# Chapter 22
# Immunotherapeutic Approaches Against Amyloid-β in Drug Discovery for Alzheimer's Disease

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**Abstract** Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common type of dementia. The major pathological hallmark and culprit of AD is aggregation of the amyloid-β (Aβ) peptide. Since the Aβ abnormality begins in the asymptomatic stage of AD, immunotherapeutic approaches clearing Aβ aggregates are investigated as the most promising treatment in clinical trials. Both active and passive immunization against Aβ showed significant reduction of Aβ levels in the brain and enhancement of learning and memory. Albeit pathologically effective, these immunotherapeutic vaccines need to overcome side effects such as vasogenic edema and microhemorrhages. In this chapter, we introduce the basic concept of immunotherapy for clearance of Aβ, compare putative immunotherapeutic vaccine candidates, and discuss their benefits, disadvantages, and challenges.

**Keywords** Alzheimer's disease • Amyloid-β • Active immunotherapy • Passive immunotherapy • Vaccination

## 22.1 Introduction

Alzheimer's disease (AD) is the most common phenomenon of dementia, characterized by the extensive loss of neurons and synapses and the progressive decline of memories (Alzheimer's 2012; Brookmeyer et al. 2007). AD is a polysynthetic disease involving aggregation and deposition of amyloid-β (Aβ) and

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hyperphosphorylated tau, accompanied by oxidative stress, glial activation and neuronal cell death (Wyss-Coray 2006). Aβ is a short peptide of 39–43 amino acids and generated throughout the serial proteolysis of amyloid precursor protein (APP) (De Strooper et al. 2010; Selkoe 2001; Wolfe 2006). In normal neurogenesis, called the non-amyloidogenic pathway, the extracellular domain of APP is cleaved by α-secretase, leading to release the soluble extracellular fragment known as sAPP-α (Edwards et al. 2008; Pietri et al. 2013). Then, γ-secretase cleaves the truncated APP in the plasma membrane into the APP intracellular C-terminal domain (Shoji et al. 1992; Golde et al. 2013; Chang and Suh 2010). In the amyloidogenic pathway, however, the sequential cleavage by β-secretase and γ-secretase generates the Aβ peptide (Zhang et al. 2012; O'Brien and Wong 2011). In the monomeric state, Aβ is a soluble and non-toxic α-helical peptide (Takano et al. 2006; Lansbury 1997; Kirkitadze et al. 2001). However, at high concentration, the peptide undergoes a conformational change to form amyloid oligomers and fibrils. Then, these fibrils aggregate into the insoluble cluster called "plaques" in the brains of AD patients (Fig. 22.1) (Jellinger 2006; Walsh et al. 2002; Shankar et al. 2007).

Aggregation of Aβ in the brain plays a pivotal role in AD as a pathological culprit (Duran-Aniotz et al. 2013; Jin et al. 2011). Deposition of Aβ aggregates is observed in the early stage during the development of AD (Leuner et al. 2012; Gowing et al. 1994; Pigino et al. 2009). Thus, overproduction and aggregation of Aβ have been the major target of AD drug candidates (Barten et al. 2006; Pohanka 2011; Doraiswamy and Xiong 2006; Lleo et al. 2006; Michaelis 2003). However, disappointing clinical trials of amyloid inhibitors, targeting APP proteolysis or Aβ aggregation, have raised concerns for alternative therapeutic approaches. As abnormal Aβ deposition precedes cognitive decline, the newly suggested mode of action is the immunotherapy to remove toxic Aβ oligomers and plaques from the brain of AD patients. While numerous clinical trials have been investigated to reduce cerebral Aβ deposits and facilitate Aβ clearance, the strongest approach to date is immunotherapy, which can be mainly divided into active or passive (Lobello et al. 2012). Active immunization utilizes administration of synthetic Aβ peptide fragments conjugated with carrier proteins, and passive immunization uses humanized monoclonal antibodies against Aβ peptides.

## 22.2 Active Immunotherapy

The active immunotherapy aims specific activation of cellular and humoral immune systems such as inducing antigen producing cells, T cells, and B cells. Once APCs are initially activated by stimulation of compromised antigens, Aβ peptides, combined with an immune adjuvant to get the high immune response, transfer their immune signals to T cells. Activated T cells progressively stimulate B cells to produce specific antibodies against Aβ. These antibodies bind to the Aβ peptides, then target for clearance (Fig. 22.2) (Lemere and Masliah 2010).

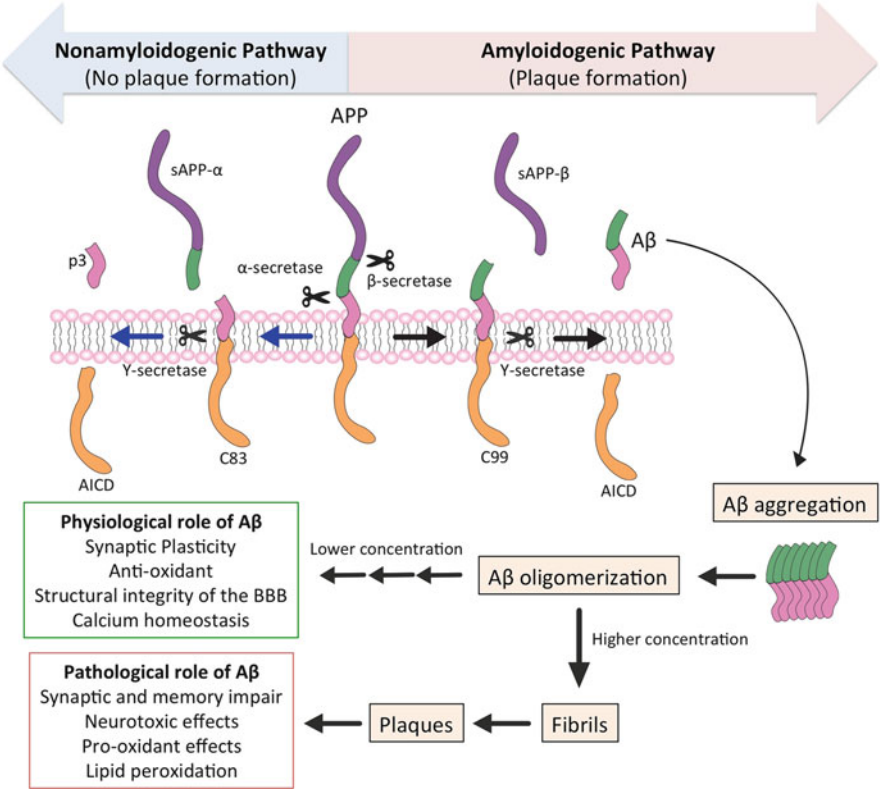


**Fig. 22.1 A diagram of amyloid precursor protein (*APP*) processing**. The transmembrane protein APP can be cleaved by two pathways. In the non-amyloidogenic pathway, α-secretase cleaves the extracellular domain of APP to release soluble extracellular fragments (sAPP-α). This truncated APP is then cleaved by γ-secretase to release the APP intracellular C-terminal domain (*AICD*) and p3 fragment. In the amyloidogenic pathway, β-secretase cleaves the extracellular domain of APP to release soluble extracellular fragments (*sAPP-β*). Then, γ-secretase cleaves the truncated APP of transmembrane part to generate Aβ monomers. At low concentration, Aβ, in monomer state, is less toxic and plays several physiological roles. At higher concentration level, the peptide undergoes the aggregation to form amyloid plaques and found in AD brains

In 1999, Schenk and his colleagues first reported that the active immunotherapy using synthetic Aβ peptides, with complete Freund adjuvant and incomplete Freund adjuvant, could prevent the development of Aβ deposition in the brain of PDAPP transgenic mice model with Aβ plaque pathology (Schenk et al. 1999). The therapeutic approaches were, then, extended to diverse animal models and demonstrated that active Aβ immunotherapeutic treatment can prevent the accumulation of Aβ in the brain and rescue the abnormal cognitive behaviors (Lemere et al. 2000; Weiner et al. 2000; Das et al. 2001; Sigurdsson et al. 2001; Maier et al. 2006).

Although the active immunotherapy is a powerful method due to its ability to induce long-term antibody production, low-cost efficiency, and easy handling, it has

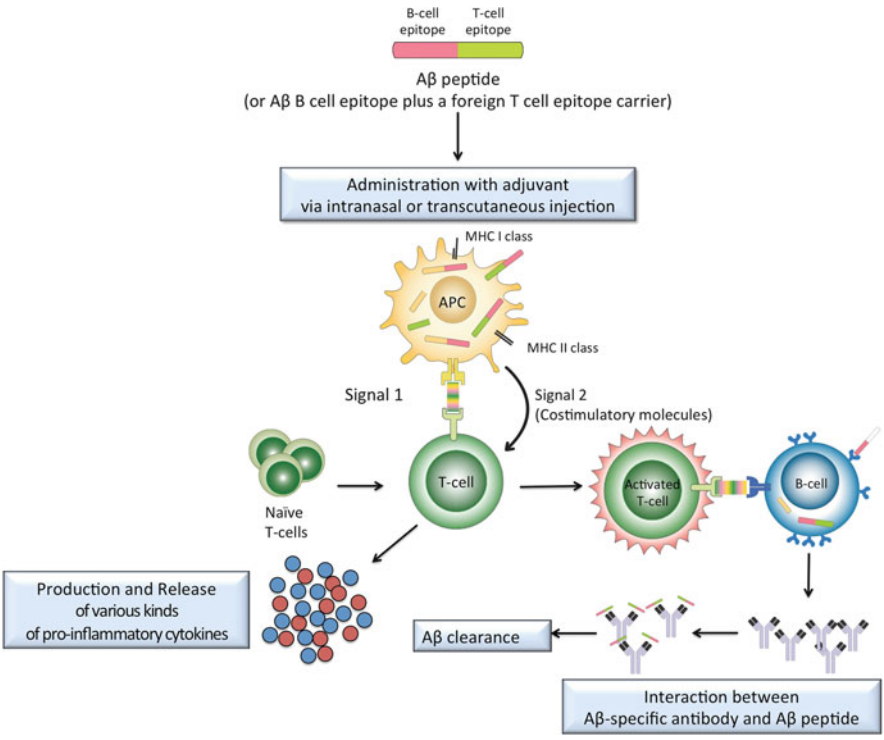


**Fig. 22.2 Active immunotherapeutic vaccination approaches**. Active immunization induces the humoral immune system to generate Aβ-specific antibodies. Aβ peptides conjugated with foreign T cell epitope carriers can be administrated as antigens and activate the antigen presenting cells (*APC*), which engulf and process the antigen. Then, a signal can be transmitted via activating naïve T lymphocytes to produce several kinds of pro-inflammatory mediators. Another signal with co-stimulatory molecules induces the enhancement of T lymphocytes, which leads to generate the antibodies against Aβ from B lymphocytes

the risk of detrimental immune response. For example, if T cells recognize the antigen as a self-protein, they do not induce the proper immune system. Also, activated T cells induce a release diverse in pro-inflammatory cytokines to affect the whole body defense mechanism. Moreover, since an active immunization leads to polyclonal antibodies production that recognize multiple epitopes of Aβ peptides, the antibodies may have low specificity or avidity against Aβ peptides, eventually lead to less effective immune responses (Delrieu et al. 2012a; Lannfelt et al. 2014b).

### *22.2.1 AN-1792*

In the late 1990s, Elan Pharmaceuticals and Wyeth Corporation introduced an active immunotherapy (AN-1792) with synthetic pre-aggregated human Aβ 1–42

in animal studies. Administration of AN-1792 blocked the formation of Aβ plaques in the brain of AD transgenic mice and dramatically reduced preformed plaques in aged mice (Schenk et al. 1999). AN-1792, in addition, induced improvement of mice performance in behavior tests related to learning and memory (Bayer et al. 2005; Ferrer et al. 2004; Masliah et al. 2005; Nicoll et al. 2003). Following the promising animal studies, AN-1792 was tested in the clinical trial Phase I to assess its therapeutic effects, safety, and tolerability in AD patients and was found with no adverse side effect (Bayer et al. 2005). However, in Phase II-A trials, the clinical investigation was suspended, when several participants developed severe inflammation in the brain and the spinal cord. AN-1792 was eventually withdrawn from the clinical trials in 2002, after 18 recipients with vaccination (about 6 % of recipients) developed the brain inflammation such as meningoencephalitis (Gilman et al. 2005; Orgogozo et al. 2003; Robinson et al. 2004).

### *22.2.2 ACC-001*

Despite the suspension of AN-1792 in the clinical trial Phase II-A for safety reasons, active Aβ vaccine is still an attractive therapeutic mode of action to treat AD and several second-generation vaccines are currently tested in clinical trials. Janssen Alzheimer Immunotherapy, a subsidiary of Johnson & Johnson, launched Vanutide cridificar (ACC-001) vaccine, as a modified version of AN-1792. ACC-001 was developed as a N-terminal short fragment of Aβ (Aβ 1–7) conjugated with a carrier protein, a non-toxic variant of diphtheria toxin, using the saponin adjuvant QS-21. ACC-001 induced a humoral immune response including antibody generation with no sign of intolerable side effects in the clinical trial Phase I (Ryan and Grundman 2009). However, this vaccine was briefly suspended in 2008, because one of the patients, in Phase II, developed skin vasculitis, indicating malfunction of immune or hypersensitive allergic responses. Although the patient recovered and the clinical trials resumed within 6 weeks, no results have been published in journals (Lemere and Masliah 2010; Okura and Matsumoto 2009). In August 2013, this immunotherapy was been discontinued from clinical development.

### *22.2.3 CAD106*

Novartis Pharmaceuticals and Cytos Biotechnology developed an active Aβ vaccine, CAD106, composed of multiple copies of the Aβ 1–6 fragment coupled with a virus-like carrier particle (Qβ). This vaccine is designed to block activation of the autoimmune Th1-cell response and to induce the Th2-cell mediated humoral response (Winblad et al. 2012). CAD106 was confirmed in animals to inhibit the formation of Aβ plaques in the brain (Wiessner et al. 2011) and advanced to clinical

trials with mild-to-moderate AD patients. In the Phase I, CAD106 induced a significant humoral antibody response when high dose of antibody was administrated. The Phase II clinical investigations of CAD106 have been reported the favorable safety, tolerability, and humoral antibody response (Kingwell 2012). Besides, chill and fever, under the permissible level, were observed in the Phase II (Winblad et al. 2012, 2014). However, numbers of concerns were raised regarding reactivity and safety during the clinical trials. First of all, the six-amino-acid synthetic Aβ fragment might not be long enough to specifically activate Th2-cells and induce humoral immune responses. Furthermore, the design of the clinical trial was re-evaluated by concerning the size and selection of patients; (1) the study was tested in the small group of subjects, (2) the duration of the vaccine administration was short to record clinical effects including safety and tolerability. In addition, intracerebral hemorrhage was found in one patient from the CAD106 administration group, who had cerebral amyloid angiopathy (Winblad et al. 2014).

### *22.2.4 Affitope AD02*

Affitope AD02, by AFFiRiS AG, is a KLH vaccine with the six N-terminal amino acids of Aβ. By introducing the non-endogenous Aβ mimic, this vaccine was designed to exhibit a favorable safety profile and to prevent development of tolerance. The composition of Affitope AD02 enabled to prevent the autoimmune T cells activation with cross-reactivity with APP by specific recognition of Aβ (Schneeberger et al. 2009). In AD animal models, Affitope AD02 reduced levels of Aβ plaques. In the clinical trial Phase I, a favorable safety profile was observed in 24 AD patients after four-time vaccination (Brody and Holtzman 2008; Madeo and Frieri 2013; Winblad et al. 2014; Mangialasche et al. 2010). No meningoencephalitis was found during the investigation. 332 AD patients were subjected to the Phase 2 trial and limited data has been reported so far. The clinical investigation is still on-going by enrolling patients.

### *22.2.5 ACI-24*

AC Immune SA's ACI-24 is an active tetra-palmitoylated Aβ 1–15 peptide vaccine, embedded within a liposome to eventually induce the generation of β-sheet conformation-specific antibody against Aβ (Muhs et al. 2007). In cynomolgus monkeys and APP/PS1 transgenic mice, the antibodies generated by ACI-24 had high titer level to induce the humoral immune response. In addition, ACI-24 significantly reduced concentration of soluble and insoluble Aβ and restored behavioral performances of learning and memory (Muhs et al. 2007; Winblad et al. 2014). ACI-24 is currently in the clinical trial Phase I/II for AD (Lemere 2013), so far little is known for more detail data in this stage.

**Table 22.1** Active amyloid-β immunotherapeutic vaccines in clinical trials

| Vaccine (company) | Epitope / Key behaviors observed | Phase status | Completion |
|---|---|---|---|
| AN-1792 (Elan/Wyeth) | Aβ 1–42 | Phase II-A | March, 2002 |
| | Blockage of plaque formation | | |
| | Inflammation during Phase II-A (meningoencephalitis) | | |
| ACC-001 (Janssen) | Aβ 1–7 with non-toxic diphtheria toxin | Phase II | August, 2013 |
| | High titers of antibody without intolerance in Phase I | | |
| | Skin vasculitis in Phase II | | |
| CAD106 (Novartis/Cytos) | Aβ 1–6 with Qβ carrier | Phase II | December, 2012 |
| | Prevention of the autoimmune Th1-cell activation | | |
| | Blockage of plaque formation | | |
| | Side effects such as chill or fever (permissible event in Phase II) | | |
| AFFITOPE AD02 (AFFiRiS AG) | Six-amino acid peptide that mimics N-terminus of Aβ | Phase II | Ongoing |
| | Prevention of the autoimmune T cell activation | | |
| | Reduction of Aβ plaques | | |
| | Favorable safety in Phase I trials | | |
| ACI-24 (AC Immune SA) | Tetra-palmitoylated Aβ 1–15 | Phase I/II | Ongoing |
| | Generation of β-sheet conformation specific antibodies | | |
| | Reduction of Aβ plaque deposition | | |
| | Recovery of learning and memory in animal studies | | |
| V950 (Merck) | N-terminal fragments of Aβ | Phase I | Ongoing |
| | Production of antibodies against N-terminal of Aβ in the serum and CSF | | |

### *22.2.6 V950*

Merck's V950 is a multivalent vaccine that links N-terminal fragments of Aβ to an adjuvant ISCO-MATRIX. V950 was reported to induce production of antibodies against N-terminal of Aβ in the serum and CSF (Savage et al. 2010). The clinical trial Phase I was performed with 86 AD patients in 51 sites for safety and tolerability. The investigation was completed recently (October 2014) (Lemere and Masliah 2010; Winblad et al. 2014) (Table 22.1).

## 22.3 Passive Immunotherapy

Passive immunotherapy refers to direct injection of monoclonal antibodies without sensitizing the humoral immune system for generation of antibody responses (Brody and Holtzman 2008; Bacskai et al. 2001). Mechanisms of the anti-Aβ

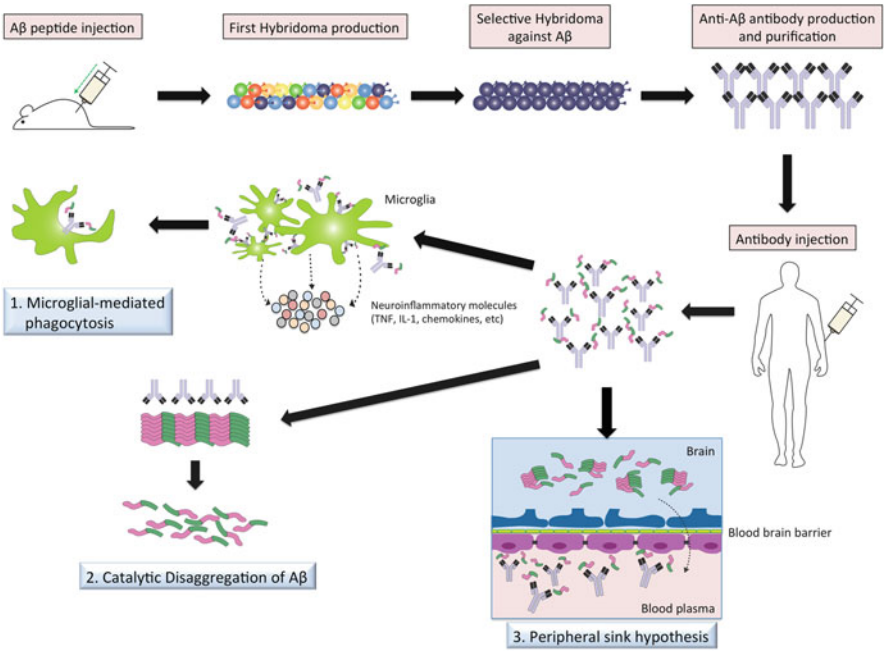


**Fig. 22.3 Passive immunotherapeutic approaches and proposed mechanisms**. The mice immunized with Aβ peptide to produce hybridoma cells. Then hybridoma cells are selected for proper antibodies against Aβ. The antibodies are then purified and administrated to patients with AD. The antibodies may clear Aβ through three kinds of proposed mechanisms: (1) microglial-mediated phagocytosis, (2) catalytic disaggregation of Aβ deposition, and (3) peripheral sink hypothesis in the bloodstream

passive immunotherapy can be categorized into microglial-mediated phagocytosis, catalytic disaggregation of Aβ deposition, and peripheral sink (Fig. 22.3) (Alves et al. 2014; Menendez-Gonzalez et al. 2011). In the microglial-mediated phagocytosis, antibodies directly bind to amyloid plaques and trigger microglial activation via their Fc receptors. Then, activated microglial cells rapidly facilitate the elimination of Aβ through phagocytosis. Meanwhile, they may induce neuroinflammatory events including secretion of various inflammatory mediators such as IL-1, IL-6, TNF, free radical, and chemokines (Wilcock et al. 2004; Cai et al. 2014; Kakimura et al. 2002). In catalytic disaggregation of Aβ deposition, administered antibodies bind to Aβ aggregates and catalyze the conformational change of Aβ peptides. Such actions eventually lead to disaggregation of Aβ aggregates and reduction of amyloid-induced neurotoxicity (Solomon et al. 1996, 1997; Legleiter et al. 2004; Frenkel et al. 2000; Bacskai et al. 2001). The peripheral sink hypothesis was first reported when the m266 anti-Aβ monoclonal antibody directly targeted and completely sequestered Aβ in the plasma (DeMattos et al. 2001). Peripheral administration of m266 to PDAPP transgenic mice induced a rapid elevation of plasma Aβ levels due to the change in Aβ distribution between

central nervous and peripheral circulatory systems. The altered equilibrium of Aβ leaded to facilitate the peripheral clearance of Aβ in the plasma instead of Aβ deposition in the brain (Deane et al. 2003, 2005; Dodart et al. 2002).

Compared to the active immunotherapy, antibody drugs shall be beneficial to patients as the dosage of antibodies in each subject is known before administration. The amount and concentration of antibodies can be easily controlled. Moreover, the administration can be immediately stopped and the antibody will be rapidly removed if there are any signs for side effects. Besides, unnecessary cellular responses can be avoided in passive immunotherapy (Mangialasche et al. 2010; Guan et al. 2012; Lemere 2013). However, high-cost humanized monoclonal antibodies and repeated drug injection for long-term treatment is a considerable disadvantage of the passive immunotherapy (McElhaney and Effros 2009). In addition, antibody drugs may act as antigens and induce immune responses, which may lead to side effects such as glomerulonephritis and vasculitis (Lemere 2013).

### *22.3.1 Bapineuzumab (AAB-001) and PF-05236812 (AAB-003)*

Bapineuzumab (AAB-001) is a humanized therapeutic monoclonal antibody against N-terminus of Aβ (3D6 clone, IgG1 isotype) developed by Elan, Wyeth, Johnson & Johnson (Janssen), and Pfizer (Brody and Holtzman 2008; Blennow et al. 2012; Panza et al. 2010). AAB-001 was reported to pass blood-brain barriers, to bind fibrillar and soluble Aβ, and to induce microglial-mediated phagocytosis the plaques in AD transgenic mice (Bard et al. 2000, 2003; Racke et al. 2005). However, in two large Phase II/III trials, no clinical benefit but serious side effects were reported including cerebral vasogenic edema, retinal vascular disorder, and microhemorrhages (Okura and Matsumoto 2009; Pfeifer et al. 2002; Racke et al. 2005). MRI scans revealed that vascogenic edema was found in AD patients with the high dose group (Khorassani and Hilas 2013; Sperling et al. 2012). These results led the clinical investigation of AAB-001 to the termination in 2012. One of the possibilities raised for the lack of clinical efficacy was that the administration of this vaccine was too late in the disease process to reverse the neurodegenerative changes.

PF-05236812 (AAB-003) was then developed as a derivative of bapineuzumab with a modified Fc domain to reduce effector functions on microglial activation. It was specifically designed to avoid amyloid-related imaging abnormalities (ARIA), a complication of bapineuzumab administration. The clinical trial Phase I was performed with 88 AD patients to evaluate the safety and tolerability of PF-05236812 and trial was completed in August 2014 (Moreth et al. 2013).

### 22.3.2 Solanezumab (LY2062430)

Eli Lilly & Co.'s Solanezumab (LY2062430) is a humanized IgG1 version of the aforementioned m266 monoclonal antibody. Unlike Bapineuzumab, Solanezumab targets the mid-domain of the Aβ peptide (Aβ 13–28) and binds selectively to soluble Aβ species (Mangialasche et al. 2010; Moreth et al. 2013; Spencer and Masliah 2014). Cognitive recovery of AD transgenic mice by m266 supports the view that soluble oligomeric Aβ is highly related to neuronal and synaptic dysfunction in AD brains. During the clinical trials, the significant increase of Aβ levels were observed in both the blood and CSF by the peripheral sink mechanism (Farlow et al. 2012; Siemers et al. 2010). Currently, solanezumab is investigated in two large clinical trial Phase III studies with a total of 2,052 subjects from 16 countries (Doody et al. 2014a, b). According to interim reports by Eli Lilly & Co., cardiac disorders and even 24 deaths were observed in Solanezumab-treated patients (Doody et al. 2014b). However, no clear relation was found between the death and Solanezumab. Although Solanezumab is considered as the first clinical evidence that anti-amyloid approach helps AD patients, it needs to consider for further development of this vaccine and the skepticism still exists on the ability of this drug to slow the rate of deterioration in patients with later-stage of diseases.

### 22.3.3 Gantenerumab (RO4909832, RG1450)

Gantenerumab (RO4909832, RG1450), by Roche, is a fully human IgG1 monoclonal antibody against Aβ that has a high affinity to specifically bind to cerebral amyloid plaques (Delrieu et al. 2012b). Gantenerumab appears to preferentially bind the fibrillar form of Aβ by recognizing both N-terminus (Aβ 3–12) and mid-domain (Aβ 18–27). Gantenerumab induces microglial-mediated phagocytosis by binding to small Aβ plaques (Bohrmann et al. 2012). Thus, unlike Solanezumab, Gantenerumab decreased Aβ deposition in the brain without increasing plasma Aβ levels. In 360 mild-to-moderate AD patients administrated with Gantenerumab of Phase II, it reduced brain amyloid load around 30 % by PET imaging analysis. However, 2 patients with ARIA were observed in the high dose group (Ostrowitzki et al. 2012). Recently, the Phase III was started with 1000 mild-AD patients via subcutaneous injection (Novakovic et al. 2013). A separate clinical trial is also under investigation in Phase III with prodromal AD patients through Dominantly Inherited Alzheimer Network (DIAN).

### 22.3.4 Gammagard (Intravenous Immunoglobulin, IVIg)

Baxter Healthcare's passive immunotherapeutic approach, Gammagard, is distinct from aforementioned monoclonal antibodies. Gammagard is an intravenous

immunoglobulin (IVIg), a pooled mixture of natural human polyclonal immunoglobulin that extracted from the plasma of over one thousand blood donors. As a result, Gammagard recognizes Aβ monomers, oligomers, and fibrils (Dodel et al. 2002, 2004). IVIg is widely used for the treatment of various pathological disorders as a replacement therapy for various immunodeficiency syndromes. Since IVIg is the product from non-selective antibody collection from various normal patients, it was doubtful for the potential clinical effect on AD. In 2002, Dodel et al reported the effects of commercially available IVIg significantly reduced the level of Aβ in the CSF and blood of AD patients after 6-month administration (Dodel et al. 2002). Notably, administered anti- Aβ antibodies detected in the CSF of patients as a indication that IVIg might transfer the blood-brain barrier and directly decreased the Aβ level in the brain (Fillit et al. 2009; Relkin et al. 2009). Currently, Baxter Healthcare and Alzheimer's Disease Consortium Study (ADCS) are investigating this vaccine in Phase III. A derivative of IVIg (Octagam) is currently investigated by Octapharma in Phase II (Lobello et al. 2012; Moreth et al. 2013). However, IVIg has potential side effects for AD patients; (1) IVIg can lead to thromboemboli because it increases serum viscosity, (2) renal dysfunction or failure can be induced because IVIg products use sucrose as a stabilizing agent (Loeffler 2013), and (3) IVIg can also lead severe allergic difficulties such as breathing or skin rashes, severe headache or fever, and dark colored urine (Levy and Pusey 2000).

### *22.3.5 Ponezumab*

Ponezumab, by Pfizer, is a humanized IgG2a monoclonal antibody, which recognizes the C-terminus of the Aβ 40 peptide (Aβ 33–40). Ponezumab was reported to reduce autoimmune T cell responses (Madeo and Frieri 2013). The clinical trial Phase I for safety and tolerability was completed without microhemorrhage, ARIA, or encephalitis. Ponezumab is currently in the Phase II with 234 AD patients (Freeman et al. 2012; Landen et al. 2013).

### *22.3.6 Crenezumab*

Crenezumab, by Genentech, is a fully humanized IgG4 monoclonal antibody targeting both Aβ monomers and oligomers. The antibody was designed to reduce the Fc receptor-mediated microglial activation and the risk of the immune cell stimulation (Poduslo et al. 2010; van der Zee et al. 1986; Bruhns et al. 2009). Crenezumab is currently in the clinical trial Phase II with 361 AD patients (Adolfsson et al. 2012; Lemere 2013).

### 22.3.7 BAN2401 (mAb158)

Conformation-dependent antibodies to selectively recognize pathogenic structures have been attractive drug candidates and BioArctic developed the monoclonal antibody 158 (mAb158) against Aβ protofibrils (Englund et al. 2007; Sehlin et al. 2012). mAb158 reduced the level of Aβ protofibrils in the brain of both young and old AD transgenic mice and eventually led the reduction of Aβ plaque formation (Lord et al. 2009). Eisai acquired the antibody and developed BAN2401, an immunotherapeutic IgG1 monoclonal antibody, by further optimization. BAN2401 is currently in clinical trial Phase II with 800 AD patients (Tucker et al. 2015; Lannfelt et al. 2014a; Araki 2010).

### 22.3.8 Aducanumab (BIIB037)

Biogen Ided's Aducanumab is a fully human IgG1 monoclonal antibody that strongly binds to aggregated forms of Aβ. Aducanumab was reported to reduce the size of plaques in the brain of APP transgenic mice models (Lemere 2013; Moreth et al. 2013; Prins and Scheltens 2013). However, in the high dose, the antibody induced microhemorrhages. The clinical trial Phase I is currently under investigation with 160 mild-AD patients (Table 22.2).

## 22.4 Conclusion and Further Discussion

In this review, we investigated current active and passive anti-Aβ antibody drugs in AD drug discovery. Albeit promising, results from clinical trials suggest further optimization of these immunotherapeutics for better efficacy and lower side effects. The First issue is the selection of target epitope with high efficiency and safety (Aisen and Vellas 2013). Newer immunotherapeutic vaccines need to avoid the autoimmune response upon the anti-Aβ antibody treatment. Several strategies to overcome this issue aim to develop a combination therapy of present adjuvants or to use foreign T cell epitopes. Another issue is the need to monitor therapeutic progression, as the clearance of Aβ cannot completely reverse clinical symptoms such as neuroinflammation, which lead to neuronal cell death and cognitive impairment. Therefore, selection for proper biomarkers is important to detect pre-clinical disease with mild cognitive impairment and predict which patients may benefit from immunotherapy. Several biomarkers are currently under investigation, but more researches are required before they can clinically be useful (Mayeux and Schupf 2011). Lastly, these antibodies have to cross the blood-brain barrier (BBB) efficiently and safely. The BBB controls the passage of most proteins and small molecules from the blood into the central nervous system. Thus, the transport of

**Table 22.2** Passive amyloid-β immunotherapeutic vaccines in clinical trials

| Vaccine (company) | Epitope/target | Isotype | Phase status | Completion |
|---|---|---|---|---|
| | Key behaviors observed | | | |
| Bapineuzumab (AAB-001) PF-05236812 (AAB-003) (Elan/Wyeth/ Janssen/Pfizer) | Aβ 1–5/soluble and aggregated Aβ | IgG1 | Phase III (AAB-001) | August, 2012 |
| | | | Phase I (AAB-003) | August, 2014 |
| | Aβ subjected to microglial-mediated phagocytosis | | | |
| | Patients found with vasogenic edema and microhemorrhages in Phase II/III | | | |
| Solanezumab (LY2062430) (Eli Lilly) | Aβ 13–28/soluble Aβ | IgG1 | Phase III | Ongoing |
| | Aβ subjected to peripheral sink hypothesis | | | |
| | Significant increase of Aβ levels in the plasma | | | |
| | Patient found with cardiac arrhythmia and cardiac ischemia in Phase III | | | |
| Gantenerumab (RO4909832, RG1450) (Roche) | Aβ 3–12/aggregated Aβ | IgG1 | Phase III | Ongoing |
| | Preferentially binding to fibril form of Aβ | | | |
| | Leading to microglial-mediated phagocytosis | | | |
| | ARIA observed at the high-dose treatment during Phase II | | | |
| IVIg (Gammagard/ Octagam) (Baxer healthcare/Octapharma) | Central and C-terminus of Aβ/ Aβ monomer, oligomer, fibrils | Pooled mixture of human polyclonal antibody | Phase III (Gammagard) Phase II (Octagam) | Ongoing |
| | Alternative therapy for various immunodeficiency syndromes | | | |
| | Aβ level reduced in the CSF | | | |
| | Patients found with thromboemboli, renal dysfunction, and allergic reactions | | | |
| Ponezumab (Pfizer) | Aβ 33–40/soluble and aggregated Aβ | IgG2a | Phase II | Ongoing |
| | Targeting C-terminus of Aβ | | | |
| | Autoimmune T-cell response reduced | | | |
| Crenezumab (Genentech) | Aβ 12–23/soluble oligomeric | IgG4 | Phase II | Ongoing |
| | Fc receptor-mediated microglial activation reduced | | | |
| BAN2401 (Eisai) | N-terminus of Aβ/ soluble Aβ protofibrils | IgG1 | Phase II | Ongoing |
| | Targeting the oligomeric form of Aβ | | | |
| | Aβ plaque formation reduced | | | |
| Aducanumab (BIIB037) (Biogen Idec) | Conformational Aβ/fibrillar Aβ | IgG1 | Phase I | Ongoing |
| | Strong binding to aggregated form of Aβ | | | |
| | Plaques reduced | | | |
| | Animal models found with microhemorrhages | | | |

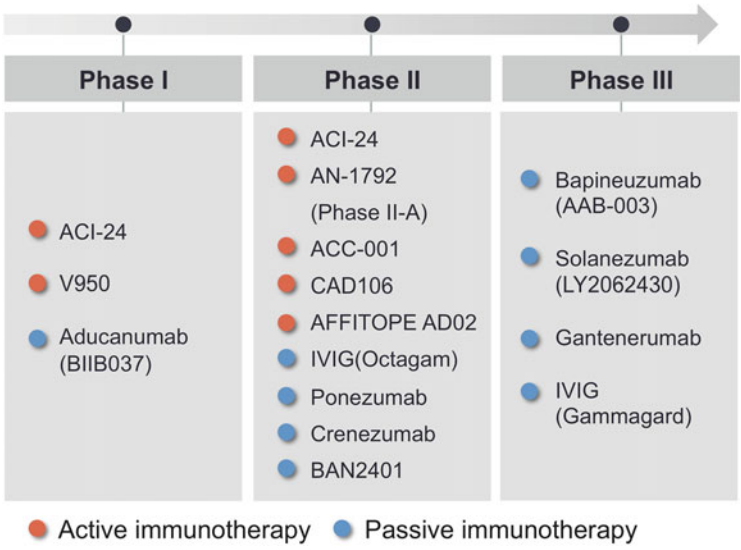


**Fig. 22.4** List of current immunotherapeutic vaccines in clinical trials

monoclonal antibodies between BBB has been believed extremely difficult (Spencer and Masliah 2014). Previous studies reported that only the small portion of administered antibody crossed the BBB while the majority was metabolized in the liver or excreted through the kidney (Banks et al. 2002). As the biological drugs commonly cost higher than chemicals, increasing the BBB penetration rate will not only contribute to the therapeutic efficacy but also the medical costs for patients. Receptor-mediated BBB penetration of monoclonal antibodies into central nervous system is currently under investigation (Boado et al. 2013).

More than 100 years has been passed since the initial observation of AD. Aβ was identified as a critical pathogen of AD (Backman et al. 2004; Hardy and Higgins 1992; Okura and Matsumoto 2009; Jia et al. 2014). Among the numerous drug mechanisms regulating amyloidogenesis, the immunotherapy using the Aβ peptides or antibody against Aβ is the leading therapeutic strategy due to the clearance action (Fig. 22.4).

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