

REVIEW

Treating Alzheimer's disease with monoclonal antibodies: current status and outlook for the future

Niels D Prins^{1,2*} and Philip Scheltens¹

Abstract

In the past decade, Alzheimer's disease drug discovery has been directed at 'disease modifying drugs' that are able to counteract the progression of Alzheimer's disease by intervening in specific parts of its neuropathological process. Passive immunization with monoclonal antibodies (mAbs) may be able to clear toxic amyloid- β species either directly or through microglia or complement activation, thereby halting the amyloid cascade and preventing neurodegeneration and cognitive and functional decline. Thus far, results from two large phase 3 trial programs with bapineuzumab and solanezumab, respectively, have brought rather disappointing results. Possible explanations could be that these compounds were either targeting the wrong amyloid- β species, or were given too late in the disease process. Several new mAbs targeting various amyloid- β epitopes are now being tested in ongoing phase 2 and 3 clinical trials. The present review discusses the various mAbs aimed at amyloid- β , summarizes trial results and provides an outlook for the future.

The pharmacological treatment of Alzheimer's disease

At present, approved pharmacological therapy for Alzheimer's disease (AD) consists of symptomatic treatment with either cholinesterase inhibitors (donepezil, rivastigmine, galantamine) in the mild to moderate stages of the disease, or with an N-methyl-d-aspartate receptor antagonist (memantine) in the more severe stage. These drugs provide a modest positive effect on cognitive function and activities of daily living in some patients, but also cause side effects in a substantial number of treated patients [1,2]. Being symptomatic treatments, these drugs do not slow down the underlying neuropathological disease process. In the past decade, drug discovery has been directed at 'disease modifying drugs' that are able to counteract the progression of AD by intervening in specific parts of its neuropathological process [3,4].

The amyloid cascade hypothesis suggests that either increased amyloid- β (A β)₄₂ production or decreased degradation, and subsequent aggregation leads to synaptic changes and causes deposition of A β ₄₂ in diffuse plaques, which in turn causes microglial and astrocytic activation. As a result, altered neuronal homeostasis and oxidative injury lead to tangle formation, and eventually to neuronal and synaptic dysfunction and selective neuronal loss [4,5]. This hypothesis provides the most important basis for novel drug development. The ultimate proof for this hypothesis would be that intervening in the cascade would prevent neuronal loss and cognitive deterioration. There are currently three main therapeutic intervention strategies aimed at A β : reducing A β production, facilitating A β clearance and preventing A β aggregation. These strategies have been tested in clinical trials: modulation of γ - and β -secretase to reduce A β production, passive immunization with monoclonal antibodies (mAbs) and active immunization to stimulate clearance of A β , and finally preventing A β aggregation with β -sheet breakers and pathological chaperone inhibitors [6]. In the present review we focus on the specific features of the various mAbs that have been or are being tested in AD clinical trials, summarize the results of

* Correspondence: nd.prins@vumc.nl

¹Alzheimer Center and Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Center, PO Box 7057, 1007 MB, Amsterdam, The Netherlands

²Alzheimer Research Center, Gebouw Cronenburg, Cronenburg 75, 1081 GM, Amsterdam, The Netherlands

the clinical trials of mAbs in AD and discuss future directions.

Modifying Alzheimer's disease with monoclonal antibodies

mAbs are antibodies made by identical immune cells that are all clones of a unique parent cell. These antibodies have monovalent affinity, in that they bind to the same epitope [7,8]. The mAbs that have been designed to treat AD are either 'humanized mAbs' or 'fully human mAbs'. Humanized mAbs are antibodies from non-human species whose protein sequences have been modified to increase their similarity to antibody variants produced naturally in humans. Fully human mAbs are derived either from transgenic mice or phage display, and avoid some of the side effects of humanised antibodies. For the disease modifying treatment of AD, several mAbs have been designed at various epitopes, that is, A β species [9,10]. These mAbs can be administered either via intravenous infusion or via subcutaneous injections.

It was long assumed that aggregated A β in the extracellular space was responsible for the cytotoxic effects on neurons. Over the past decade, however, there is increasing evidence that prefibrillar, soluble forms of A β are also pathogenic, and are able to cause synapse loss and neuronal injury [11]. The existence of this large variation of soluble forms of A β can be understood from the processing of amyloid precursor protein [5,12]. Amyloid precursor protein is first cleaved by β -secretase, an aspartyl protease (also called β -amyloid cleaving enzyme-1, BACE-1), at the amino terminus of the A β domain, resulting in shedding of the large ectodomain into the luminal and extracellular fluid and leaving a membrane bound carboxy-terminal stub. This 99 amino acid long stub is subsequently cleaved by γ -secretase, releasing A β . Depending on the exact point of cleavage by γ -secretase, three principal forms of A β , comprising 38, 40 or 42 amino acid residues, respectively, are produced. The A β 42 form is more prone to oligomerise and form amyloid fibrils than the more abundantly produced A β 40 peptide. A β oligomers are thought to exert their harmful effects by binding directly to the membranes of neurons, or to specific receptors needed for neuronal signaling, although more research and also harmonization of the methodology used are needed to fully understand the deleterious effect of A β oligomers [12-14].

The self-association of A β peptides results in aggregates with varying morphology and molecular weight. The activated monomeric state is in rapid equilibrium with low molecular weight aggregates. Many distinct A β aggregates have been described, including dimers, trimers and so forth [11]. These further associate, forming various transient intermediates and mature insoluble

A β fibrils, which accumulate in the AD brain as senile plaques.

Moreth and colleagues [9] have pointed out that, with respect to the selection of different A β species for treatment with mAbs, a complicating factor is that the identification and characterization of these species depend upon the definitions, protocols, and methods used for their preparation and characterization. Due to the fact that definitions, protocols and methods may differ, controversy exists regarding the reported specific A β aggregates and their pathophysiological effects [9]. This has been corroborated by Benilova and colleagues [14], who have pointed out the lack of a common, agreed-upon experimental description of the toxic A β oligomer, which makes interpretation and direct comparison of data between different research groups difficult.

The mechanism of action of mAbs comprises firstly the capture of a target and secondly an effector function linked to the Fc domain of the mAb. Several hypotheses have been proposed regarding the mechanism of action of mAbs in clearing amyloid in AD [7]. The first proposed mechanism is that antibody binding to amyloid leads to macrophage phagocytosis and complement activation [15]. This hypothesis assumes that sufficient antibody enters the brain and binds to the amyloid to trigger this phagocytic action of either resident microglia, or infiltrating monocytes/macrophages. A second proposed mechanism is the so-called 'peripheral sink' hypothesis in which the equilibrium of amyloid across the blood-brain barrier is altered in favour of efflux owing to the reduced free A β concentration in blood. Data on the mechanism of action of different epitope-specific antibodies are conflicting, as are data on their passage across the blood-brain barrier, and it is not unlikely that more than one process takes place during passive A β immunotherapy.

A new approach for the treatment of AD with mAbs is passive immunization against pyroglutamate-3 A β . Pyroglutamate-3 A β resists degradation, is neurotoxic, and may act as a seed for A β aggregation. In preclinical studies, passive immunization with pyroglutamate-3 A β mAbs reduced plaque deposition while limiting potential side effects of vaccination [16,17].

Side effects of monoclonal antibodies: amyloid-related imaging abnormalities

Amyloid-related imaging abnormalities (ARIA) have been reported in clinical trials of mAbs in AD. The spectrum of ARIAs includes signal hyperintensities on fluid attenuation inversion recovery sequences, thought to represent 'vasogenic oedema' and/or sulcal effusion (ARIA-E), as well as signal hypointensities on GRE/T2*, thought to represent hemosiderin deposits (ARIA-H), including microhemorrhage and superficial siderosis

[18]. For ARIA-E, a reproducible and easily implemented magnetic resonance imaging (MRI) scale has been developed [19]. The etiology of ARIA remains unclear but the prevailing data support vascular amyloid as a common pathophysiological mechanism leading to increased vascular permeability. In the phase 2 bapineuzumab trial, dose-related vasogenic edema (ARIA-E) was observed [20]. Twelve cases of vasogenic edema were reported, all in treated patients, and all resolved over time. Ten of these cases were reported in apolipoprotein E ϵ 4 (ApoE4) carriers, with two cases in ApoE4 non-carriers. Eight of the twelve cases were reported in the highest dose group, including both cases seen in ApoE4 non-carriers. As a consequence of this dose-related side effect, the highest dose (2 mg/kg) was not tested in the phase 3 studies [21]. The occurrence of ARIAs in mAb treatment for AD is compound-dependent and ARIAs have thus far not occurred in patients treated with crenezumab, BAN 2401, or GSK 933776. In the phase 3 solanezumab study the incidence of vasogenic edema (ARIA-E) was approximately 1 %, occurring in 11 patients treated with solanezumab and 5 patients on placebo, which was not statistically significant.

Results of monoclonal antibodies tested in Alzheimer's disease

Table 1 gives an overview of monoclonal antibodies that have been or are being tested for the treatment of AD. Below, we provide a summary of the results of clinical trials in AD with these antibodies, and their current development status.

Bapineuzumab

Bapineuzumab is a humanised mAb directed at the amino terminus of A β . In a phase 2 multiple-ascending-dose trial in 234 patients with mild to moderate AD, no significant differences were found with the Alzheimer's Disease Assessment Scale for Cognition and the Disability Assessment for Dementia in the primary efficacy analysis [20]. Exploratory analyses, however, showed potential treatment differences for cognitive and functional endpoints in study completers and ApoE4 non-carriers. Furthermore, treatment with bapineuzumab reduced fibrillar amyloid burden in subjects with AD, shown by standardized uptake value ratio analyses of Pittsburgh compound B positron emission tomography (PET) [35]. Interestingly, one patient treated with bapineuzumab showed no neuropathological or biochemical evidence of lasting plaque regression or clearance of A β due to bapineuzumab treatment [36]. A safety concern was the occurrence of reversible vasogenic edema (ARIA-E), detected on brain MRI in 10 % of the bapineuzumab-treated patients.

Despite these promising phase 2 findings, phase 3 trials in mild to moderate AD patients (1,121 ApoE4 carriers and 1,331 non-carriers) showed no benefit on primary cognitive or functional outcome measures for bapineuzumab over placebo [22,23]. Biomarker results showed that bapineuzumab does lower phospho-tau in the cerebrospinal fluid (CSF). In August 2012, phase 3 clinical trials of intravenous bapineuzumab, and a phase 2 trial with subcutaneous bapineuzumab, were halted in patients with mild to moderate AD due to these disappointing results.

Table 1 Overview of monoclonal antibodies that have been or are being tested for the treatment of Alzheimer's disease

Compound	Company	Epitope	Trial results	References
Bapineuzumab, humanized 3D6	Janssen/Pfizer	Amino terminus	Phase 3 trials did not meet cognitive and functional endpoints	[22,23]
Solanezumab, humanized m266	Eli Lilly	Central (amino acids 16 to 24), accessible only on soluble amyloid- β	Phase 3 trials did not meet functional endpoint; did meet cognitive endpoint in pooled analyses in mild AD	[24,25]
Gantenerumab, full human	Hoffmann-La Roche	Amino terminus and central portions of amyloid- β	Phase 2a trial showed reduction in brain amyloid β on PET	[26,27]
Crenezumab, humanized IgG4	Genentech	Conformational epitopes, including oligomeric and protofibrillar forms	Phase 1 trial showed compound was safe and well-tolerated	[28,29]
BAN2401, humanized mAb158	Eisai Inc.	Binds large-size amyloid- β protofibrils (>100 kDa)	Phase 1 trial showed compound was safe and well-tolerated	[9,30]
GSK 933776, humanized IgG1	GlaxoSmithKline	Amino terminus	Phase 1 trial showed compound was safe and well-tolerated	[9,31]
AAB-003, Fc-engineered bapineuzumab	Janssen/Pfizer	Amino terminus	Phase 1 trial ongoing	[9,32]
SAR228810, humanized 13C3	Sanofi	Protofibrils, and low molecular weight amyloid- β	Phase 1 trial ongoing	[9,33]
BIB037/BART, full human IgG1	Biogen Idec	Insoluble fibrillar human amyloid- β	Phase 1 trial ongoing	[9,34]

Adapted from Moreth and colleagues [9]. AD, Alzheimer's disease; Ig, immunoglobulin; mAb, monoclonal antibody; PET, positron emission tomography.

Solanezumab

Solanezumab is a humanized mAb against the central part of soluble A β . In a phase 2, randomized, double-blind, placebo-controlled clinical trial, 52 patients with Alzheimer's disease received placebo or antibody for 12 weeks. Antibody administration was well tolerated at doses up to 400 mg weekly. Treatment with solanezumab was associated with a dose-dependent increase in unbound CSF A β (1–42), suggestive of a shift in equilibrium sufficient to mobilize A β (1–42) from amyloid plaques [24].

The two phase 3 double-blind, placebo-controlled solanezumab trials included more than 2,050 patients with mild to moderate AD. The trials were 18 months in duration. Both the Expedition 1 and 2 studies did not meet co-primary cognitive and functional endpoints. In a prespecified secondary analysis of the total pooled subjects from the Expedition 1 and 2 trials, however, mild subjects (Mini-Mental State Examination (MMSE) 20 to 26 at entry) showed treatment differences favoring solanezumab over placebo according to the ADAS-cog11, ADAS-cog14, and the MMSE [25].

At present, a new very large phase 3 study of solanezumab (400 mg intravenous solanezumab every 4 weeks for 18 months) is recruiting 2,100 patients with early AD. In order to prevent misclassification of cases, participants need to have a positive florbetapir PET scan or a CSF result consistent with the presence of amyloid pathology at screening.

Gantenerumab

Gantenerumab is a full human mAb directed against both the amino terminus and central portions of A β . A small phase 2a multicenter, randomized, double-blind, placebo-controlled, ascending-dose PET study showed that treatment of patients with mild to moderate AD with gantenerumab leads to a measurable reduction in the level of A β in the brain [26,37]. Two consecutive cohorts of patients received two to seven infusions of intravenous gantenerumab (60 or 200 mg) or placebo every 4 weeks. The mean percentage change from baseline difference relative to placebo (n = 4) in cortical brain amyloid level was –16 % for the 60 mg group (n = 6) and –36 % for the 200 mg group (n = 6). Two patients in the 200 mg group showed transient and focal areas of inflammation or ARIA-E on MRI scans at sites with the highest level of amyloid reduction. A phase 3 study with gantenerumab in patients with prodromal AD, that is, amnesic mild cognitive impairment plus decreased A β levels in the CSF, is currently recruiting participants to evaluate the effect of gantenerumab using the Clinical Dementia Rating scale Sum of Boxes, and on brain amyloid over time assessed with amyloid PET.

Crenezumab

Crenezumab is a humanized mAb that acts on monomeric and conformational epitopes, including oligomeric and protofibrillar forms of A β [28,29,38]. A phase I, randomized, placebo-controlled, double-blind, multicenter clinical study was conducted with the primary objective of determining the safety and tolerability of intravenous crenezumab in patients with mild to moderate AD. Secondary objectives of this study were to characterise pharmacokinetics and pharmacodynamics after single and multiple doses of crenezumab. The study consisted of a single-dose, dose-escalation stage, followed by a randomized placebo-controlled, double-blind, parallel multidose stage. No patients receiving crenezumab developed vasogenic edema, in either the single or multidose study. Importantly, patients were genotyped and randomized in the multidose study to ensure that at least 40 % of enrolled patients were ApoE4 carriers (48 % were carriers), as these patients were previously shown to be at higher risk of developing vasogenic edema. An additional phase 2 open label extension study is recruiting.

BAN2401

BAN2401 is a humanized immunoglobulin G1 (IgG1) mAb that selectively binds to A β protofibrils and is thought to either enhance clearance of A β protofibrils and/or to neutralize their toxic effects on neurons in the brain. The first human study evaluated this compound in subjects with mild to moderate AD [9,30]. This study consisted of a single ascending dose and a multiple ascending dose part, both being randomized, double-blind, placebo and controlled, using sequential ascending dose schemes. Six single ascending dose cohorts (48 subjects) received a single dose of BAN2401 by intravenous infusion (or matching placebo) at 0.1, 0.3, 1, 3, 10 and 15 mg/kg. There were also three multiple ascending dose cohorts (24 subjects) who received four doses of BAN2401 (or matching placebo) at 0.3, 1 and 3 mg/kg administered once every 4 weeks and one multiple ascending dose cohort (eight subjects) who received seven doses of BAN2401 (or matching placebo) at 10 mg/kg administered once every 2 weeks. In each cohort six subjects were treated with BAN2401 and two subjects with placebo.

Safety and tolerability data indicate that BAN2401 is well-tolerated at single doses up to 15 mg/kg intravenously and at multiple doses of up to 10 mg/kg intravenously biweekly. In particular, no clinical adverse central nervous system effects, such as ARIAs, were identified. An 18-month phase 2 trial to evaluate safety, tolerability and efficacy of intravenous BAN2401 at three dose levels (2.5, 5, and 10 mg/kg) in subjects with early AD has started recruiting.

GSK 933776

GSK 933776 is a humanised IgG1 monoclonal antibody directed against the amino terminus of A β . The Fc domain of GSK933776 was mutated to reduce the risk for vasogenic edema. In 2011, a multicenter, randomized, single-blind, placebo-controlled phase 1/2a study assessed the safety and tolerability of GSK933776 after single and multiple dose intravenous administration in 44 subjects with mild to moderate AD, of whom 33 were exposed to the active compound [9,31]. Results indicated that GSK 933776 was well-tolerated and safe at multiple doses (maximum 6 mg/kg) for a maximum duration of 12 months. Development for AD was discontinued after phase I.

AAB-003

AAB-003 is Fc-engineered bapineuzumab. The safety and tolerability of AAB-003 is currently being studied in a phase 1, multicenter, randomized, double-blind, placebo-controlled, adaptive, multiple ascending dose study on the safety, tolerability and pharmacokinetics of AAB-003 (PF-05236812) in subjects with mild to moderate AD [9,32]. Patients received 0.5 to 8 mg/kg AAB-003 or placebo by intravenous infusion. Each patient participated for approximately 41 weeks.

SAR228810

SAR228810 is a humanized mAb directed against protofibrils and low molecular weight A β . It is currently being tested in a multicenter, parallel-group, double-blind, placebo-controlled single and multiple dose escalation study to assess the safety and tolerability and the pharmacokinetic properties of SAR228810 given as intravenous infusion or as subcutaneous injection in patients with mild to moderate AD [9,33].

BIIB037/BART

BIIB037/BART is a full human IgG1 against insoluble fibrillar human A β . A phase 1 randomized, blinded, placebo-controlled single ascending dose study on the safety, tolerability, and pharmacokinetics of BIIB037 in subjects with mild to moderate AD is ongoing [9,34]. In this trial, safety and MRI tolerability are the primary outcome measures and secondary outcome measures are pharmacokinetics of BIIB037/BART and the immunogenicity of BIIB037 after single dose administration.

Treatment window for monoclonal antibodies in Alzheimer's disease

With phase 3 bapineuzumab and solanezumab studies yielding disappointing results, the research community is growing uneasy with the mAb approach, and it is now often suggested that mAbs may only be efficacious as a preventive measure and should therefore be tested in

patients with prodromal AD or in asymptomatic subjects, such as in preclinical AD. Attacking amyloid plaques in symptomatic patients is sometimes referred to as 'too little, too late'. It has also been suggested that plaques may be the body's way of sequestering the toxic A β oligomers. Three initiatives are under way to investigate the efficacy of mAbs when administered early in the AD disease course, that is, in the preclinical stage: the Alzheimer's Prevention Initiative (API), the Dominantly Inherited Alzheimer Network (DIAN), and the Anti-Amyloid Treatment of Asymptomatic Alzheimer's Disease (A4) study [39]. In the API study, 300 members of Colombian families, including 100 carriers of a mutated *PSEN1* gene, will receive crenezumab or placebo to study the effect on cognitive and biomarker outcomes, including brain scans to measure amyloid accumulation and brain atrophy. DIAN will be recruiting 240 members of families with early-onset AD, of whom 60 have a mutation in one of three genes. Treatment will consist of solanezumab and gantenerumab as the first two drugs. A third drug is still under consideration. The A4 initiative will study the effect of one anti-amyloid therapy to be determined in 1,500 healthy seniors, including 500 with amyloid-positive brain scans, on cognition and biomarker outcomes. With the gantenerumab trial ongoing in prodromal AD, and the API, DIAN and A4 initiatives on their way, answers to these questions will come in the next few years.

Conclusion

mAbs have been designed against various A β species with the aim to clear toxic A β from the brain in order to halt the amyloid cascade and prevent neurodegeneration and cognitive and functional decline. Results from two large phase 3 trials with bapineuzumab and solanezumab have been disappointing. Possible explanations could be that these compounds either target the wrong A β species or were given too late in the disease course. Several new mAbs targeting various different A β epitopes are now being tested in ongoing phase 2 and 3 clinical trials, some of which are targeting subjects in the asymptomatic or prodromal disease stages.

Notes: This article is part of a series on *Immunotherapy in Alzheimer's disease*, edited by Philip Scheltens. Other articles in this series can be found at <http://alzres.com/series/immunotherapy>

Abbreviations

A4: Anti-Amyloid Treatment of Asymptomatic Alzheimer's Disease; AD: Alzheimer's disease; API: Alzheimer's Prevention Initiative; ApoE4: Apolipoprotein E ϵ 4; ARIA: Amyloid-related imaging abnormality; A β : Amyloid- β ; CSF: Cerebrospinal fluid; DIAN: Dominantly Inherited Alzheimer Network; Ig: Immunoglobulin; mAb: Monoclonal antibody;

MMSE: Mini-Mental State Examination; MRI: Magnetic resonance imaging; PET: Positron emission tomography.

Competing interests

The authors declare that they have no competing interests. PS is co-Editor-in-Chief of *Alzheimer's Research & Therapy* and receives an annual honorarium.

Published: 11 Nov 2013

References

- Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE: **Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis.** *Clin Interv Aging* 2008, **3**:211–225.
- Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, van den Bussche H: **Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials.** *BMJ* 2005, **331**:321–327.
- Ozudogru SN, Lippa CF: **Disease modifying drugs targeting β -amyloid.** *Am J Alzheimers Dis Other Demen* 2012, **27**:296–300.
- Selkoe DJ: **Alzheimer Disease: mechanistic understanding predicts novel therapies.** *Ann Intern Med* 2004, **140**:627–638.
- Hardy J: **The amyloid hypothesis for Alzheimer's disease: a critical reappraisal.** *J Neurochem* 2009, **110**:1129–1134.
- Wisniewski T, Sadowski M: **Preventing β -amyloid fibrillization and deposition: β -sheet breakers and pathological chaperone inhibitors.** *BMC Neurosci* 2008, **9**(Suppl 2):S5.
- Morgan D: **Immunotherapy for Alzheimer's disease.** *J Intern Med* 2011, **269**:54–63.
- Reichert JM: **Which are the antibodies to watch in 2013?** *MAbs* 2013, **5**:1–4.
- Moreth J, Mavoungou C, Schindowski K: **Passive anti-amyloid immunotherapy in Alzheimer's disease: what are the most promising targets?** *Immun Ageing* 2013, **10**:18.
- Schnabel J: **Vaccines: chasing the dream.** *Nature* 2011, **475**:S18–S19.
- Walsh DM, Selkoe DJ: **A beta oligomers - a decade of discovery.** *J Neurochem* 2007, **101**:1172–1184.
- Selkoe DJ: **Soluble oligomers of the amyloid β -protein impair synaptic plasticity and behavior.** *Behav Brain Res* 2008, **192**:106–113.
- Schnabel J: **Amyloid: little proteins, big clues.** *Nature* 2011, **475**:S12–S14.
- Benilova I, Karran E, De Strooper B: **The toxic A β oligomer and Alzheimer's disease: an emperor in need of clothes.** *Nat Neurosci* 2012, **15**:349–357.
- Bard F, Cannon C, Barbour R, Burke RL, Games D, Grajeda H, Guido T, Hu K, Huang J, Johnson-Wood K, Khan K, Kholodenko D, Lee M, Lieberburg I, Motter R, Nguyen M, Soriano F, Vasquez N, Weiss K, Welch B, Seubert P, Schenk D, Yednock T: **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**:916–919.
- Frost JL, Liu B, Kleinschmidt M, Schilling S, Demuth HU, Lemere CA: **Passive immunization against pyroglutamate-3 amyloid- β reduces plaque burden in Alzheimer-like transgenic mice: a pilot study.** *Neurodegener Dis* 2012, **10**:265–270.
- Venkataramani V, Wirths O, Budka H, Hörtig W, Kovacs GG, Bayer TA: **Antibody 9D5 recognizes oligomeric pyroglutamate amyloid- β in a fraction of amyloid- β deposits in Alzheimer's disease without cross-reactivity with other protein aggregates.** *J Alzheimers Dis* 2012, **29**:361–371.
- Sperling RA, Jack CR, Black SE, Frosch MP, Greenberg SM, Hyman BT, Scheltens P, Carrillo MC, Thies W, Bednar MM, Black RS, Brashear HR, Grundman M, Siemers ER, Feldman HH, Schindler RJ: **Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup.** *Alzheimers Dement* 2011, **7**:367–385.
- Barkhof F, Daams M, Scheltens P, Brashear HR, Arrighi HM, Bechten A, Morris K, McGovern M, Wattjes MP: **An MRI rating scale for amyloid-related imaging abnormalities with edema or effusion.** *AJNR Am J Neuroradiol* 2013, **34**:1550–1555.
- Salloway S, Sperling R, Gilman S, Fox NC, Blennow K, Raskind M, Sabbagh M, Honig LS, Doody R, van Dyck CH, Mulnard R, Barakos J, Gregg KM, Liu E, Lieberburg I, Schenk D, Black R, Grundman M, Bapineuzumab 201 Clinical Trial Investigators: **A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease.** *Neurology* 2009, **73**:2061–2070.
- Sperling R, Salloway S, Brooks DJ, Tampieri D, Barakos J, Fox NC, Raskind M, Sabbagh M, Honig LS, Porsteinsson AP, Lieberburg I, Arrighi HM, Morris KA, Lu Y, Liu E, Gregg KM, Brashear HR, Kinney GG, Black R, Grundman M: **Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: a retrospective analysis.** *Lancet Neurol* 2012, **11**:241–249.
- Salloway S: **A randomized, double-blind, placebo-controlled clinical trial of intravenous bapineuzumab in patients with Alzheimer's disease who are apolipoprotein E e4 non-carriers.** *Eur J Neurol* 2012, **19**:SC312.
- Sperling R: **A randomized, double-blind, placebo-controlled clinical trial of intravenous bapineuzumab in patients with Alzheimer's disease who are apolipoprotein E e4 carriers.** *Eur J Neurol* 2012, **19**:SC3012.
- Farlow M, Arnold SE, van Dyck CH, Aisen PS, Snider BJ, Porsteinsson AP, Friedrich S, Dean RA, Gonzales C, Sethuraman G, DeMattos RB, Mohs R, Paul SM, Siemers ER: **Safety and biomarker effects of solanezumab in patients with Alzheimer's disease.** *Alzheimers Dement* 2012, **8**:261–271.
- Tayeb HO, Murray ED, Price BH, Tarazi FI: **Bapineuzumab and solanezumab for Alzheimer's disease: is the 'amyloid cascade hypothesis' still alive?** *Expert Opin Biol Ther* 2013, **13**:1075–1084.
- Bohrmann B, Baumann K, Benz J, Gerber F, Huber W, Knoflach F, Messer J, Oroszlan K, Rauchenberger R, Richter WF, Rothe C, Urban M, Bardroff M, Winter M, Nordstedt C, Loetscher H: **Gantenerumab: a novel human anti-A β antibody demonstrates sustained cerebral amyloid- β binding and elicits cell-mediated removal of human amyloid- β .** *J Alzheimers Dis* 2012, **28**:49–69.
- Ostrowitzki S, Deptula D, Thurfjell L, Barkhof F, Bohrmann B, Brooks DJ, Klunk WE, Ashford E, Yoo K, Xu ZX, Loetscher H, Santarelli L: **Mechanism of amyloid removal in patients with Alzheimer disease treated with gantenerumab.** *Arch Neurol* 2012, **69**:198–207.
- Adolfsson O, Pihlgren M, Toni N, Varisco Y, Buccarello AL, Antonello K, Lohmann S, Piorkowska K, Gafner V, Atwal JK, Maloney J, Chen M, Gogineni A, Weimer RM, Mortensen DL, Friesenahn M, Ho C, Paul R, Pfeifer A, Muhs A, Watts RJ: **An effector-reduced anti- β -amyloid (A β) antibody with unique a β binding properties promotes neuroprotection and glial engulfment of A β .** *J Neurosci* 2012, **32**:9677–9689.
- Garber K: **Genentech's Alzheimer's antibody trial to study disease prevention.** *Nat Biotechnol* 2012, **30**:731–732.
- A Randomized, Double-blind, Placebo-controlled, Combined Single Ascending Dose and Multiple Ascending Dose Study.** [http://www.clinicaltrials.gov/ct2/show/NCT01230853?term=ban2401&rank=2].
- A Clinical Study to Assess Single and Repeat Doses of a New Medication (GSK933776) in Patients With Alzheimer's Disease.** [http://www.clinicaltrials.gov/ct2/show/NCT00459550?term=GSK933776&rank=2].
- Study Evaluating The Safety Of AAB-003 (PF-05236812) In Subjects With Alzheimer's Disease.** [http://www.clinicaltrials.gov/ct2/show/NCT01193608?term=aab003&rank=1].
- Single and Repeated Dosing Study to Assess the Safety and the Concentration-time Profile of SAR228810 in Alzheimer's Patients.** [http://www.clinicaltrials.gov/ct2/show/NCT01485302?term=SAR228810&rank=1].
- Single Ascending Dose Study of BILB037 in Subjects With Alzheimer's Disease.** [http://www.clinicaltrials.gov/ct2/show/NCT01397539?term=BILB037&rank=2].
- Rinne JO, Brooks DJ, Rossor MN, Fox NC, Bullock R, Klunk WE, Mathis CA, Blennow K, Barakos J, Okello AA, Rodriguez Martinez de Liano S, Liu E, Koller M, Gregg KM, Schenk D, Black R, Grundman M: **11C-PiB PET assessment of change in fibrillar amyloid-beta load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study.** *Lancet Neurol* 2010, **9**:363–372.
- Roher AE, Maarouf CL, Dausgs ID, Kokjohn TA, Hunter JM, Sabbagh MN, Beach TG: **Neuropathology and amyloid- β spectrum in a bapineuzumab immunotherapy recipient.** *J Alzheimers Dis* 2011, **24**:315–325.
- Delrieu J, Ousset PJ, Vellas B: **Gantenerumab for the treatment of Alzheimer's disease.** *Expert Opin Biol Ther* 2012, **12**:1077–1086.
- Callaway E: **Alzheimer's drugs take a new tack.** *Nature* 2012, **489**:13–14.
- Miller G: **Alzheimer's research. Stopping Alzheimer's before it starts.** *Science* 2012, **337**:790–792.

10.1186/alzrt220

Cite this article as: Prins and Scheltens: Treating Alzheimer's disease with monoclonal antibodies: current status and outlook for the future. *Alzheimer's Research & Therapy* 2013, **5**:56