brain. The question is whether the subsequent pathological processes such as inflammation, tau pathology, free radical activation, and calcium mobilization can be suppressed by the amyloid vaccine. Concerns have been raised that such pathological processes once induced by amyloid may not be suppressed even when amyloid is removed by amyloid vaccine administration.

As a result of such discussions, the protocol for the clinical trials of Alzheimer's disease has been reviewed. In Alzheimer's disease, changes such as amyloid deposition in the brain and abnormality of tau protein have occurred for more than 10 years before the onset of clinical symptoms. One of the methods to make amyloid vaccine administration effective enough to improve clinical symptoms might be to administrate the vaccine early enough before the onset of the following pathological events. It is possible to select an individual who is likely to develop a clinical symptom in the near future by using adequate biomarker before the clinical symptom appears. For example, selecting individuals having mutations in the gene causing familial Alzheimer's disease is possible. Individuals with amyloid deposition identified using positron emission tomography (PET) have a decreased amyloid β42 level, as well as an increased level of tau protein and phosphorylated tau protein through cerebrospinal fluid tapping.

Currently, clinical trials for patients with Alzheimer's disease drug including amyloid immunotherapy are based on the protocol targeting at individuals with brain pathologies before the onset of clinical symptoms. In other words, we will investigate the individuals in the period before having clinical symptoms to find whether administering drug can significantly delay the onset of clinical symptoms, through follow-up for the changes of biomarkers for several years. As shown in Figure 4, the recent clinical trials are now conducted based on this protocol [40].

Conclusion

Originally, the amyloid cascade hypothesis was derived from the findings of familial Alzheimer's disease caused by mutations in the APP, PS-1, or *PS-2* genes, and the new finding

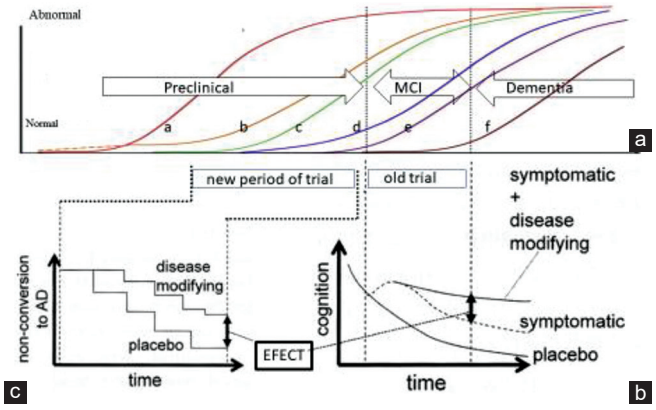

Figure 4. New protocol for drug development using biomarkers. (a) The upper panel of Figure 4 depicts the stages from preclinical, to MCI, and MCI to dementia in cognitive function against the sequential changes in biomarkers of Alzheimer's disease; line a, beta amyloid accumulation in CSF and/or PET; line b, synaptic dysfunctions represented by FDG-PET and/or fMRI; line c, tau-mediated neuronal injury in CSF; line d, brain structure in volumetric MRI; line e, cognition, and line f, clinical function. (b) The lower right panel of Figure 4 shows the conventional protocol for antidementic drug development in which the recruited individuals are usually under treatment with symptomatic drug, and it is difficult to demonstrate the drug effect of a candidate disease-modifying drug. (c) The lower left panel of Figure 4 shows a new protocol for disease-modifying drug development, in which the individuals are recruited using biomarkers, and the conversion rate from preclinical to clinical stage is to be compared between disease-modifying drug and placebo. MCI, mild cognitive impairment; AD, Alzheimer's disease; FDG-PET, fluorodeoxyglucose-positron emission tomography; fMRI, functional magnetic resonance imaging; CSF, cerebrospinal fluid. Modified from Jack et al., 2010.

of familial Alzheimer's disease is that the ratio of amyloid β42/amyloid β40 significantly increases due to higher production of amyloid β42. The increase in amyloid β42 occurs more than a decade before the onset of clinical symptoms. It has been later proved that the amyloid cascade hypothesis is valid in sporadic patients with Alzheimer's disease.

Clinical trials of amyloid immunotherapy have raised a serious question whether the pathological process after amyloid β deposition in humans can be completely recovered by removing amyloid β. Even though amyloid antibody removes the deposited amyloid in the brain, a strong opinion exists that improvement of the cognitive function of individuals with clinical symptoms of dementia might be difficult. The pathological process once triggered though amyloid β may continue to run even when amyloid β is removed. Because microglia and inflammatory cytokines are involved in the pathological process after amyloid deposition, these processes might be kept activated without amyloid β.

There is a finding that reducing the expression of tau in APP and tau double transgenic model animals reduces the pathological process, suggesting that the pathological process can be changed by the amount of tau regardless of amyloid deposition. Although tau pathology is yet to be studied, tau phosphorylation levels are regulated by protein kinases such as GSK3, cyclin-dependent kinase 5, and protein dephosphorylates such as PP1, PP2A, and PP2B. Excessive protein phosphorylation occurs in the brain of Alzheimer's disease, and tau protein is also overphosphorylated and insolubilized to form neurofibrillary tangles. Although it has the potential to be a therapeutic drug for patients with Alzheimer's disease, currently, no therapeutic drugs exist to be related with tau pathology.

Financial Support and Sponsorship

None.

Conflicts of Interest

The authors declare no potential conflicts of interest in writing this review.

References

1. Shinfuku N: What is happening in the mental health system in Japan: some observations. *Taiwan J Psychiatry* (Taipei) 2012; 26: 70-6.
2. Gompertz B: On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. *Philos Trans R Soc* 1825; 115: 513-85.
3. Arai H, Ouchi Y, Toba K, et al.: Japan as the front-runner of super-aged societies: perspectives from medicine and medical care in Japan. *Geriatr Gerontol Int* 2015; 15: 673-87.
4. Kraepelin E: *Psychiatrie: Ein Lehrbuch für Studirende und Aerzte*. 8th ed. Leipzig: J. A. Barth, 1913: 668.
5. Takeda M, Shen WW: The hypothesis of cognitive reserve. *Taiwan J Psychiatry* (Taipei) 2015; 29: 70-9.
6. American Psychiatric Association: *The Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association, 2000.
7. Suzuki J: Trends in change of names for mental diseases in Japan. *Seishin Shinkeigaku Zasshi* 2005; 107: 1139.
8. American Psychiatric Association: *The Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association, 2000.
9. Selkoe DJ, Ihara Y, Salazar FJ: Alzheimer's disease: insolubility of partially purified paired helical filaments in sodium dodecyl sulfate and urea. *Science* 1982; 215: 1243-5.
10. Nishimura T, Hariguchi S, Tada K, et al.: Changes in water-soluble brain protein in normal and abnormal ageing. In: Hirano A, Miyoshi K, (eds).: *Neuropsychiatric Disorders in the Elderly*. Tokyo: Igakushoin, 1983: 79-84.
11. Takeda M, Tada K, Nishimura T: Alteration of cytoskeletal proteins in Alzheimer's disease brain. *JANO* (Barcelona) 1989; 3: 323-31.
12. Tanaka J, Murakoshi K, Takeda M, et al.: A high level of anti-GFAP autoantibody in the serum of patients with Alzheimer's disease. *Biomed Res* 1988; 9: 209-16.
13. Nukina N, Ihara Y: One of the antigenic determinants of paired helical filaments is related to tau protein. *J Biochem* 1986; 99: 1541-4.
14. Grundke-Iqbal I, Iqbal K, Quinlan M, et al.: Microtubule-associated protein tau: a component of Alzheimer paired helical filaments. *J Biol Chem* 1986; 261: 6084-9.
15. Ihara Y, Nukina N, Miura R, et al.: Phosphorylated tau protein is integrated into paired helical filaments in Alzheimer's disease. *J Biochem* 1986; 99: 1807-10.
16. Cooper RE, Tye C, Kuntsi J, et al.: Omega-3 polyunsaturated fatty acid supplementation and cognition: a systematic review and meta-analysis. *J Psychopharmacol* 2015; 29: 753-63.
17. Forbes SC, Holroyd-Leduc JM, Poulin MJ, et al.: Effect of nutrients, dietary supplements and vitamins on cognition: a systematic review and meta-analysis of randomized controlled trials. *Can Geriatr J* 2015; 18:

231-45.
18. Geng J, Dong J, Ni H, et al.: Ginseng for cognition. *Cochrane Database Syst Rev* 2010; 12: CD007769.
19. Laws KR, Sweetnam H, Kondel TK: Is ginkgo biloba a cognitive enhancer in healthy individuals? a meta-analysis. *Hum Psychopharmacol* 2012; 27: 527-33.
20. Fond G, Micoulaud-Franchi JA, Brunel L, et al.: Innovative mechanisms of action for pharmaceutical cognitive enhancement: a systematic review. *Psychiatry Res* 2015; 229: 12-20.
21. Giurgea C: Vers une pharmacologie de l'active integrative du cerveau (in French): [Tentative du concept nootrope en psychopharmacologie]. *Actual Pharmacol* (Paris) 1972; 25: 115-56.
22. Hu MC, Huang MS, Wang CS: Possible piracetam-induced Raynaud's phenomenon in a male patient. *Taiwan J Psychiatry* (Taipei) 2020; 34: 138-40.
23. Gualtieri F, Manetti D, Romanelli MN, et al.: Design and study of piracetam-like nootropics, controversial members of the problematic class of cognition-enhancing drugs. *Curr Pharm* 2002; 2: 125-38.
24. Sugaya N, Ikeda K: Roles of GIRK channels in the reward system. *Jpn J Biol Psychiatry* 2011; 22: 263-7.
25. Sugaya N, Ogai Y, Aikawa Y, et al.: A randomized controlled study of the effect of ifenprodil on alcohol use in patients with alcohol dependence. *Neuropsychopharmacol Rep* 2018; 38: e12001.
26. Shen W: Anticraving therapy for alcohol use disorder: a clinical review *Psychochopharmacol Rep* 2018: 38: 105-16.
27. Whitehouse PJ, Price DL, Struble RG, et al.: Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. *Science* 1982; 215: 1237-9.
28. Ogane N, Giacobini E, Struble R: Differential inhibition of acetylcholinesterase molecular forms in normal and Alzheimer disease brain. *Brain Res* 1992; 589: 307-12.
29. Schegg KM, Nielsen S, Zweig RM, et al.: Decrease in membrane-bound G4 form of acetylcholinesterase in postmortem Alzheimer brain. *Prog Clin Biol Res* 1989; 317: 437-52.
30. Kang J, Lemaire HG, Unterbeck A, et al.: The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. *Nature* 1987; 325: 733-6.
31. Wilcock GK, Black SE, Hendrix SB, et al.: Efficacy and safety of tarenflurbil in mild to moderate Alzheimer's disease: a randomised phase II trial. *Lancet Neurol* 2008; 7: 483-93.
32. Tagami S, Takeda M, Okochi M: Clinical trials for Alzheimer disease and perspectives. In: *Cognition and Rehabilitation*. (Osaka) 2020; 1 (1): 12-9.
33. Schenk D, Barbour R, Dunn W, et al.: Immunization with amyloid-β attenuates Alzheimer disease-like pathology in the PDAPP mouse. *Nature* 1999; 400: 173-7.
34. Janus C, Pearson J, McLaurin J, et al.: A beta peptide immunization reduces behavioural impairment and plaques in a model of Alzheimer's disease. *Nature* 2000; 408: 979-82.
35. Bard F, Cannon C, Barbour, R, et al.: Peripherally administered antibodies against amyloid β-peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease. *Nat Med* 2000; 6: 916-9.
36. Hock C, Konietzko U, Papassotiropoulos A, et al.: Generation of antibodies specific for β-amyloid by vaccination of .patients with Alzheimer disease. *Nat Med* 2002; 8: 1270-5.
37. Hock C, Konietzko U, Streffer JR, et al.: Antibodies against β-amyloid slow cognitive decline in Alzheimer's disease. *Neuron* 2003; 38: 547-54.
38. Orgogozo JM, Gilman S, Dartigues JF, et al.: Subacute meningoencephalitis in subset of patients with AD after Aβimmunization. *Neurology* 2003; 61: 46-54.
39. Doody RS, Gavrilova SI, Sano M, et al.: Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled study. *Lancet* 2008; 372: 207-15.
40. Jack CR, Knopman DS, Jagust WJ, et al.: Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* 2010; 9: 119-28.