Cognitive Enhancers (Nootropics). Part 3: Drugs Interacting with Targets other than Receptors or Enzymes. Disease-Modifying Drugs. Update 2014

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Abstract. Scientists working in the field of Alzheimer’s disease and, in particular, cognitive enhancers, are very productive. The review “Drugs interacting with Targets other than Receptors or Enzymes. Disease-modifying Drugs” was accepted in October 2012. In the last 20 months, new targets for the potential treatment of Alzheimer’s disease were identified. Enormous progress was realized in the pharmacological characterization of natural products with cognitive enhancing properties. This review covers the evolution of research in this field through May 2014.

Keywords: Amyloid-β aggregation inhibitors, antibodies, antioxidants, cognitive enhancers, metal chelators, natural products, nootropics, peptides, psychostimulants, stem cells, tau, vaccines

INTRODUCTION

As of June 14, 2014, there are 28,317 entries in PubMed under the term cognitive enhancers, 28,336 entries under the term nootropic, and 313 entries under the term cognition enhancers. Scifinder lists 5,732 references under the research topic nootropic, 661 references under the term cognitive enhancer, and 11,334 references for cognition enhancers. The Thomson Reuters Cortellis database lists 1,306 drugs as nootropic agents. The term nootropics was coined by the father of piracetam Corneliu Giurgea in 1972/1973 [1, 2] NOOS = mind and TROPEIN = toward.

Nootropics are drugs to treat cognition deficits, which are most commonly found in patients suffering from Alzheimer’s disease (AD), schizophrenia, stroke, attention deficit hyperactivity disorder (ADHD), or aging. Mark J. Millan and 24 eminent researchers [3] presented an excellent overview on cognitive dysfunction in psychiatric disorders in the February 2012 issue of Nature Reviews Drug Discovery and define cognition as “a suite of interrelated conscious (and unconscious) mental activities, including pre-attentional sensory gating, attention, learning and memory, problem solving, planning, reasoning and judgment, understanding, knowing and representing, creativity, intuition and insight, spontaneous thought, introspection, as well as mental time travel, self-awareness and meta cognition (thinking and knowledge about cognition)”.

Since a first review in 1989 on “Families of Cognition Enhancers” by Froestl and Maitre [4], substantial progress has been made in the understanding of the mechanism(s) of cognitive enhancers. Therefore, we propose a new classification to assign cognition enhancing drugs to 19 categories:

1. Drugs interacting with Receptors (Part 1)
2. Drugs interacting with Enzymes (Part 2)
3. Drugs interacting with Cytokines (Part 3)
4. Drugs interacting with Gene Expression (Part 3)
5. Drugs interacting with Heat Shock Proteins (Part 3)
6. Drugs interacting with Hormones (Part 3)
7. Drugs interacting with Ion Channels (non-Receptors) (Part 3)
8. Drugs interacting with Nerve Growth Factors (Part 3)
9. Drugs interacting with Re-uptake Transporters (Part 3)
10. Drugs preventing amyloid-β aggregation (Part 3)
11. Ligands interacting with amyloid-β (Part 3)
12. Inhibitors of serum amyloid P component binding (Part 3)
13. Vaccines against amyloid-β (Part 3)
14. Antibodies against amyloid-β (Part 3)
15. Drugs preventing tau, prion, or α-synuclein aggregation (Part 3)
16. Ligands interacting with tau and α-synuclein aggregation (Part 3)
17. Vaccines against tau and α-synuclein (Part 3)
18. Stem Cells (Part 3)
19. Miscellaneous (Part 3)

In the first paper, drugs interacting with receptors were described [5]; in the second paper, drugs interacting with enzymes [6]. In this third part, we give an overview of drugs interacting with targets 3 to 10 and compounds and preparations of categories 11 to 19 [7]. Disease modifying drugs are aimed to counteract the progression of a disease [8]. In Part 2 of this series of reviews, Drugs interacting with amyloid-β (Aβ) and tau including immunotherapy are described in Part 3. For excellent novel overviews on therapeutics for AD, see [9–14].

However, this field is very dynamic. Potential new targets were identified for the treatment of cognitive deficits. Some compounds progressed in their development, while many others were discontinued. The thorough pharmacological characterization of natural products with cognitive enhancing properties was significantly expanded. Therefore, an update is appropriate.

DRUGS INTERACTING WITH CYTOKINES

There is abundant evidence that inflammatory mechanisms within the central nervous system (CNS) contribute to cognitive impairment via cytokine-mediated interactions between neurons and glial cells [15]. A current hypothesis is that an extracellular insult to neurons could trigger the production of inflammatory cytokines by astrocytes and microglia [16]. Knocking down the IL-12/23 signaling subunit p40 in the brain of SAMP8 mice ameliorated their spatial memory [17]. See also Chapter 11. Antioxidants, because inflammation is tightly connected with the oxidative cascade.

Diammonium glycyrrhizinate attenuated Aβ1-42 induced neuroinflammation and regulated MAPK and NF-κB pathways in vitro and in vivo [18].

The development of SEN-1176 (Senexis, [19]), TT-301 (MW01-6-189WH; MW-189), and TT-302 (MW01-7-084WH, MW-084; Transition Therapeutics) was terminated. However, this field is very dynamic. Potential new targets were identified for the treatment of cognitive deficits. Some compounds progressed in their development, while many others were discontinued. The thorough pharmacological characterization of natural products with cognitive enhancing properties was significantly expanded. Therefore, an update is appropriate.

DRUGS INTERACTING WITH GENE EXPRESSION

A genome-wide association study (GWAS) of the rate of cognitive decline in AD revealed that the minor alleles of the spondin 1 gene (SPON1) were significantly associated with a slower rate of cognitive decline [20]. A GWAS implicated the APOE locus in nonpathological cognitive aging [21]. Another GWAS elucidated the correlation between butyrylcholinesterase expression and Aβ deposition [22]. Apabetalone (RVX-208, Resverlogix, Calgary; Fig. 1) is an apolipoprotein A1 (ApoA1) gene expression stimulator for the potential prevention of Aβ plaque accumulation in AD. In January 2011, data from an analysis of AD biomarkers in the Phase II ASSERT trial in 299 patients showed that after 12 weeks of treatment with 150 mg/day, a positive effect on Aβ40 was seen. Apabetalone significantly increased HDL-
C ($p=0.001$), the primary endpoint of the Phase IIb SUSTAIN trial. SUSTAIN also successfully met secondary endpoints and showed increases in levels of Apo-AI ($p=0.002$) and large HDL particles ($p=0.02$), both believed to be important factors in enhancing reverse cholesterol transport activity. Apabetalone is a unique selective bromo and extraterminal (BET) bromodomain antagonist [23, 24] (Thomson Reuters Pharma, update of June 12, 2014).

There are several drugs interacting with gene expression in preclinical evaluation (in alphabetical order):

**Adeno-associated virus vector-5-delivered GDNF gene therapy** (Cedars-Sinai Regenerative Medicine Institute, Los Angeles, CA) secreted glial cell-derived neurotrophic factor (GDNF) directly into muscle cells for the potential treatment of amyotrophic lateral sclerosis (ALS) (Thomson Reuters Pharma, update of April 4, 2014).

**Crct-1 gene therapy** (Universitat Autonoma de Barcelona) acts by inducing the production of CREB regulated transcription coactivator-1 (Crtc1) for the potential prevention and treatment of AD. The gene therapy activated Crtc1 and prevented the loss of memory in mice (Thomson Reuters Pharma, update of April 25, 2014).

**DRUGS INTERACTING WITH HEAT SHOCK PROTEINS**

Overexpression of Hsp27 ameliorated symptoms of AD in AβPP/PS1 mice [25]. Intranasally-administered Hsp70 rapidly entered the brain and mitigated multiple AD-like morphological and cognitive abnormalities in model animals [26]. Tau triage decisions are mediated by the chaperone network [27]. Hsp90 inhibits α-synuclein aggregation by interacting with soluble oligomers [28].

**17-Allylamin-17-demethoxygeldanamycin** (17-AAG) is a potent inhibitor of Hsp90. A high dose of 17-AAG decreased neurofibrillary tangles in male P301L mutant mice [29]. It attenuated Aβ-induced synaptic toxicity and memory impairment [30]. University of Siena medicinal chemists published novel 1,2,3-triazoles as Hsp90 inhibitors [31].
YM-08 (University of Michigan, Ann Arbor, MI; Fig. 1) is a novel brain penetrant Hsp70 inhibitor, which reduced phosphorylated tau levels in cultured brain slices [32]. The allosteric heat shock protein 70 inhibitor YM-01 (University of South Florida, Tampa, FL) rapidly rescued synaptic plasticity deficits by reducing aberrant tau [33]. A new class of Hsp90 inhibitors designed by energy-based pharmacophore virtual screening was described [34].

An excellent review on heat shock proteins was published recently [35].

The development of Hsp90 inhibitors of Lundbeck was terminated.

**DRUGS INTERACTING WITH HORMONES**

Melanocortins, in particular MC4 receptor-stimulation melanocortins, protected against progression of AD in triple transgenic mice [36].

Resistin, also known as *adipose tissue-specific secretory factor* or C/EBP-β/H9255-regulated myeloid-specific secreted cysteine-rich protein (XCP1) is a cysteine-rich adipose-derived peptide hormone, protected against endogenous Aβ neuronal cytotoxicity [37].

The development of leuprolide acetate implant (VP-4896, Memryte; Curaxis Pharmaceuticals and DURECT) was terminated.

**DRUGS INTERACTING WITH ION CHANNELS (NON-RECEPTORS)**

Dysregulation of Ca2+ homeostasis plays a crucial role in the pathogenesis of AD [38–42]. The topic “Calcium channel blockers and dementia” was discussed [43].

ARC-029 (Archer Pharmaceuticals, Sarasota, FL, a spin-out from the Roskamp Institute, Sarasota, FL) is a blood-brain barrier crossing formulation of nilvadipine (for the structure, see [7]). It is evaluated in a multisite Phase III clinical trial enrolling more than 500 AD patients in Europe since May 2013 (Thomson Reuters Pharma, update of May 20, 2013).

RNS-60 (Revalesio Corporation, Tacoma, WA) is in Phase II clinical trials since May 2010. RNS-60 enhanced synaptic transmission and induced morphological plasticity by stimulating NMDA- and AMPA-dependent calcium influx [44] (Thomson Reuters Pharma, update of May 16, 2014). The structure was not communicated.

ST-101 (ZSET-1446; Sonexa Therapeutics, San Diego, CA under license from Zenyaku Kogyo, Tokyo) is in Phase II clinical trials for AD since February 2009 and for the treatment of essential tremor since May 2011 (for the structure, see [7]). Combination effects of ZSET1446/ST101 with memantine on cognitive function and extracellular acetylcholine in the hippocampus of rats were described [45]. It was recognized that ST-101 targeted T-type voltage-gated calcium channels in mediating improved cognition in the CNS [46] (Thomson Reuters Pharma, update of October 8, 2013).

Phenchlobenpyrone (Yunnan Spirin Biotechnology, Kunming Yunnan, the Kunming Institute of Botany of the Chinese Academy of Sciences and the Kunming Institute of Zoology of the Chinese Academy of Sciences, Kunming Yunnan, China) is a nerve cell calcium channel blocker and glycine receptor antagonist for the potential treatment of AD and amnesia in Phase I clinical trials since May 2008 (Thomson Reuters Pharma, update of October 4, 2013). The structure was not communicated.

ML-297 (VU-0456810; CID-56642816; Vanderbilt University, Nashville, TN and AfaSci, Burlingame, CA; Fig. 1) is a selective G-protein coupled inward rectifying potassium (GIRK) channel activator for the potential treatment of epilepsy. ML-297 improved cognitive activity in mice (Thomson Reuters Pharma, update of June 30, 2014).

Tx3-1, a peptidic toxin and selective blocker of A-type K+ currents (IA), enhanced both short- and long-term memory consolidation of mice tested in the novel object recognition task. Moreover, Tx3-1 restored memory of Aβ25-35-injected mice [47].

Topiramate (Johnson & Johnson, launched in 1996) is a blocker of voltage-dependent sodium channels and widely used as an antiepileptic drug. It alleviated behavioral deficits and reduced neuropathology in AβPP/APPswe/PS1dE9 transgenic mice [48]. It was tested in clinical settings for the treatment of aggressive behavior in dementia [49–51].

The development of ARC-031-SR (a non-calcium channel blocking and solute Aβ reducing nilvadipine derivative in a slow release formulation, Archer Pharmaceuticals) and of SPI-017 oral (Sucampo) was terminated.

**DRUGS INTERACTING WITH NERVE GROWTH FACTORS**

Early brain-derived neurotrophic factor (BDNF) treatment ameliorated cell loss in the entorhinal cortex...
of AβPP transgenic mice [52]. Aβ oligomers impaired BDNF retrograde trafficking by down regulating ubiquitin C-terminal hydrolase, UCH-L1 [53]. Plasma BDNF levels are correlated with aggressiveness in patients with amnestic mild cognitive impairment (aMCI) or AD [54]. Decreased levels of BDNF were found in patients with non-AD tauopathies [55].

Nerve growth factor (NGF) and AD, new facts for an old hypotheses were communicated [56, 57]. Nerve growth factor metabolic dysfunction in AD and Down’s syndrome was reviewed recently [868]. Ganglioside GM1 treatment prevented Aβ-induced cognitive deficits in rats by preventing Aβ-induced alteration on Na⁺, K⁺-ATPase by its antioxidant properties [58].

NeuroAid (MLC-901; Danqi Plantan Jiaonang; Molec Pvt Ltd, Singapore; a BDNF stimulator for the potential oral prevention of stroke including cerebral infarction and ischemic stroke and for the potential treatment of traumatic brain injury (TBI) in a randomized, double-blind, placebo-controlled, multicenter, Phase III trial (n = 1100) since November 2007 in Singapore and the Philippines. The drug was launched in Singapore in February 2013 for the treatment of cerebral infarction and ischemic stroke (Thomson Reuters Pharma, update of April 28, 2014).

CERE-110 (AA V2-NGF, NeuroRescue AD; Sangamo BioSciences, Richmond, CA, following the acquisition of Ceregene, San Diego, CA) is an AAV2 vector based gene delivery system containing cDNA for NGF in Phase II clinical trials in mild-to-moderate AD patients (n = 50) since May 2009 in the US. In April 2013, top-line data were expected by late 2014 (Thomson Reuters Pharma, update of June 2, 2014).

Basic fibroblast growth factor entrapped in nanoparticles (Fudan University, Shanghai) significantly improved spatial learning and memory in AD rats following intranasal administration [59].

Neuropep-1, a BDNF modulating peptide, ameliorated learning and memory deficits in an AD mouse model [62].

There are several drugs or preparations interacting with neurotrophic factors in preclinical evaluation (in alphabetical order):

209-B-5 (Molcode, Tartu, Estonia) is a small molecule mimetic of GDNF, which activated the GDNF family receptor-α/RET receptor complex for the potential treatment of neurological disease including ALS, neuropathic pain, PD, and AD (Thomson Reuters Pharma, update of September 27, 2013). The structure was not communicated.

AM-206 (Seoul National University) is an antagonim, which enhanced BDNF levels, synaptogenesis, and neurogenesis including cognitive improvement in an AD transgenic mouse model. By January 2013, studies had shown that the lead compound was effectively delivered to the brain through intranasal delivery by crossing the blood-brain barrier. Data also showed that the cognitive function was restored through synapse regeneration in mice with AD (Thomson Reuters Pharma, update of July 12, 2013).
mimetics; Molcode), KP-544 (KRX-0501, CXB-909; Krenitsky), tetrapirinim (AIT-082, SFI-205; Neotrofin; Spectrum Pharmaceuticals, Henderson, NV formerly NeoTherapeutics). It is now evaluated in a Phase I clinical trial for the potential treatment of chemotherapy-induced neuropathy since December 2012 in the US; Thomson Reuters Pharma, update of March 25, 2014), NGF agonists (Rhone-Poulenc/Regeneron), Pan-Neurotrophin-1 (Regeneron) and PYM-50028 (Smilagenin, Cogane, PS5, P63; Phytopharma; [63]).

DRUGS INTERACTING WITH RE- UPTAKE TRANSPORTERS (PSYCHOSTIMULANTS)

For a recent review on psychostimulants and cognition, see [64]. An analysis of student use (and abuse) of cognitive enhancers was presented [65].

There are several drugs interacting with re-uptake transporters in preclinical evaluation (in alphabetical order):

AMY-GLY-1, AMY-GLY-3, and AMY-GLY6 (Albany Molecular Research, Albany, NY) are glycine transporter-1 (GlyT-1) inhibitors for the potential treatment of schizophrenia (Thomson Reuters Pharma, update of September 26, 2013). The structures were not communicated.

Excitatory amino acid transporter-2 (EAAT-2) stimulators (Fig. 2) are investigated by scientists from the Ohio State University (Columbus, OH) in collaboration with the Brigham & Women’s Hospital (Boston, MA) for the potential treatment of neurodegenerative diseases (Thomson Reuters Pharma, update of July 23, 2013).

Glycine transporter-1 (GlyT-1) inhibitors are evaluated for the potential treatment of cognitive impairments in patients with AD and schizophrenia by the company Datt Neuroscience LLC (San Diego, CA); Thomson Reuters Pharma, update of January 30, 2013. Structures were not communicated.

ML-352 (Vanderbilt University, Nashville, TN, Fig. 2) is a novel choline transporter inhibitor for the potential treatment of AD (Thomson Reuters Pharma, update of September 18, 2013).

Selective Serotonin Re-uptake Inhibitors (SSRIs) showed cognitive enhancing effects [869]. Patients treated with citalopram showed significant improvements on a cognitive subscale. Citalopram dose-dependently decreased amyloid-β in brain interstitial fluid. It arrested the growth of preexisting plaques and reduced the appearance of new plaques by 78%. The ability to safely decrease Aβ concentration is potentially important as a preventive strategy for AD [870].

The development of AHN-2-005 (National Institute of Drug Abuse and US Naval Medical Research Center), of AMG-747 (a GlyT-1 inhibitor; Amgen), ASP-2535 and AS-1522489-00 (GlyT-1 inhibitors; Astellas; [66]), bitopertin (RG-1678, Ro-4917838; a GlyT-1 inhibitor, Roche), of flufenoxina (FAES Pharma, the preclinical evaluation for the treatment of depression is continuing; Thomson Reuters Pharma, update of September 27, 2013), Lu-A442202 (Lundbeck, a triple dopamine, noradrenaline and serotonin re-uptake inhibitor), and NS-2359 (NeuroSearch) was terminated.

The vesicular monoamine transporter 2 (VMAT2) located on the membrane of vesicles is responsible for storing and packaging neurotransmitters into monoamine vesicles or granules. Imaging VMAT2 in the brain provides a measurement reflecting the integrity of dopaminergic, noradrenergic, and serotonergic neurons [67]. Positron emission tomography (PET) ligands for the VMAT2 became valuable diagnostic tools.

18F-Florbenazine (18F-AV-133; 18F-FP-DTBZ; Avid Radiopharmaceuticals, Philadelphia PA, a subsidiary of Eli Lilly, Indianapolis, IN under license from the University of Michigan, Ann Arbor, MI; Fig. 2) is in Phase III clinical evaluation. In May 2012, an open
A single-blind, Phase II/III study (NCT01550484; 18F-A V-133-B04) was initiated in patients with undiagnosed movement disorders ($n=150$) in the US to assess the safety and efficacy of florbenazine in diagnosing PD. At that time the study was scheduled to complete in September 2014. Preclinical and clinical data were published [68, 69] (Thomson Reuters Pharma, update of April 25, 2014).

DRUGS INTERACTING WITH TRANSCRIPTION FACTORS

No new developments.

ANTIOXIDANTS

Oxidative stress in AD was reviewed [70]. Oxidative stress mediated mitochondrial and vascular lesions serve as markers in the pathogenesis of AD [71]. See also Chapter 3: Cytokines, as inflammation is tightly connected with the oxidative cascade.

Over years clinicians have explored treatment of AD patients with antioxidants. Free radicals can be scavenged by dietary means. For a review on diet, cognition, and AD, see [72]. In the TEAM-AD V A cooperative randomized trial, patients with mild to moderate AD receiving \( \alpha \)-tocopherol showed a slower functional decline compared with placebo [73]. Participants received either 2,000 IU/d \( \alpha \)-tocopherol, memantine, the combination, or placebo. There were no significant differences in the groups receiving memantine alone or memantine plus \( \alpha \)-tocopherol. For a comment, see [74]. The combination of omega-3 fatty acid and \( \alpha \)-lipic acid slowed cognitive and functional decline in AD patients over 12 months [75].

BN-82541 (Ipsen, Boulogne-Billancourt, France, Fig. 3) is a mitochondrial protectant with antioxidant, COX-1/2 inhibitory and selective Na$^+$ channel blocking activities for the potential treatment of HD and PD. In January 2014, the drug was listed as being in Phase II development for HD (Thomson Reuters Pharma, update of January 7, 2014).

VP-20629 (OX1; IN-OX1; OX1; OXIGON, Indole-3-propionic acid; ViroPharma, Exton PA, under license from Intellect Neurosciences, New York University and Mindset BioPharmaceuticals) is an antioxidant and Aβ aggregation/deposition inhibitor for the treatment of Friedreich’s ataxia. A Phase II clinical trial was initiated in January 2014 (Thomson Reuters Pharma, update of March 13, 2014).

There are several antioxidants in preclinical evaluation (in alphabetical order):

CAT-SKL is a cell-penetrating, peroxisome-targeted, protein biologic, which entered neurons and reversed Aβ-induced oxidative stress [76].

CNSB-002 (AM-36, Relevare, Melbourne; formerly Zenyth Therapeutics; Fig. 3) is an antioxidant.
sodium channel blocker and sigma opioid modulator for the potential treatment of inflammatory and neuropathic pain [77–79] (Thomson Reuters Pharma, update of July 21, 2014).

JHX-4 (University of Nebraska Medical Center (UNMC), Omaha, NE; Fig. 3) has antioxidant and metal chelating activity for the potential oral treatment of age-related diseases such as macular degeneration, cataract and AD (Thomson Reuters Pharma, update of April 3, 2013).

L-NNNBP (Fourth Military Medical University, Xi’an, China) is a new chiral pyrrolyl-α-nitroaryl nitroxide radical showing potential antioxidant effects. It inhibited cell apoptosis induced by Aβj exposure. In vivo treatment for 1 month induced a marked decrease in brain Aβj deposition and tau phosphorylation in AβjPP/PS1 transgenic mice [80].

Nicotinamide forestalled pathology and cognitive decline in AD mice [81]. It also reduced the levels of oxidative stress, apoptosis, and PARP-1 activity in an Aβj1-42-induced rat model of AD [82].

Nicotinamide riboside restored cognition in AD mouse models [83].

Potassium 2-(1-hydroxypentyl)-benzoate (dL-PHPB) improved memory deficits and attenuated Aβj and tau pathologies in a mouse model of AD [84]. Its neuroprotective effects are probably due to an attenuation of hydrogen peroxide-induced apoptosis [85].

SkQ1 (plastoquinonyl-decyltriphenylphosphonium bromide, Fig. 3) is a mitochondria-targeted antioxidant, which partially retarded AD-like pathology in senescence-accelerated OXYS rats [86, 87].

The development of antioxidants was terminated: of disufenton sodium (Cerovive, NXY-059, AstraZeneca, which was in Phase III clinical trials for the treatment of acute ischemic stroke; [88]; the company Onconos, Oklahoma City, OK investigates the drug for the potential treatment of cancer including malignant glioma; Thomson Reuters Pharma, update of April 17, 2014) and of FRP-0924 (gemifloxacin, Neuron BioPharma).

METAL CHELATORS

The metallobiology of AD was investigated in great detail. Excellent reviews were published (in chronological order) 2012: [89], 2013: [90–93], 2014: [94–97]. The current understanding of the roles of Aβj, tau, and metal ions in AD pathogenesis was described recently [98]. For reviews on selenium and AD, see [99, 100]. High manganese induced amyloid-β related cognitive impairment [871]. For age-associated changes of brain copper, iron, and zinc in AD see [872].

DP-699 (D-Pharm, Rehovot, Israel) is an i.v. prodrug of the calcium and zinc chelator BAPTA for the potential treatment of stroke and TBI in Phase III clinical trials for stroke since October 2009 in the US, Canada, Europe, Israel, South Africa, and Brazil and since August 2001 in South Korea. For the structure, see [7] (Thomson Reuters Pharma, update of June 13, 2014).

Several metal chelators are currently in preclinical evaluation (in alphabetical order): p.p’-Methoxy-diphenyl diselenide (University of Santa Maria, Rio Grande do Sul, Brazil and University of Lisbon) showed neuroprotective effects in a model of sporadic dementia of Alzheimer-type in mice [101–104].

NA-571 (Nerve Access, Chicago Ridge, IL) is a nasal formulation of clioquinol for the potential treatment of neurodegenerative diseases. Clioquinol, however, caused subacute myelo-optico-neuropathy [105] (Thomson Reuters Pharma, update of September 4, 2013). The structure was not communicated.

2-Phenylethynyl-butyltellurium attenuated Aβj1-42 induced learning and memory impairments in mice [106].

Selenomethionine, a major organic form of selenium in yeasts, plants, and mammals, ameliorated cognitive decline, reduced tau hyperphosphorylation and reversed synaptic deficit in triple transgenic AD mice [107].

A Tetrachloro-Platinum complex on a 8-(1H-benzimidazol-2-yl)-quinoline (8-BQ) scaffold was shown to reduce the number of Aβj plaques by 29% after an oral treatment for 18 weeks of Tg2576 mice with a daily dose of 15 mg/kg [108].

Triazole-pyridine derivatives as inhibitors of metal-induced Aβj aggregation were described [109].

Triethylene tetramine dihydrochloride (trien-amine), a Cu2+-selective chelator, reduced BACE1 activity and mitigated amyloidosis via the AGE/RAGE/NF-kB pathway in a transgenic mouse model of AD [110].

The development of AEN-100 (Synthetic Biolog- ics, formerly Adeona Pharmaceuticals) and Aom-0937 (Hangzhou Adamerck Pharmlabs) was terminated.
NATURAL PRODUCTS

Excellent reviews on naturally occurring phytochemicals for the prevention and treatment of AD and PD were presented [111, 112]. Overviews on “natural substances and AD: from preclinical studies to evidence based medicine” were published [113, 114]. The treatment of AD using Chinese medicinal plants was reviewed [115]. For the role of traditional Chinese medicine for neural regeneration, see [116]. Marine natural products showed acetylcholinesterase inhibiting properties [117]. Screening and identification of neuroprotective compounds relevant for AD from medicinal plants of Sao Tomé e Príncipe was described [874].

(-)-Clausenamide (Beijing Qilin Tiansheng Medicine under license from the Institute of Materia Medica Chinese Academy of Sciences, Fig. 4) was isolated from Clausenia lansium (lour) shells for the potential treatment of AD [118–120]. By December 2012 a Phase II trial had been initiated in AD patients in China (Thomson Reuters Pharma, update of March 14, 2014). The structure was not communicated.

Sodium oligomannururate (HSH-971; Shanghai Green Valley Pharmaceutical under license from the Ocean University of China, Shandong), is a marine sulfated oligosaccharide for the potential treatment of AD [118–120]. By December 2012 a Phase II trial had been initiated in AD patients in China (Thomson Reuters Pharma, update of March 1, 2013).

STA-1 (Sinphar Pharmaceutical, Dongshan Yilan, Taiwan) is an oral capsule formulation of phenylethanoid glycosides extracted from plants for the potential treatment of dementia and AD. In March 2012, the drug was in Phase II trials for dementia in China and in March 2012 in Phase II trials for AD in Taiwan. In 2012 the drug was approved for Phase II trials in the US (Thomson Reuters Pharma, update of March 14, 2014). The structure was not communicated.

Pinocembrin (DL-0108; CSPC Zhongqi Pharmaceutical Technology, Shijiazhuang, Hebei, under license from the Institute of Materia Medica Chinese Academy of Sciences, Beijing; Fig. 4) is a natural flavone for the potential i.v. treatment of acute ischemic stroke and for oral treatment of patients with AD. By December 2012 a Phase I trial for acute ischemic stroke had been completed. Several preclinical data were reported [122–124, 125] (Thomson Reuters Pharma, update of March 28, 2014).

There are many natural products in preclinical evaluation as potential drugs for the treatment of AD (in alphabetical order):

9714 (Jiangzhong Pharmaceutical, Nanchang, China, in collaboration with the Chinese Academy of Medical Military Services, Beijing) is a compound extracted from a natural product for the potential oral treatment of AD (Thomson Reuters Pharma, update of January 31, 2013). The structure was not communicated.

6-Shogaol, an active constituent of ginger, attenuated neuroinflammation and cognitive deficits in animal models of dementia [126].

Acanthopanax senticosus harms (EAS) extract showed neuroprotective effects in SH-SY5Y cells overexpressing wild-type or A53T mutant α-synuclein [127].

Acetylcorynoline, the major alkaloid component derived from Corydalis bungeana, a traditional Chinese medical herb, attenuated dopaminergic...
neurodegeneration and α-synuclein aggregation in animal models of PD [875, 876].

**Acteoside** isolated from *Orobanche minor* inhibited Aβ aggregation [128].

**AF-243** (Dendrogenin B, DDB; 5α-hydroxy-6β-[3-(4-aminobutylamino) propylamino]-cholest-7-en-3β-ol; Affichem, Toulouse, France) is an inducer of neuron survival and neuronal differentiation for the potential treatment of PD and AD (Thomson Reuters Pharma, update of June 9, 2013).

Agramine improved cognitive dysfunction in a streptozotocin-induced AD rat model [129]. For the role of agramine in neurodegenerative disease, see [130].

Akebia saponin D, extracted from a traditional herbal medicine *Dipycusus asper* Wall, showed protective effects against ibotenic acid- and Aβ-induced cognitive deficits in rats [131, 132].

Therapeutic albumin (Albatin 20%, Grifols, Barcelona) inhibited Aβ self-association by selectively binding Aβ aggregates rather than monomers and by preventing further growth of the Aβ assemblies [133].

Allantoin from *Nelumbo nucifera* (lotus) on sub-chronic administration of 1, 3, or 10 mg/kg for 7 days significantly increased the latency time measured during the passive avoidance task in scopolamine-induced cholinergic blockade and normal naive mice [134].

Aloe polymannose multinutrient complex elicited significant improvements of the Alzheimer’s Disease Assessment Scale - Cognitive Subscale score in AD patients after 9 and 12 months [135].

Anatamine reduced Aβ production in vitro and in vivo [136, 137].

Annocin, a chemical found in some fruits such as the custard apple, increased phosphorylation of tau in the brain of FTDP-17 transgenic mice [138].

Apigenin (4',5,7-trihydroxyflavone), baicalein and nordihydroguaiaretic acid were potent inhibitors of liposome permeabilization by Aβ42 oligomers [139, 140]. The effects of C-glycosylation on the anti-AD potential of apigenin were described [141]. Apigenin reduced human insulin fibrillation [142].

Arctigenin from *Arctium lappa* (L.) inhibited Aβ production by suppressing BACE1 expression and promoted Aβ clearance by enhancing autophagy through AKT/mTOR signaling inhibition [143, 144].

i.v. Ascorbate (vitamin C) improved spatial memory in middle-aged AβPP/PSEN 1 and wild type mice [145].

Asperthecin, Asperrbenzaldehyde, and 3α,20-dihydroxyemodin, secondary metabolites of the fungus *Aspergillus nidulans*, inhibited tau aggregation [146].

Astaxanthine (NeuroBio Pharm, Laval, Québec), a terpene combined with long-chain omega-3 phospholipids carrying eicosapentaenoic acid and docosahexaenoic acid (DHA) is investigated for neurological applications including AD (Thomson Reuters Pharma, update of May 21, 2014).

Astragaloside IV showed protective effects against Aβ1-42 neurotoxicity [147].

Bacopa monnieri (Brahmi) showed memory free recall enhancing effects in adult humans [148]. Neuroprotective effects in experimental models of dementia were described [149]. A review on the nootropic herb just appeared [150]. Doses of 320 mg and 640 mg were evaluated in a double-blind, placebo-controlled crossover study in Melbourne [151]. Brahmi may be a novel therapeutic agent for the treatment of cognitive deficits in schizophrenia [152, 153]. A meta-analysis of randomized controlled clinical trials on cognitive effects of Bacopa monnieri extract was published [154].

Improved neuroprotective effects were achieved by combining Bacopa monnieri and Rosmarinus officinalis extracts [155].

Bacilein (5,6,7-trihydroxyflavone) protected cortical neurons from Aβ1-42-15-induced toxicity [156] and in a one dose pre-treatment at 5 and 10 mg/kg i.p. attenuated Aβ1-42-induced amnesia in mice in a step-through passive avoidance paradigm. Apigenin (4',5,7-trihydroxyflavone), baicalein and nordihydroguaiaretic acid were potent inhibitors of liposome permeabilization by Aβ42 oligomers [139].

Bacilein, the glucuronide of baicalein, inhibited the Aβ-induced microglial cell activation via the JAK2/STAT3 signaling pathway [157].

Bajiijsa, a ditermucrope isolated from the Chinese herb Radix Morinda officinalis, protected against Aβ1-42-induced neurotoxicity in PC12 cells [158, 159].

Bavachinin and isobavachalcone from *Pterocelastrus fructus* modulated the Aβ42 aggregation process through different mechanisms in vitro [160].

Berberine is a primary component of extracts of *Coptis rhizome* and was used in traditional Chinese medicine for centuries. It attenuated tau hyperphosphorylation in HEK293 cells [161] and ameliorated Aβ pathological and cognitive impairment in an AD transgenic mouse model [162]. It protected SN2a cells against calyculin induced axonal transport impairment [163].

Betaine attenuated AD-like pathological changes and memory deficits induced by homocysteine [164]. Betaine suppressed Aβ generation by altering AβPP processing [165].
Black tea extract and rosmarinic acid were the most potent mito-protectants of six polyphenols against the toxic effects of Aβ aggregates [186].

Blueberry (Vaccinium vitis-idaea) leaf extracts protected against Aβ-induced cytotoxicity and cognitive impairment [167].

**Bombyx excrementum** reduced amyloid-β oligomer-induced memory impairments, neurodegeneration and neuroinflammation in mice [877].

DL-3-o-Butylphthalide (CSPC-NBP Pharmaceutical, Beijing, China) is a natural antioxidant extracted from seeds of *Apium* and a powerful free radical scavenger [168]. It protected dopamine neurons in a rotenone model for PD [169].

**BV-7003** (Bioved Pharmaceuticals, San Jose, CA) is a natural product for the potential treatment of memory loss (Thomson Reuters Pharma, update of July 4, 2014).

Caffeoylquinic and dicaffeoylquinic acids present in the water extracts of *Centella asiatica* attenuated the reduced expression of nicotinic receptors and enhanced apoptosis caused by Aβ peptide in SH-SYSY cells [170, 171].

Carnosic acid, a phenolic diterpene compound found in the labiate herbs rosemary and sage, suppressed Aβ40 and Aβ42 production by activating α-secretase in cultured SH-SYSY human neuroblastoma cells and Aβ1-42 and Aβ1-43 in U373MG human astrocytoma cells. Carnosic acid treatment enhanced the mRNA expression of an α-secretase TACE (tumor necrosis factor-α-converting enzyme, i.e., ADAM17) [172, 173].

Carnosine, a dipeptide, beta-alanyl-L-histidine, naturally occurring in the brain, inhibited Aβ42 aggregation by perturbing the H-bond network in and around the central hydrophobic cluster [174].

Celastrol, a triterpenoid antioxidant compound isolated from the Chinese Thunder of God vine (*T. wilfordii*) reduced Aβ pathology in a transgenic mouse model of AD [175]. It inhibited Aβ production induced by lipopolysaccharide in vitro [176].

**Centella asiatica** modulated the aggregation dynamics of α-synuclein [177].

Chungnyuulian (Qingxue-dan in Chinese and Daio-Overigedokato in Japanese) showed neuroprotective effects through inhibition of microglia-mediated neuroinflammation in *in vitro* and *in vivo* AD-like models induced by Aβ1-42 toxicity [178].

1,8-Cineole (Eucalyptol) mitigated inflammation in Aβ intoxicated PC12 cells [179].

Cinnamon extract reduced Aβ oligomerization and corrected cognitive impairment in animal models of AD [180]. Two components of active cinnamon extract are cinnamaldehyde and epicatechin, which inhibited tau aggregation *in vitro* [181, 182]. A systematic review on the medicinal properties of *Cinnamomum zeylanicum* was provided [183].

Cocoa extracts reduced oligomerization of amyloid-β [878].

Coconut oil attenuated the effects of Aβ on cortical neurons in *vitro* [184].

Congrongyizhi Capsule, a Chinese medicine, increased brain activation in amnestic MCI patients [185].

Coriander volatile oil, extracted from Coriander sativum var. macrocarpum, ameliorated Aβ1-42-induced spatial memory impairment in a rat model of AD [186, 187].

Corynoxine B, isolated from *Uncaria rhynchophylla* (Miss.) Jacks (Gouteng in Chinese) is a Beclin-1-dependent autophagy inducer. It promoted the clearance of α-synuclein via the Akt/mTOR pathway [189, 190].

Cotinine, a natural metabolite of nicotine, may be a potential new therapeutic agent against AD [191]. It reduced Aβ aggregation and improved memory in AD mice [192]. For medicinal chemistry, see [193].

p-Coumaric acid and ursolic acid from *Cornus frutescens* attenuated Aβ25-35-induced toxicity through the regulation of NF-κB signaling pathway in PC12 cells [194].

Crocin displayed a protective effect on the amyloid fibril formation of Aβ42 peptide *in vitro* [195].

Cryptontshinone, an active component of the medicinal herb *Salvia miltiorrhiza*, inhibited Aβ aggregation and protected SH-SYSY cells from damage by Aβ [196]. It upregulated α-secretase by activating the PI3K pathway in cortical neurons [197].

The Sun Yat-Sen University (Guangzhou, China) is evaluating a capsule formulation for the potential treatment of AD. By September 2013 an IND had been filed with the Guangdong Food and Drug Administration (Thomson Reuters Pharma, update of February 11, 2014).

α-Isocubebeol, a natural compound isolated from the *Schisandra chinensis* fruit, suppressed Aβ1-42 fibril-induced neutrophil inflammatory molecules in primary microglia via suppression of NF-κB/inhibitor of xBol and MAPK [198].
Curcumin cochinichinesis attenuated Aβ protein-mediated microglial activation and promoted glia-related clearance of Aβ protein [199].

Curcumin showed potent anti-amyloidogenic effects for AD Aβ fibrils in vitro and in vivo. Mechanistic insights of curcumin interaction with the core-recognition motif of Aβ peptide was presented [200, 201]. Curcumin attenuated Aβ-induced toxicity through β-catenin and PI3K signaling [203–205] and by suppression of CRMP-2 hyperphosphorylation [206]. Curcumin is an Aβ-specific dye in Escherichia coli [207]. Curcumin attenuated Aβ-induced tau hyperphosphorylation in human neuroblastoma SH-SY5Y cells [208] and suppressed soluble tau dimers in aged human tau transgenic mice [209]. Curcumin ameliorated memory deficits via neuronal nitric oxide synthase in aged mice [210]. A novel nanocurcumin formulation was tested in AD Tg2576 mice [211]. For curcumin-decorated nanoliposomes, see [212, 213]. Curcumin-gold nanoparticles inhibited Aβ fibril growth [214].

Trifluoromethylcurcumin (FMeC1), of which the enol form is able to bind to Aβ aggregates, was used in 19F nuclear magnetic resonance (NMR) imaging of the whole head of Tg2576 mice [212]. For curcumin-decorated nanoliposomes, see [212, 213]. Curcumin-gold nanoparticles inhibited Aβ fibril growth [214].

Ferricenium tetraphenylborate (FMeC1), of which the enol form is able to bind to Aβ aggregates, was used in 19F nuclear magnetic resonance (NMR) imaging of the whole head of Tg2576 mice [212]. For curcumin-decorated nanoliposomes, see [212, 213]. Curcumin-gold nanoparticles inhibited Aβ fibril growth [214].

Cyanidin 3-O-glucoside exerted protective effects on Aβ peptide-induced cognitive impairments in rats [217].

Cyperus rotundus L. (Cyperaceae) (EECR) ethanol extracts showed protective effects on behavior and cognitive function in a rat model of hypoxia injury [879].

Danshen (Salvia Miltiorrhiza) diversity may help to defeat dementia [218].

Dendrobiun nobile Lindl (EDNLA) is a Chinese medicinal herb. Alkaloid extracts of it attenuated tau protein hyperphosphorylation and apoptosis induced by lipopolysaccharide in rat brain [219].

Dihydrofuroyricetin ameliorated behavioral deficits and reversed neuropathology of transgenic AD mice [220]. 7,8-Dihydroxyflavone, a TrkB receptor agonist and BDNF mimic, reversed memory deficits in a mouse model of AD [221, 222]. It improved memory consolidation processes in rats and mice [223–227]. Further characterization is performed at Emory University, Atlanta, GA (Thomson Reuters Pharma, May 22, 2014).

Docosahexaenonic and eicosapentaenoic acids increased global cognitive performance scores (p < 0.05) in elderly volunteers [228]. For a review on DHA and the aging brain, see [229]. Omega-3 fatty acids do cross the blood-brain barrier [230]. Eicosapentaenoic acid displayed neuroprotective effects against Aβ-induced impairment of LTP and memory [231–233]. The beneficial effects of fish-oil containing diets can be enhanced by adding other specific nutrients such as vitamins, phospholipids, and selenium [234].

Eugallocatechin-3-gallate (EGCG; Sunphenon) present in green tea reduced Aβ-mediated cognitive impairment presumably via flavonoid-mediated presenilin-1 phosphorylation, which reduced Aβ production. New insights into the mechanism were published recently [235–238]. Surface plasmon resonance imaging of Aβ aggregation kinetics in the presence of EGCG and metals was described [239].

Epsilon-viniferin glucoside inhibited the formation of Aβ toxic aggregates [240].

Ergothioneine and melatonin attenuated oxidative stress and protected against learning and memory deficits in C57BL/6J mice treated with D-galactose [241].

Erythropoietin, intranasally administered, showed potent protective activity against Aβ toxicity in the Aβ1–42 non-transgenic mouse model of AD [242].

ESP-806, the lignin-rich extract of Schisandra chinensis fruits, on oral treatment at a dose of 100 mg/kg significantly attenuated the Aβ1–42-induced memory impairment in mice [243].

Eucommia ulmoides Oliv. (EUE) aqueous extracts showed beneficial effects on learning and memory impairments in mice [244]. For a review, see [245].

Evodiamine, a natural alkaloid, was the basis for medicinal chemistry efforts. The heptol carbamate of 5-derox-3-hydroxyevodiamine exhibited an IC50 of 77 nM for BChE and showed pronounced antioxidant properties [880].

Ferulic acid had disruptive effects on Aβ fibrils [246–248]. It inhibited the transition of Aβ1–42 monomers to oligomers, but accelerated the transition from oligomers to fibrils [249]. It acted as a β-secretase.
modulator [250]. It showed protective effects in a AβPP/PS1 transgenic mouse model of AD [251].

Fisetin is a flavonol that belongs to the flavonoid group of polyphenols. Via modulation of p25 and inflammatory pathways fisetin maintained cognitive function in AD transgenic mice [252].

Flavonoids in AD and neuroinflammation were discussed in depth [253, 254].

Fortasy Connect (FC; Nutricia Research, Utrecht) is a multi-nutrient diet comprising DHA, eicosapentaenoic acid, uridine monophosphate, choline, isoflavones, inhibited Aβ fibril formation [263].

Gallic acid from grape seed polyphenol extract may be useful for the treatment of AD [262]. It inhibited Aβ fibril formation [263].

Gastrodin protected primary cultured rat hippocampal neurons against Aβ peptide-induced neurotoxicity via ERK1/2/CREB pathway [264]. It alleviated memory deficits in a mouse model of AD [265].

Geraniol (and Corilagin) from Geranium thunbergii showed BACE1 inhibitory activity in vitro [188].

Geranin attenuated α-synuclein expression [272, 273].

Ginger root extract (CT-0109 series of Zingiber officinale, Cognition Therapeutics, Pittsburgh, PA) effected inhibition of Aβ1-42 aggregation [274].

CT-0093 and CT-0134 prevented Aβ oligomers' binding with EC50 values of 1.03 and 3.88 μM. CT-013461 and CT-013441 reverted the cognitive impairment in a water maze test in transgenic AD mice with a sustained improvement for over 5 months at doses of 10 and 30 mg/kg/day (Thomson Reuters Pharma, update of May 12, 2014).

Ginkgo biloba (EGb 761, Tanakan, Tanamin) treatment prevented age-related spatial memory deficits in a transgenic mouse model of AD. In a large study of 2,854 participants over 5 years it was found that standardized Ginkgo biloba extract did not reduce the risk of progression to AD compared with placebo [275]. A 20-year follow-up population-based study was communicated [276]. Catechins and procyanidins of Ginkgo biloba showed potent activities towards the inhibition of Aβ aggregation [277].

Ginkgolide B in a novel oil-body nanoemulsion formulation achieved memory improvement in a Morris water maze test in rats [278]. The effects and mechanisms of ginseng and ginsenosides on cognition were reviewed [279].

Ginsenoside Rd, a traditional Chinese medicine, prevented cognitive deficits in a rat model of AD [280–282]. Ginsenoside Rg5 improved cognitive dysfunction and Aβ deposition in STZ-induced memory impaired rats [283]. Ginsenoside Rg1 showed protective effects on chronic restraint stress induced learning and memory impairments in male mice [284].

Glutathione has an emerging role in AD [285].

D-Govadine improved impairments in compromised memory function in delayed response tasks possibly through selective increases in DA efflux in the frontal cortex [286, 287].

Gramicidin S inhibited Aβ1-40 fibril formation [288].

Grape-derived polyphenolics from Vitis vinifera grape seeds attenuated cognitive deterioration in a mouse model of AD. Ultrastructural alterations of AD paired helical filaments by grape seed-derived polyphenolics was studied [289].

Green tea polyphenols protected against okadaic acid-induced acute learning and memory impairments in rats [290].

Guarana (Paullinia cupana Mart.), popularly consumed in Brazil, was able to prevent protein glycation, Aβ aggregation, in vitro methylglyoxal, glyoxal, and ACR (20 μM)-induced toxicity on neuronal-like cells (SH-SY5Y) [291].

gx-50 derived from Sichuan pepper (Zanthoxylum Bungeanum) disassembled Aβ oligomers, inhibited...
AJ induced neuronal apoptosis and apoptotic gene expression and reduced neuronal calcium toxicity [292].

Gypenoside XVII (GP-17) is a novel phytoestrogen isolated from Gynostemma pentaphyllum or Panax notoginseng. Pretreatment with GP-17 (10 μM) for 12 h increased estrogen response element reporter activity, activated PI3K/Akt pathways, inhibited GSK-3β, induced Nrf2 nuclear translocation, augmented antioxidant responsive element enhancer activity, upregulated heme oxygenase 1 expression and activity, and provided protective effects against Aβ25-35-induced neurotoxicity including oxidative stress, apoptosis, and autophagic cell death. GP-17 conferred protection against Aβ25-35-induced neurotoxicity through estrogen receptor-dependent activation of PI3K/Akt pathways [293].

Heparin sulfate hexa- to dodecasaccharides showed inhibiting properties of β-secretase [294]. HL-O0362 (2, 2'-4'-trihydroxychalcone; Shanghai Institute of Materia Medica of the Chinese Academy of Sciences), isolated from Glycyrrhiza glabra, a new inhibitor of BACE1, efficiently ameliorated memory impairment in mice [295]. Structure optimization is ongoing (Thomson Reuters Pharma, update of September 11, 2013).

Homocysteine exacerbated Aβ and tau pathology and cognitive deficits in a mouse model of AD [296].

Homosolavonoids may be valuable imaging agents for Aβ plaques in AD [297].

Hesperidin and hesperetin (vide infra) showed inhibiting properties of β-secretase [298].

HP-012 and HP-050 (NeuMed and Il Dong Pharmaceuticals, both Seoul) are natural products and anti-dementia agents with high efficacy, good safety and tolerability (Thomson Reuters Pharma, updates of August 13, 2013 and August 7, 2013, respectively).

Huanglian-Jie-Du-Tang (HLJDT) is a famous traditional Chinese herbal formula that has been widely used clinically to treat cerebral ischemia. Treatment of N2a mouse neuroblastoma cells stably expressing human APP with the Swedish mutation (N2a-SwedAPP) significantly decreased the levels of full-length APP, phosphorylated APP at threonine 668, C-terminal fragments of APP, soluble APP (sAPPα and sAPPβ)-Swedish and reduced the generation of Aβ peptide in the cell lysates of N2a-SwedAPP [881].

Hypericine A (Cerebra; Shanghai Institute of Materia Medica) is a natural Lycopodium alkaloid found in extracts from Huperzia serrata [299]. It is a potent acetylcholinesterase inhibitor and was launched in China for the treatment of AD in 1995. Its pharmacology, efficacy and safety was extensively described [300–304]. See also Part 2, Chapter 1. Drugs interacting with Acetyl- and Butyrylcholinesterase and Butyrylcholinesterase and Butyrylcholinesterase.

Huperzine A (Cerebra; Shanghai Institute of Materia Medica) is a potent acetylcholinesterase inhibitor and was launched in China for the treatment of AD in 1995. Its pharmacology, efficacy and safety was extensively described [300–304]. See also Part 2, Chapter 1. Drugs interacting with Acetyl- and Butyrylcholinesterase and Butyrylcholinesterase and Butyrylcholinesterase.

Hypericum perforatum (St. John’s Wort). Imm-H004, a novel coumarin derivative, protected against Aβ-induced neurotoxicity [317].

Improflavone is a synthetic isoflavone which may be used to inhibit bone resorption, maintain bone density and to prevent osteoporosis in postmenopausal women. It protected human neuroblastoma SH-SY5Y cells against Aβ-induced toxicity [318].

Ispahavachalone and baravchini from Poriaeae Fructus modulate the Aβ aggregation process through different mechanisms in vitro [160].
Isothiocyanate (IRN), the major chemical ingredient of Uncaria rhynchophylla, inhibited GSK-3β activity and activated the phosphorylation of phosphatidylinositol 3-kinase (PI3K) substrate Akt. IRN improved the Aβ-induced cognitive impairment in rats via inhibition of neuronal apoptosis and tau protein hyperphosphorylation [319, 320]. IRN improved learning and memory impairments induced by D-galactose in mice [882].

Jujishoside A, a neuroprotective agent from semen of Ziziphi Spinosae ameliorated behavioral disorders in an AD mouse model induced by Aβ1-42 [321].

Juzen-taiho-to is a herbal medicine, which reduced Aβ burden in a mouse model of AD [322].

Kaempferol-3-O-rhamnoside abrogated Aβ toxicity by modulating monomers and remodeling oligomers and fibrils to non-toxic aggregates [324].

Lanthionine ketimine ester treatment substantially diminished cognitive decline and brain Aβ peptide deposition and phospho-tau accumulation in 3x transgenic AD mice [325].

Laurus nobilis leaf polar extracts showed antiamyloidogenic efficacy in Aβ25-35 fragment oxidized cell systems [326].

Z-Ligustilide, a component of Radix Angelica Sinensis, promoted adult neurogenesis to mediate recovery from cognitive impairment [327]. The neuroprotective effects may be due to an upregulation of Klotho, an aging-suppressor gene [328, 329].

Limonoid compounds are investigated by scientists of the Johns Hopkins University (Baltimore, MD) for the potential treatment of acute and chronic neurodegenerative disorders including AD, multiple sclerosis (MS), HD, PD, AIDS related dementia, ALS, stroke, and spinal cord trauma (Thomson Reuters Pharma, update of May 29, 2013). Structures were not communicated.

Lipoprotein-based nanoparticles, apolipoprotein E-reconstituted high density lipoprotein (ApoE-HDL), after four weeks of treatment decreased Aβ deposition, attenuated microgliosis, ameliorated neurologic changes and rescued memory deficits in an AD animal model [330].

Liunwei Dihuang decoction is a well-known prescription of traditional Chinese medicine and consists of six crude drugs including Rehmannia glutinosa Lobosch (family: Scrophulariaceae), Cornus officinalis Sieb. (family: Cornaceae), Dioscorea oppositifolia L. (family: Dioscoreaceae), Phaeonia ostii (family: Paeoniaceae), Alisma orientale (G. Samuelsson), Juj (family: Alismataceae) and Portia cocoa (Schw.) Wolf (family: Polyporaceae). It significantly improved cognition deficits of diabetic encephalopathy in streptozotocin-induced diabetic rats [331].

Loganin isolated from Corni fructus showed BACE1 inhibitory activity in vitro [332, 333].

LP-226A1 (Lipopharma Therapeutics, Palma de Mallorca) is the lead compound from a series of polyunsaturated fatty acid derivatives for the potential oral treatment of CNS diseases including AD (Thomson Reuters Pharma, update of December 26, 2013). The structure was not communicated.

Ethanol extract of Magnolia officinalis prevented lipopolysaccharide-induced memory deficiency via its antineuroinflammatory and antiamyloidogenic effects [334].

Luteolin protected against high fat diet-induced cognitive deficits in obesity mice [883].

Mannotol is a potent inhibitor of α-synuclein aggregation [335].

Marine metabolites showed dual acetylcholinesterase and Aβ aggregation inhibiting properties [336].

Melatonin in AD was reviewed [337]. It protected against Aβ-induced impairments of hippocampal LTP and spatial learning in rats [338]. It also improved spatial learning and memory in Ts65Dn mice, a model of Down syndrome [339].

Milletia pulchra polysaccharide showed a protective effect on cognitive impairment induced by D-galactose in mice [340].

N-acetylcysteine showed protective effects against the up-regulation of b-amyloidogenesis by 24- and 27-hydroxycholesterol [341]. For the impact of N-acetylcysteine on cerebral Aβ plaques, see [342].

Naringenin from citrus aurantium significantly reduced Aβ brain levels in IVC-STZ rats [343].

Naringin from Pomelo peel, a Citrus species, enhanced CaMKII activity and improved long-term memory in AD mice [344].

Neoechinulin A, an indole alkaloid isolated from marine-derived Microsporum sp., significantly suppressed the production of neurotoxic inflammatory mediators tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and prostaglandin E2 (PGE2) in activated BV-2 cells [345].

NeurocentRX Pharma (Edinburgh) is investigating a natural product-based compound for the treatment of cognitive diseases (Thomson Reuters Pharma, update of February 18, 2012).

Neuroprotectin D1 (NPD1) is a natural oxidation product of DHA. It reduced the Aβ42 peptide release
from aging human brain cells by down-regulating BACE1 while activating the α-secretase ADAM10. The downregulation of BACE1 is PPAR-γ-dependent [346–348]. ND91 induced homeostatic regulation of neuroinflammation and cell survival [349].

NeurTriptin (Pharmacogenesis, Redwood City, CA) is a prodrug of triptolide (PG-490, Fig. 4), an active constituent of PG-27, an immunosuppressive fraction purified from an extract of the Chinese medical plant Tripterygium wilfordii hook F for the potential i.v. treatment of neurodegenerative diseases including AD and PD disease and ALS (Thomson Reuters Pharma, update of February 7, 2013).

Nicotine interacted with the β-sheet of Aβ(1–22) and transformed it to an α-helical structure, which helped to prohibit the aggregation of Aβ protein [350]. Nicotine exerted its neuroprotective effects against Aβ-induced neurotoxicity through the Erk1/2-p38-JNK-dependent signaling pathway [351]. For medicinal chemistry, see [193].

Nobilin, a citrus flavonoid, ameliorated cognitive impairment, oxidative burden, and hyperphosphorylation of tau in senescence–accelerated mice [352].

Oleocanthal, a phenolic component of extra-virgin olive oil, enhanced Aβ clearance [353].

Oleuropein promoted the α-secretase cleavage of the AβPP [354]. Oleuropein aglycon, the main secoirsidoid phenol present in extra virgin olive oil, counteracted Aβ1-42 toxicity in rat brain [355].

Omega-3 fatty acids produced cognitive enhancement [356]. They also regulated the interaction of Aβ1-38 peptide with lipid membranes [357]. The combination of omega-3 fatty acid and α-lipoic acid slowed cognitive and functional decline in AD patients over 12 months [75].

Osthole is an O-methylated coumarin found in plants Osmunda monnieri, Angelica archangelica, and Angelica pubescens. It reduced intracellular Aβ levels in neural cells, which was associated with decreased BACE1 protein. It reversed exogenous Aβ1-35-induced cell viability loss, apoptosis and synapsin-1 reduction, which was related to the reestablishment of phosphorylation of cyclic AMP response element-binding protein (CREB) [358].

Panax ginseng was neuroprotective in a novel progressive model of PD [361].

Pentamethoxyquercetin protected against diabetes-related cognitive deficits in diabetic rats [362].

L-Phosphoserine and 3-hydroxyanthranilic acid, two endogenous brain molecules, bound to the HHQK region of Aβ15-28 and were able to inhibit Aβ aggregation [363].

Piper nigrum fruits methanolic extracts improved memory impairment in a rat model of AD [364].

Polyphenols probably interacted with Aβ through π–π stacking interactions via the aromatic amino acids of Aβ [365, 366]. Natural phenols protected against pathological conditions associated with Aβ aggregation [367]. For naturally occurring polyphenolic inhibitors of amyloid-β aggregation see [368].

Polyunsaturated fatty acids showed properties of cognitive enhancers [356, 368].

Pomegranate polyphenols inhibited nuclear factor of activated T-cell activity and microglial activation in vitro and in a transgenic mouse model of AD [369].

PT-3, a N-benzylcinnamamide purified from Piper submultinerve, protected rat cultured cortical neurons from Aβ peptide-induced neurotoxicity [370].

Pterocarpus marsupium (PM, Fabaceae) and Erythrina jambolana (El. Myrtaceae) extracts inhibited dipeptidyl peptidase-4 and ameliorated streptotocin induced AD in rats [885].

Puerarin, a phytoestrogen isolated from Pueraria lobata, attenuated Aβ-induced cognitive impairment [371, 372]. It decreased Aβ immunopositive staining in hippocampus of ovarioctomized guinea pigs [373].

Quercetin improved cognitive function in AD transgenic mice [374]. Oxidized quercetin inhibited α-synuclein fibrillation [375].

Quercetin-O-glucuronide significantly reduced the generation of Aβ peptide [376].

Rapamycin, a product of the bacterium Streptomyces hygroscopicus and a valuable immunosuppres- sant drug, improved after chronic treatment memory in AD transgenic mice [377].

Rhein lysinate, one of the major bioactive con- stituents in the rhizome of rhubarb, decreased the generation of Aβ in the brain tissues of AD model mice [378].

Rhus verniciflua bark extract showed cognitive- enhancing effects [379].

Rosamine bearing mild thiol reactivity effectively inhibited oligomerization and fibrillation processes of tau in vitro [381].
Rosmarinic acid protected PC12 cells from Aβ-induced neurotoxicity. The molecular recognition of the Aβ1-42 peptide and rosmarinic acid was investigated by NMR [382].

Rutin (3,3’,4’,5,7-pentahydroxyflavone-3-rhamnosylglucoside) inhibited Aβ aggregation and cytotoxicity, attenuated oxidative stress, decreased the production of nitric oxide and proinflammatory cytokines [383], activated the MAPK pathway and BDNF gene expression [384] and improved spatial memory in AD transgenic mice by reducing Aβ oligomer level [385]. Rutin reduced the elevated matrix metalloproteinase-9 level in rats [386].

Salidroside showed neuroprotective effects against Aβ-induced oxidative stress in rats [387]. It also showed protective effects in a model of PD [388].

Salvianolic acid A, a polyphenolic derivative from Salvia miltiorrhiza Bunge, inhibited Aβ self-aggregation and disaggregated pre-formed fibrils [389]. Salvia sahendica attenuated memory deficits, modulated CREB and decreased apoptosis in Aβ-injected rats [390]. It also attenuated acetylcholinesterase activity [391]. A systematic review on clinical trials assessing the pharmacological properties of salvia species on memory, cognitive impairment and AD was presented [392].

Saposin C, a small heat-stable glycoprotein derived from a common precursor protein prosaposin, protected glucocerebrosidase against α-synuclein inhibition [393].

Sarsasapogenin, extracted from traditional Chinese medicine Rhizoma Anemarrhenae, is evaluated by the Shenyang Pharmaceutical University for the potential treatment of AD (Thomson Reuters Pharma, update of August 16, 2013).

Sauroine derivatives, i.e., monoacetyl and diacetyl sauroine, an alkaloid from Huperzia saururs, improved learning performance of rats [394].

Schisandrin A recovered Aβ-induced neurodegeneration with cognitive decline in mice [395].

Sciadopitysin, the active component from Taxus chinensis, potently inhibited Aβ aggregation [396].

Scutellarin isolated from Scutellaria barbata and Scutellaria lateriflora attenuated neurotoxicity of Aβ [397, 398].

Silymarin, a flavonoid from the plant Silybum marianum (milk thistle), showed multiple neuroprotective effects [399]. The beneficial effect of silymarin and its main component, i.e., silibinin, is related to its capacity to disaggregate Aβ plaques and to suppress AβPP expression [400]. Silymarin ameliorated memory deficits in a mouse model of dementia [401].

Souvenaid (Nutricia, Châtel-St-Denis, Switzerland) is a mix of nutrients including the omega-3 fatty acid DHA, uridine monophosphate, and choline, dietary precursors for the synthesis of phospholipids. Two clinical trials, Souvenir I, which lasted 12 weeks, and Souvenir II, which lasted 24 weeks, were concluded [402, 403].

Soybean isoflavone ameliorated Aβ1-42-induced learning and memory deficits in rats [404]. It antagonized the oxidative cerebrovascular injury induced by Aβ1-42 in rats [405].

Spermine, spermidine, and putrescine (polyamines) reduced toxicity of soluble Aβ peptide aggregates associated with AD [406].

St. John’s Wort extract (final hyperforin concentration 5%) reduced Aβ accumulation in a double transgenic AD mouse model [407].

SuHeXiang Wan, a Chinese traditional medicine, suppressed Aβ42-induced extracellular signal-related kinase hyperactivation [408].

Sulforaphane, a potent antioxidant derived from broccoli, ameliorated cognitive function in AD mice in the Y-maze and in passive avoidance behavior tests [409]. Sulforaphane protected mouse brains from amyloid-β deposits [886].

Tannic acid interacted with tau peptide by forming a hairpin binding motif in addition to hydrogen bonding, hydrophilic/hydrophobic interactions, and electrostatic interactions [410].

Tanshinones extracted from the Chinese herb Danshen (Salvia Miltiorrhiza Bunge) inhibited Aβ aggregation, disaggregated Aβ fibrils and protected cultured cells from damage by Aβ [411]. Tanshinone IIA promoted non-amyloidogenic processing of AβPP in platelets via estrogen receptor signaling to phosphatidylinositol 3-kinase/Akt [887].

Taurine attenuated Aβ1-42-induced mitochondrial dysfunction by activating SIRT1 in SK-N-SH cells [412]. It showed a therapeutic effect against aluminum-induced impairment on learning, memory and brain neurotransmitters in rats [413].

Tetrahydrohyperforin, a semi-synthetic derivative of hyperforin, decreased cholinergic markers...
associated with Aβ plaques and caspase-3 activation in AβPP/PS1 mice [417]. It prevented mitochondrial Ca2+ overload after Aβ challenge in rat hippocampal neurons [418].

2,3,4,4-Tetramethyl-5-methylene-cyclopent-2-enone, a monoterpene neocadene ketone, dose-dependently inhibited BACE-1 in cellular and mouse models of AD [888].

Thymoquinone present in the essential oil of the seeds of Nigella sativa Linn protected cultured rat primary neurons against Aβ-induced neurotoxicity [419] and cultured hippocampal and human induced pluripotent stem cell-derived neurons against α-synuclein-induced synapse damage [420]. An independent study corroborated these findings [421].

Essential oil compositions of Trigogonon latifolius var. angustifolius and Lycopsis orientalis exhibited moderate inhibitory activity against acetyl- and butyryl-cholinesterase enzymes [422].

Tripchlorolide (T4), an extract from the natural herb Tripterygium wilfordii Hook F, improved age-associated cognitive deficits by reversing hippocampal plasticity impairment in SAMP8 mice [423].

Tripolidile (Fig. 4, a) is a biologically active natural product from Tripterygium wilfordii, protected neurons by inhibiting Aβ production and by inhibiting CXCR2 activity [424].

Troxerutin, a bioflavonoid, significantly improved the synaptic failure induced by Aβ peptide [425].

Ursolic acid and p-coumaric acid from cornus frutus attenuated Aβ25-35-induced toxicity through the regulation of NF-κB signaling pathway in PC12 cells [194].

Valeriana amurensis improved Aβ1-42 induced cognitive deficits in mice [426]. The neuroprotective active constituents of Valeriana amurensis were described [889].

Viniphenol A, a resveratrol hexamer from Vitis vinifera stalks, showed protective effects against Aβ induced toxicity in PC12 cells [427].

Vitisinol C from Vitis vinifera grapevine shoots extracts exerted a significant activity against Aβ aggregation [428].

Walnut extract inhibited the fibrillization of amyloid-β protein [890] and protected against amyloid-β peptide-induced cell death and oxidative stress in PC12 cells [891]. Dietary supplementation of walnuts improved memory deficits in a transgenic mouse model of AD [892].

Xanthoceraside, a tripenoid saponin, rescued learning and memory deficits through attenuating amyloid-β deposition and tau hyperphosphorylation in APP mice [893]. It inhibited pro-inflammatory cytokine expression in Aβ25-35/IFN-γ-stimulated microglia [894] and attenuated tau hyperphosphorylation and cognitive deficits in intracerebro-ventricular-streptozotocin injected rats [895].

Yokukansan (TJ-54), a traditional Japanese herbal medicine, was tested in clinics for potential anti-dementia effects [429]. Spatial memory was improved in a rat model of early AD [430].

Yuzu (citrus junos Tanaka) extract prevented cognitive decline in Aβ infused rats [431].

The development of AMR-109 (ultra-pure eicosapentanoic acid, Amerin Corporation), AX-00111 (Axonal Consultoria Tecnologica), polyphenol derivatives (Pharma Eight) and of PTX-200 (Phytix) was terminated.

**NOOTROPICS (“DRUGS WITHOUT MECHANISM”)**

In this chapter compounds are described whose mechanism(s) of action are unknown. Initiation of clinical trials was based on positive effects on impaired brain functions in experimental animals after proof of good tolerability.

TRI-102-ADD-001 (Tris Pharma, Monmouth Junction, NJ) is a small molecule therapeutic for the potential treatment of ADHD. In March 2014, a randomized, double-blind, parallel-assign, Phase III trial was initiated in ADHD patients (expected n = 90) in the US to evaluate the safety and efficacy (Thomson Reuters Pharma, update of March 20, 2014). The structure was not communicated.

LND-101001 (Lupin, Mumbai, India) is a small molecule therapeutic for the potential treatment of AD. In October 2013 a randomized, double-blind, placebo-controlled, parallel group, comparative, multicenter Phase II study was initiated in Poland and Lithuania in patients (n = 171) with mild to moderate AD (Thomson Reuters Pharma, update of January 28, 2014). The structure was not communicated.

PXT-864 (Pharnext, Ile-de-France) is a drug for the potential treatment of AD and age-related memory loss (ARML) in Phase II clinical trials since December 2013 in France (Thomson Reuters Pharma, update of June 30, 2014). The structure was not communicated.

ASP-3662 (Astellas Pharma, Tokyo) is in Phase I clinical trials in Japan for the potential oral treatment of AD since May 2013 (Thomson Reuters Pharma, update of May 12, 2014). The structure was not communicated.
GSK-2981710 (GSK) is a medium chain triglyceride in Phase I clinical trials in the UK since December 2012 (Thomson Reuters Pharma, update of January 3, 2014). The structure was not disclosed.

JNJ-54861911 (Janssen Research & Development LLC, Raritan, NJ) is investigated for the potential oral treatment of AD. In May 2013, a Phase I trial was initiated in Belgium in healthy subjects (expected n = 40) (Thomson Reuters Pharma, update of June 5, 2014). The structure was not communicated.

KU-046 (Kareus Therapeutics, Atlanta, GA and Connexios Life Sciences, Bangalore, India) is a potent NADPH oxidase inhibitor and significantly reduced superoxide production in vitro and improved cognitive function in both rat and mouse models. In January 2013, an IND was approved by the FDA and a randomized, double-blind, placebo-controlled two-part, safety, tolerability and pharmacokinetics Phase I trial was initiated in the US with healthy volunteers (expected n = 54) (Thomson Reuters Pharma, update of June 9, 2014). The structure was not disclosed.

MRZ-99030 (Merz, Frankfurt am Main) is an ophthalmic solution for the potential treatment of glaucoma in Phase I clinical trials since October 2012 in Germany (Thomson Reuters Pharma, update of June 5, 2014). The structure was not communicated.

Pentylenetetrazole (pentetrazol, PTZ, BTD-001; Balance Therapeutics, San Bruno, CA) is investigated for the potential treatment of cognitive impairment in Down’s syndrome. In August 2012, a Phase Ib, double-blind, randomized, placebo-controlled, parallel group, safety, tolerability, preliminary efficacy and pharmacodynamic study of was initiated in young adults and adolescents (expected n = 90) with Down’s syndrome in Australia and New Zealand (Thomson Reuters Pharma, update of March 31, 2014).

PF-06412562 (Pfizer) is in Phase I clinical trials in healthy subjects (expected n = 38) for the potential oral treatment of cognitive disorders since August 2013 in the US (Thomson Reuters Pharma, update of May 12, 2014). The structure was not communicated.

There are many nootropic agents in preclinical evaluation (in alphabetical order):

ARO-01 (Applied Research using OMIC Sciences SL, AROMICS, Barcelona) is a compound for the potential treatment of AD (Thomson Reuters Pharma, update of September 27, 2013). The structure was not disclosed.

CPC-001, CPC-201, and CPC-252 (Chase Pharmaceuticals, Washington, DC) are compounds for the palliative treatment of AD and PD (Thomson Reuters Pharma, update of May 12, 2014). The structure was not communicated.

D-110 and D-180 (Envoy Therapeutics, Jupiter, FL, a subsidiary of Takeda Pharmaceuticals, Osaka) are compounds that target a protein specifically expressed

Fig. 5. Two nootropics, a peptide and three amyloid-β aggregation inhibitors.
in D₂ receptor-expressing neurons in brain striatum and are designed to mimic deep brain stimulation for the potential oral treatment of PD (Thomson Reuters Pharma, update of February 7, 2013). The structure was not disclosed.

Gre-213 (Grespo, Stockholm) is an oral combination of two undisclosed compounds for the potential treatment of CNS disorders including MCI and AD and PD (Thomson Reuters Pharma, update of March 28, 2014). The structures were not disclosed.

IPR-088 (Iproteso, Barcelona) is a peptidomimetic for the potential oral treatment of cognitive impairment associated with schizophrenia (Thomson Reuters Pharma, update of November 22, 2013). The structure was not disclosed.

IRL-752 (Integrative Research Laboratories Sweden, Göteborg) is a cortical enhancer for the potential oral treatment of behavioral and psychological symptoms of dementia and/or attention disorders (Thomson Reuters Pharma, update of November 19, 2013). The structure was not disclosed.

JBD-401 (Jinis Biopharmaceuticals, Wanju, South Korea) is a small molecule therapeutic for the potential treatment of dementia (Thomson Reuters Pharma, update of March 17, 2014). The structure was not communicated.

KIH-110 (Chengdu Kanghong Pharmaceuticals, China) is a small molecule therapeutic for the potential treatment of AD (Thomson Reuters Pharma, update of October 24, 2013). The structure was not communicated.

MK-8189 (Merck) is investigated for the potential treatment of schizophrenia. In July 2014 a Phase I trial was planned (Thomson Reuters Pharma, update of July 14, 2014). The structure was not communicated.

P7C3-A20 (University of Texas, Southwestern Medical Center, Dallas, TX; Fig. 5) is a small molecule neuroprotectant for the potential treatment of PD, HD, and ALS. In a rat model of age-related cognitive decline and in a zebrafish model of retinal degeneration it demonstrated protective effects. The neuroprotective efficacy after TBI was described [432]. For the synthesis, see [433] (Thomson Reuters Pharma, update of December 10, 2013).

PK-048 (PharmaKure, a spin out from the University of Manchester; Fig. 5) is a neuroprotectant at an unspecified drug target for the potential treatment of AD (Thomson Reuters Pharma, update of April 2, 2014).

Q-50 and Q-134 (Avidin Biotechnology, Szeged, Hungary) are gonadonol analogues, called kinolols, for the potential treatment of anxiety and AD (Thomson Reuters Pharma, update of January 22, 2014). The structures were not communicated.

SPO-1112 (Seoul Pharma, Siheung, South Korea) is a nootropic agent for the potential treatment of dementia (Thomson Reuters Pharma, update of July 6, 2013). The structure was not communicated.

The development of alaptide (VUFB), AQW-051 (Novartis; Phase II trials for treatment of schizophrenia and PD are ongoing; Thomson Reuters Pharma, update of February 4, 2014), AVN-397 (Avinir Pharmaceuticals; Phase II trials for the treatment of anxiety are ongoing; Thomson Reuters Pharma, update of October 22, 2012), DWJ-209 (Daewoong Pharmaceuticals; the investigations for a potential use in pancreatic and lung cancer continue; Thomson Reuters Pharma, update of May 21, 2014), IWB1-84-1 (Medical College of Georgia; [434, 435]), KTX-0101 (KetoCytonx), LSI-001 (Laboratoire S. Lastier), MRZ-99030 (Merz; clinical evaluation for the indication glaucoma continues; Thomson Reuters Pharma, update of December 31, 2013), OG-635 (Oryzon Genomics), PN-403 (Wellstadt Therapeutics) and procain (Samaritan) was terminated.

**PEPTIDES**

Davunetide (intranasal, AL-108, NAP, Tel Aviv University, previously Allon Therapeutics, Vancouver, BC) is an 8-amino acid peptide (NAPVSIPQ) derived from the activity-dependent neuroprotective protein. Phase II clinical trials were initiated for the potential treatment of AD and schizophrenia in the US and for age-related macular degeneration, glaucoma, autism, cognitive disorders, and motor neuron disease in Israel in November 2013. The effects of davunetide on cognition and functional capacity in schizophrenia were described [436] (Thomson Reuters Pharma, update of May 26, 2014). Davunetide is not an effective treatment for progressive supranuclear palsy [35].

NNZ-2566 (Neuren Pharmaceuticals, Auckland, NZ; Fig. 5) is an analogue of glypromate with an additional α-methyl-group on the proline moiety, which resulted in an improved half-life and better oral bioavailability. In March 2012, a randomized, double-blind, placebo-controlled Phase I study was initiated in healthy volunteers (n = 32) in Australia. Potential indications are mild TBI, Rett syndrome, PD and AD [437–439, 440]. In March 2013, a Phase II trial for the treatment of Rett syndrome in adolescent/adult patients was initiated in the US. Neuren received orphan drug designation from the FDA for NNZ-2566 in fragile X syndrome.
syndrome. A Phase II trial for fragile X syndrome was initiated in January 2014 in the US. Neuren is also developing a formulation for intravenous infusion for severe TBI. A Phase II trial for TBI began in May 2010 in the US in collaboration with the US Army (Thomson Reuters Pharma, update of June 5, 2014).

There are many peptides in preclinical evaluation for the potential treatment of AD (in alphabetical order): acALY-18 (Therinunex, Doylestown, PA) is a synthetic peptide moiety of 1-peptidyl-2,3-diacylglyceride (pDAG), an immunostimulatory agent first isolated from Capra hircus (goat) serum as an injectable formulation for the potential prevention and treatment of AD [441] (Thomson Reuters Pharma, update of September 13, 2013).

Amphiphile (PA) (with a laminine epitope IKVAV (IKVAV-PA) can be triggered into three-dimensional nanostructures in vivo. Injection of IKVAV-PA into the hippocampus of transgenic AD mice significantly improved cognitive impairment accompanied by enhanced neurogenesis in the hippocampus [442].

Amyloid-β interacting peptides (University of Essex, Colchester, UK) were generated by an intracellular protein-fragment complementation assay approach [443].

BN-201 (G-79, Bionure, Barcelona) is a peptide for the potential treatment of MS, ALS, AD, PD, glaucoma, and neuronelitis optica. Oral, i.v., and topical formulations are evaluated (Thomson Reuters Pharma, update of May 28, 2014).

CB-102, HNG6FA, and S14G-humanin (S14G-HN) (CohBar, Pacific Palisades, CA) are humanin analogues, a peptide encoded within the mitochondria, and ghrelin prevented hippocampal dysfunction [451]. Leptin influences many central processes including cognition [454]. The dysregulation of leptin signaling in AD was reviewed [455]. Leptin prevented hippocampal synaptic disruption and neuronal cell death induced by Aβ [456]. Leptin regulated Aβ production via the γ-secretase complex [457]. Leptin and ghrelin prevented hippocampal dysfunction induced by Aβ oligomers [458, 459]. Lower leptin plasma levels were observed in people with MCI or with AD than in subjects with normal cognition [460]. Scientists of Neurotez (Bridgewater, NJ) are investigating leptin as an Aβ synthesis and tau phosphorylation inhibitor for the potential treatment of AD (Thomson Reuters Pharma, update of May 22, 2014).

Colostrinin-derived peptides (ReGen Therapeutics, London) are evaluated for the potential treatment of neurodegenerative diseases such as AD and for the potential treatment of obesity (Thomson Reuters Pharma, updates of October 22, 2012). Structures were not communicated.

D-Ala2GIP (glucose-dependent insulinotropic polypeptide) facilitated synaptic plasticity and reduced plaque load in aged wild type mice and in an AD ApP/PS1 mouse model [444, 445].

Ferroene-Octy-Pro-Arg conjugates showed inhibitory effects on Aβ1-42 fibrillogenesis and Aβ induced cytotoxicity in vitro [446].

G3MLMVG37, the sequence of the glycine zipper region of the C-terminal of Aβ inhibited the Aβ-induced synaptotoxicity [447].

Ghrelin was used as a neuroprotective and palliative agent in AD and PD [448]. It successfully rescued the abnormality of neurogenesis in 5xFAD mice [449].

Ψ-Glutathione (psi-GSH) is a stable glutathione analogue, in which the amide bond is replaced by a ureide linkage. It crossed the blood-brain barrier via the glutathione active uptake machinery, protected cells against chemical oxidative insult and lowered the cytotoxicity of Aβ [450]. Researchers of the University of Minnesota (Minneapolis, MN) showed that the restoration of glyoxalase enzyme activity precluded cognitive dysfunction in AD mice [451].

Leptin inhibited Aβ protein degradation through a decrease of neprilysin expression [452] and inhibited amyloid-β protein fibrillogenesis [897]. Leptin gene therapy attenuated neuronal damages evoked by Aβ and rescued memory deficits in AβPP/PS1 mice [453]. Leptin influences many central processes including cognition [454]. The dysregulation of leptin signaling in AD was reviewed [455]. Leptin prevented hippocampal synaptic disruption and neuronal cell death induced by Aβ [456]. Leptin regulated Aβ production via the γ-secretase complex [457]. Leptin and ghrelin prevented hippocampal dysfunction induced by Aβ oligomers [458, 459]. Lower leptin plasma levels were observed in people with MCI or with AD than in subjects with normal cognition [460]. Scientists of Neurotez (Bridgewater, NJ) are investigating leptin as an Aβ synthesis and tau phosphorylation inhibitor for the potential treatment of AD (Thomson Reuters Pharma, update of May 22, 2014).

Min-301 (NRG-101; Minerva Neurosciences Cambridge, MA following the acquisition of Mind-NRG, Geneva, Switzerland, previously under license from ProteoSys, Mainz, Germany) is an injectable neuropeptide for the potential treatment of PD, AD, and schizophrenia (Thomson Reuters Pharma, update of April 17, 2014).

Neu-AZ1 (Neurim, Tel Aviv) is a CD44-derived octapeptide for the potential treatment of AD. Neu-AZ1 gave a full protection from Aβ1-42 by daily s.c. administration in a Morris water maze and new object recognition assays (Thomson Reuters Pharma, update of May 29, 2014). The structure was not communicated.
Neuropeptide Y prevented spatial memory deficits and oxidative stress following Aβ42 administration in mice [461]. The roles of neuropeptides including neuropeptide Y in learning and memory were discussed [462].

NRP-2945 (formerly called NNZ-4945; CuroNZ, Auckland NZ under license from Neuren Pharmaceuticals, Auckland NZ) is an 11-mer neuronal regeneration peptide (NRP) for the potential treatment of MS and motor neuron disease [463] (Thomson Reuters Pharma, update of February 4, 2014). The structure was not communicated.

P-8 (Cenna Biosciences, San Diego, CA) is an eight amino acid peptide for the potential intranasal administration to AD patients (Thomson Reuters Pharma, update of May 29, 2013). The structure was not communicated.

A synthetic peptide corresponding to a region of the human pericentriolar material 1 (PCM-1) protein was not communicated.

Rattin, a specific derivative of humanin in rats, protected against Aβ-induced deficits of spatial memory and synaptic spasticity in rats [465, 466].

RGX-100 (Cortica Neuroscience, Wilmington, DE following its merger with RemeGenix, Bethesda, MD) is an Aβ production-inhibiting BRI2-derived peptide for the intranasal administration to AD patients [467–475]. Transgenic BRI2-Aβ mice showed normal cognition [476]. The role of BRI2 in dementia was discussed [477] BRI2-BRICHOS is increased in human amyloid plaques in early stages of AD [478]. The molecular and neurophysiological mechanisms of Aβ and cognition in AD were outlined [481]. Amyloid burden correlated with cognitive decline in AD patients presenting with aphasia [489]. Fibrillar Aβ correlated with preclinical cognitive decline [490]. Cognitive decline in adults with high Aβ load was evaluated [491]. Aβ deposition was estimated to take 19 years in an almost linear fashion and slowed towards a plateau [492, 493]. The case for soluble Aβ oligomers as a drug target in AD was made [494–496]. Also N-truncated Aβ42 forms stable aggregates and induced acute and long-lasting behavioral deficits [497].

The inhibition and reversion of Aβ misfolding and aggregation is an approach, which has been followed up by many research groups during years. Excellent reviews dealing with this subject were published (in chronological order) 2012: [498], 2013: [499–502], 2014: [502, 503].

ALZ-801 (BLU-8499; NRM-8499; Alzheon, Lexington, MA under license from Bellus Health, formerly Neurochem, Laval, Québec) is a prodrug of tramiprosate. It showed improved gastrointestinal tolerability and lower inter-individual variability of drug exposure compared to comparable doses of tramiprosate (Thomson Reuters Pharma, update of May 7, 2014). There are many Aβ aggregation inhibitors in preclinical evaluation (in alphabetical order):

DRUGS PREVENTING AMYLOID-β AGGREGATION

The role of Aβ in the regulation of memory was discussed [485]. Low concentrations of Aβ are necessary for LTP expression and memory formation. Cyclic adenosine monophosphate (cAMP) controls AβPP translation and Aβ levels [486]. It is the cerebral microvascular rather than the parenchymal Aβ pathology, which promoted early cognitive impairment [487]. The molecular and neurophysiological mechanisms of Aβ and cognition in AD were outlined [488].

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ALZ-801 (BLU-8499; NRM-8499; Alzheon, Lexington, MA under license from Bellus Health, formerly Neurochem, Laval, Québec) is a prodrug of tramiprosate. It was evaluated in a single-center, randomized, double-blind, placebo-controlled Phase I study in 84 young and elderly healthy subjects to assess safety, tolerability and pharmacokinetics, which started in March 2010. It showed improved gastrointestinal tolerability and lower inter-individual variability of drug exposure compared to comparable doses of tramiprosate (Thomson Reuters Pharma, update of May 7, 2014).

There are many Aβ aggregation inhibitors in preclinical evaluation (in alphabetical order):

8-Hydroxyquinolines (Whitehead Institute for Biomedical Research, Cambridge, MA including cloquinol and positive isomers as Aβ inhibitors for the potential treatment of AD [505, 506]) (Thomson Reuters Pharma, update of March 5, 2014). For a combination of resveratrol and cloquinol see [899].

ACI-260 (AC Immune, Lausanne, Switzerland) is a small molecule Aβ β-sheet formation inhibitor developed using the company’s Morphomer technology for the potential treatment of glaucoma (Thomson Reuters,
Pharma, update of January 21, 2014). The structure was not communicated.

ACI-812 (AC Immune, Lausanne, Switzerland) is a small molecule that inhibited aggregation of the β-sheet form of Aβ peptide to oligomeric and fibrillar species developed using the company’s Morphomer technology for the potential treatment of AD (507). The concept of a donor-acceptor-donor hydrogen bond pattern complimentary to that of the β-sheet of Aβ42 was first investigated by Schrader and coworkers [508] (Thomson Reuters Pharma, update of December 4, 2013). The structure was not communicated.

ALZT-0P1 and ALZT-0P2 (AZTherapies, Boston, MA) are combinations of repurposed FDA approved drugs delivered using the company’s ALZT-patch, which acts by inhibiting the aggregation of Aβ peptides for the potential treatment of AD and MCI (Thomson Reuters Pharma, update of May 26, 2014). Structures were not communicated.

Aβ aggregation inhibitors (Baxter Healthcare, Deerfield, IL and the University of Illinois at Urbana-Champaign) are peptide-based inhibitors coupled to polymer backbones for the potential treatment of AD (Thomson Reuters Pharma, update of November 19, 2013). Structures were not communicated.

Aβ aggregation-mitigating peptide analogues (Louisiana State University, Baton Rouge, LA) demonstrated a better in vitro and in vivo Aβ fibrillogenesis interference compared to previously existing peptide analogs (Thomson Reuters Pharma, update of November 28, 2013). Structures were not communicated.

Amyloid-β inhibitors (BSIM2, a spin-off company founded in 2011 of the University of Coimbra, in collaboration with the University of Leeds) for the potential treatment of AD (Thomson Reuters Pharma, update of July 25, 2014). No structures were disclosed.

Aβ oligomer cellular prion protein binding inhibitors (AstraZeneca under a sublicense from Axemyx Therapeutics, Branford, CT under license from Yale University, New Haven, CT) are interacting with the cellular prion protein (PrP6), the high affinity receptor for Aβ oligomers [509, 510]. Prion protein also interacts with mature Aβ fibrils [511]. This program was selected for support by the National Institutes of Health Blueprint Neurotherapeutics Network Program (Thomson Reuters Pharma, update of September 27, 2013). No structures were disclosed.

Aβ oligomer inhibitors (Virginia Commonwealth University, Richmond, VA) are investigated for the potential treatment of AD (Thomson Reuters Pharma, update of December 26, 2013). No structures were disclosed.

APP-E2 blockers (Fritz-Lipmann Institut E V Leibniz-Institut für Altersforschung, Jena and Ascension, Munich) are therapies targeting the extracellular domain 2 of AβPP for the potential prevention and treatment of AD (Thomson Reuters Pharma, update of February 12, 2013). Structures were not communicated.

AβPP synthesis inhibitor (National Institute of Aging, Bethesda, MD) is evaluated for the potential treatment of neurological diseases including AD and dementia (Thomson Reuters Pharma, update of May 10, 2013). The structure was not disclosed.

Beta-Breaker Dipeptides (BBDP) reversed the aggregation of Aβ1-40 self-assembly [512]. Carmustine, a β-chloro-nitrosourea compound used as an alkylating agent in chemotherapy, significantly reduced Aβ plaque burden in an AD mouse model [513].

Ceftriaxone, a β-lactam antibiotic, binds with good affinity to β2-amyloid and blocks its in vivo polymerization [514].

D1 and D3 peptides (Fritz-Lipmann-Institut E V Leibniz-Institut für Altersforschung, Jena and Ascension, Munich) specific to Aβ42 plaques are investigated for the potential treatment of AD (Thomson Reuters Pharma, update of December 13, 2012). The structures were not communicated.

D3 (University of Duesseldorf) is an Aβ oligomer directed 12-mer D-enantiomeric peptide with an additional lysine at the C-terminal bearing the fluorescent ligand FITC. D3 removed Aβ deposits, reduced inflammation and improved cognition in aged AβPP/PS1 double transgenic mice [515-517].

Decapeptide RYVAAFFARR inhibited Aβ aggregation because of its high affinity for Aβ1-23 [518].

A dual-functional nanoparticle drug delivery system based on a PEGylated poly lactic acid polymer to which TGN, a peptide targeting the blood brain barrier and QSH, a peptide with high affinity for Aβ1-42, efficiently targeted amyloid plaques in the brains of AD mice [519].

Epigenetix (Montréal) is investigating small molecule modulators of amyloidogenesis for the potential treatment of AD (Thomson Reuters Pharma, update of July 18, 2014). Structures were not disclosed.

GAG/carbohydrate compounds (ProteoTech, Kirkland, WA) are glycosaminoglycan modulators for the potential treatment of AD (Thomson Reuters Pharma, update of May 6, 2014). Structures were not disclosed.
A binding ligands [527].

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Poly-4-styrenesulfonate acted as an inhibitor of Aβ aggregation [528].

Selenium compounds prevented Aβ peptide neurotoxicity in rat primary hippocampal neurons [529].

SG1 is a novel pseudopeptidic Aβ aggregation inhibitor designed to bind at the Aβ self-recognition site [530].

A Tetrachloro-Platinum complex on a 8-(1H-benzoimidazol-2-yl)-quinoline (8-BQ) scaffold was shown to reduce the number of Aβ plaques by 29% after an oral treatment for 18 weeks of Tg2576 mice with a daily dose of 15 mg/kg [531]. For a review, see [532].

Transferrin-derived peptides acted as Aβ inhibitors [533].

Tricyclic pyrones (Kansas State University, Manhattan, KS) decreased the aggregation of Aβ plaques (Thomson Reuters Pharma, update of February 15, 2013). Structures were not communicated.

University of Arkansas scientists found a series of peptoids modulating the aggregation of Aβ [534] (Thomson Reuters Pharma, update of May 8, 2014). University of California San Diego scientists are investigating inhibitors of ion channel activity of Aβ oligomers for the potential treatment of AD (Thomson Reuters Pharma, update of July 11, 2013). Structures were not communicated.

Excellent papers on theoretical calculations on Aβ aggregation inhibitors were presented: 2013: [535–542], 2014: [543–545, 922]. Excellent papers on theoretical calculations on Aβ aggregation inhibitors were published: 2013: [546], 2014: [547–550]. The development of Aβ inhibitor (Icogenex), BMS-869780 (Bristol-Myers Squibb), capropinol (SP-233; Samaritan Pharmaceuticals; [551–554]), CLR-01 (a molecular tweezer, University of Duisburg-Essen, Remselaer Polytechnic Institute, UCLA and Clear Therapeutics, a spin-off from UCLA; [555–566]), DBT-1339 (Medifron), IPS-04001 and IPS-04003 (InnoPharmaScreen, Asan, South Korea), KMS-88 series (Hammi Pharmaceutical, the Korea Institute of Science and Technology and Seoul
Ligands Interacting with amyloid-β

Since the discovery of the 11C-PiB-PET ligand tremendous progress has been made in the development of new PET ligands. The development of PET Aβ imaging agents was described [572–574]. Appropriate use criteria for amyloid PET studies were proposed [575–578]. Amyloid tracers detected multiple binding sites in AD brain tissue [579]. Via molecular dynamics simulations a common binding mode for imaging agents was identified [580]. A summary of primary findings and conclusions on Aβ PET in the diagnostic evaluation of AD was presented [581]. For excellent reviews, see [582–584]. A selective PET template method for spatial normalization of amyloid imaging with 11C-PiB was presented [905].

18F-Florbetapir (18F-AV-45; Amyvid; Avid Radiopharmaceuticals, Philadelphia, PA, a subsidiary of Eli Lilly, under license from the University of Pennsylvania) was approved by FDA as a PET imaging agent to estimate Aβ neuritic plaque density in patients with cognitive impairment on April 6, 2012 [585] (for the structure, see [7]). Florbetapir was approved in the EU on January 15, 2013. The highlights on the European marketing approval were described [586] Florbetapir imaging allows analyses of white and grey matter in early AD patients [906]. A comparison of amyloid PET imaging with 11C-PiB, 18F-florbetapir and 18F-flutemetamol was presented [907] (Thomson Reuters Pharma, update of May 20, 2014).

18F-Flutemetamol (18F-Vizamyl; AH-110690, 18F-6-OH-BTA-1; 18F-GE-067; 18F-PiB; GE-067; Uppsala Imanet, a part of GE Healthcare, Chalfont, UK and the Universities of Pittsburgh and Uppsala) was approved by FDA on October 28, 2013 (for the structure, see [7]). By April 2014 GE Healthcare subsidiary and licensee Nihon Medi-Physics planned to file an application in Japan (Thomson Reuters Pharma, update of June 4, 2014). 18F-Florbetaben (Neuraceq; 18F-BAY 94-9172; 18F-AV-1/ZK; Piramal Healthcare, Mumbai, India from an asset acquisition from Bayer under license from Avid Pharmaceuticals, Philadelphia, PA and the University of Pennsylvania) received marketing authorization from EMA for the detection of Aβ for the diagnosis of AD in February 2014 (for the structure, see [7]). FDA approved Neuraceq for PET imaging of Aβ neuritic plaque density on March 20, 2014 Aβ imaging with 18F-florbetaben in prodromal AD was published [908] (Thomson Reuters Pharma, update of June 11, 2014).
encephalopathy. In March 2013, an open-label, single group assignment, Phase II study was initiated in healthy volunteers (expected \( n = 50 \)) at risk for chronic traumatic encephalopathy in the US (Thomson Reuters Pharma, update of January 3, 2014).

\(^{123}\text{I}-\text{ABC-577} \) (Nihon Medi-Physics, Tokyo) is developing a radioiodinated imidazopyridine derivative \( \text{A}^{\beta} \text{H9252} \) imaging agent for the potential use in the diagnosis of AD. By July 2014 clinical studies had begun (Thomson Reuters Pharma, update of July 17, 2014). The structure was not communicated.

BAY-1006578 (Piramal Imaging following an asset acquisition from Bayer) was in Phase I clinical trials in Finland and Sweden since June 2010 (\( n = 36 \)). By October 2011 the trial was completed (Thomson Reuters Pharma, update of August 9, 2013). The structure was not communicated. A potential follow up compound is BAY-1008472 (Fig. 6) [592].

\(^{123}\text{I}-\text{DRM-106} \) (Fujifilm RI Pharma, Tokyo, Fig. 6) is a SPECT ligand for potential use in imaging of \( \text{A}^{\beta} \text{H9252} \) in the diagnosis of AD. \(^{125}\text{I}-\text{DRM-106} \) showed excellent brain permeability and metabolic stability in rats, with an \textit{in vitro} IC\( _{50} \) value of 1.86 nM. In \textit{ex vivo} samples from Tg2576 mice, \(^{125}\text{I}-\text{DRM-106} \) was more sensitive in detecting \( \text{A}^{\beta} \) plaque deposits than \(^{123}\text{I}-\text{IMPY} \) and, in a \textit{post mortem} human brain, the agent detected \( \text{A}^{\beta} \) plaque-associated radioactivity in the hippocampus of an AD patient. \textit{In vivo} imaging in transgenic mice showed the agent to have an excellent correlation with \(^{11}\text{C}-\text{PiB} \) in detecting \( \text{A}^{\beta} \) plaque deposits (Thomson Reuters Pharma, update of July 23, 2014).

\(^{18}\text{F}-\text{FC-119S} \) (Korea Institute of Radiological and Medical Sciences, KIRAMS, Seoul, Fig. 6) is a PET tracer to image \( \text{A}^{\beta} \) deposition for the diagnosis of AD in Phase I clinical studies (Thomson Reuters Pharma, update of September 4, 2013).

\(^{18}\text{F}-\text{Flubatine} \) (Helmholtz Zentrum Dresden Rossendorf and Ascenion, Munich; Fig. 6) is a potential PET imaging agent for the diagnosis of AD in Phase I clinical trials since November 2012 in Germany (Thomson Reuters Pharma, update of October 25, 2013).

\(^{18}\text{F}-\text{FPYBF-1} \) (Fig. 6) and \(^{18}\text{F}-\text{FPYBF-2} \) (Kyoto University) are pyridyl benzofuran derivatives as PET tracers for the potential use in imaging of \( \text{A}^{\beta} \) plaques. A Phase I clinical trial was initiated in March 2013 in Japan [593] (Thomson Reuters Pharma, update of June 9, 2014).
throughout the brain [596–598]. A Pronucleon peptide (Adlyfe, Rockville, MD and Pronucleon Biotechnology, Zurich and Novartis, Basel) is an Aβ imaging agent [595] (Thomson Reuters Pharma, update of March 24, 2013).

Pharmacological evaluation (in alphabetical order):

**3A Peptide**
A random peptide oligomer, was used to vaccinate 3xTg AD mice. 3A peptide reduced total plaque load (Aβ burden) and improved cognitive function in the 3xTg AD mouse brains as compared to controls. Vaccination with this nonhuman amyloid oligomer generated high titers of antibodies specifically recognizing Aβ oligomers, which in turn inhibited accumulation of Aβ pathology in mice. There was a significant decline in the level of hyperphosphorylated tau [613].

**ADC-2203** (BAN-2203, BioArctic Neuroscience, Stockholm) is an immunotherapeutic vaccine targeting Aβ protofibrils (Thomson Reuters Pharma, update of January 21, 2014).

**Affitope-AD-03** (MV-01, MinoVax; Affiris, Vienna, AT and licensee GlaxoSmithKline Biologicals), an AFFITOPE-based vaccine targeting truncated and modified forms of Aβ, entered a Phase I clinical trial in October 2010 in Austria (Thomson Reuters Pharma, update of April 29, 2014).

**Aβ-F-BF-227** (Ichor Medical Systems, San Diego, CA in collaboration with the University of California Irvine and the Institute for Molecular Medicine, IMM, and did not show crossreactivity to Aβ or viral epitopes. The antibody response is focused exclusively on Aβ, which in turn inhibited accumulation of Aβ pathology in mice. There was a significant decline in the level of hyperphosphorylated tau [613].

**Affitope-AD-02** (Affiris, Vienna, AT and licensee GlaxoSmithKline Biologicals) is a six amino acid peptide vaccine targeting the N-terminus of Aβ only, when it is free. The adjuvant is aluminium hydroxide. The antibody response is focused exclusively on Aβ and did not show crossreactivity to AβPP [611, 612]. A European Phase II clinical trial in 420 patients started in April 2010. Proof-of-concept data were communicated on June 4, 2014. A statistically significant correlation with biomarker hippocampus volume was not seen within the observation period of 18 months (Thomson Reuters Pharma, update of June 11, 2014).

**CAD-106** (presumed to be amilomotide, Cytos Biotechnology, Zurich and Novartis, Basel) is an Aβ1-6 peptide linked to a Qβ virus-like particle for the s.c. treatment of patients with AD. In March 2010 a randomized, placebo-controlled, multicenter, Phase II trial began in patients (n = 120) in the US, Canada and Europe with mild AD (Thomson Reuters Pharma, update of March 24, 2014). A phase I/II clinical trial in Denmark, Finland and Sweden (Thomson Reuters Pharma, update of March 24, 2014).

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South Laguna, CA) is a DNA vaccine using the Tri-Grid electroporation technology [614]. Translational studies in macaques were published [615]. Additional papers were disclosed [616–619] (Thomson Reuters Pharma, update of March 3, 2014).

**AFFITOPE AD-0X** (Affiris, Vienna, Austria) is a peptide-based vaccine that targets Aβ and modified Aβ peptides for the potential s.c. treatment of AD (Thomson Reuters Pharma, update of November 25, 2013).

**ALZ-101, ALZ-102, and ALZ-103** (Alzinoiva, a spin-off of MIVAC Development, both Gotteborg, Sweden) are specific oligomer-directed peptide vaccines, which acted as mimetics of natural Aβ42 oligomers (Thomson Reuters Pharma, updates of November 27, 2013, of June 19, 2013 and of June 20, 2013, respectively).

**BS-1 BACE inhibitor mAb vaccine** (NasVax, Ness-Ziona, Israel under license from Ramot at Tel Aviv University) is based on a lead mAb candidate blocking β-site-1, which inhibited the ability of BACE to cleave AβPP (Thomson Reuters Pharma, update of January 22, 2014).

**Lu AF20513** (Lundbeck, Valby, DK in collaboration with Otsuka, Tokyo) is a novel AD epitope vaccine, in which the T-helper (Th) cell epitopes of Aβ42 were replaced by two foreign Th epitopes from tetanus toxoid (TT), P2 and P30, and the immunodominant B-cell epitope of Aβ58-42. Lu AF20513 induced robust non-self T-cell responses and the production of anti-Aβ antibodies that reduced AD-like pathology in the brains of Tg2576 mice without inducing microglial activation [620] (Thomson Reuters Pharma, update of May 15, 2014).

**MER-5101** (Mercia Pharma, New York, NY) is a vaccine comprised of an Aβ peptide conjugate coupled to an immunogenic carrier protein and the company’s Th2-biased adjuvant MAS-1. The vaccine generated a robust anti-Aβ antibody response and attenuated Aβ pathology and cognitive deficits in APP695/PS1ΔE9 transgenic mice [621] (Thomson Reuters Pharma, update of April 29, 2013).

**Polypeptide vaccine** (Zhejiang Xianju Pharmaceutical, Zhejiang, China) is evaluated for the potential prevention and treatment of AD (Thomson Reuters Pharma, update of July 11, 2013).

**Protasome-based vaccine V-2 Intranasal (GSK)** is investigated by for the potential treatment of AD (Thomson Reuters Pharma, update of June 5, 2013).

**RGD-DiFox** [382–401]-KK-Albeta [1–13] (Daiichi Sankyo, Tokyo) is a novel Aβ peptide vaccine, which significantly increased cognitive performance in mice (Thomson Reuters Pharma, update of July 15, 2014).

University of California San Diego scientists are investigating an Aβ anti-idotype vaccine developed using a polypeptide based targeting molecule that shows great selectivity for AD plaques (Thomson Reuters Pharma, update of July 11, 2013).

Excellent papers on Aβ vaccines from universities were presented (in chronological order): 2012: non-human random sequence amyloid oligomer mimic [622], a new gene vaccine encoding ten repeats of Aβ1-40 [623], active DNA Abeta42 vaccination [624], short Aβ immunogens [625], mutated Aβ sensitized dendritic cells [626], preventive immunization [627] 2013: immunotherapeutic efficiency of a tetravalent Aβ1-15 vaccine [628], recombinant DNA vaccine [629], multivalent Aβ3-10 DNA vaccine [630], a peptide prime-DNA boost immunization [631], a new DNA vaccine YM-3711 [632], an effective DNA epitope chimeric vaccine [633], 2014: vaccination, which induced changes in pro-inflammatory cytokine levels and lead to cognitive improvement [634] and recombinant chimeric vaccines [635]. The novel vaccine peptide GV1001 effectively blocked Aβ aggregation and modified 42 oligomers into 3-10 [623], active DNA Abeta42 vaccination [624], short Aβ immunogens [625], mutated Aβ sensitized dendritic cells [626], preventive immunization [627]

Excellent reviews on Aβ vaccines have been provided (in chronological order): 2012: [637], 2013: [638, 639], 2014: [640, 641].

The development of **EB-101** (Atlas Pharmaceuticals, NURN-Biotech, V-950 (Merck; [642, 643]) and vanustide certificar (ACC-001, PF-05236806; Janssen Alzheimer Immunotherapy acquiring Elan’s Alzheimer’s Immunotherapy Program and Pfizer; [642, 644]) was terminated.

**Antibodies against amyloid-β**

Solanezumab (LY-20622430; Lilly) is a mid-domain humanized monoclonal antibody selective for soluble Aβ. Solanezumab failed to meet the cognitive and functional primary endpoints of two Phase III AD trials, but showed a significant reduction in cognitive decline in patients with mild AD [645, 646]. In July 2013 a randomized, double-blind, parallel-group, Phase III trial (Expedition 3) was initiated to compare the effect of solanezumab in slowing the cognitive and functional decline of AD versus placebo in patients with mild AD (expected n = 2100) in the US, Europe, Canada and Australia (Thomson Reuters Pharma, update of May 20, 2014).

The National Institute on Aging (Bethesda, MD) announced funding of a three-year AD prevention trial, which will enroll 1’000 patients of age 70–85 years,
who have evidence of the abnormal Aβ protein building up in the brain detected by PET scans. For a review, see [647].

**Gantenerumab** (R-1450, RG-1450; Roche, Basel in collaboration with its Japanese subsidiary Chugai, Tokyo under license from MorphoSys, Martinsried, Germany) is a human anti-Aβ monoclonal antibody. By January 2011 a Phase II trial in patients with prodrome AD had been initiated. In June 2012 the trial was expanded to a phase II/III trial from 360 to 770 participants in the US, Canada, EU, Mexico and Argentina. A Phase III study in mild AD patients was expected to start in May 2014 (Thomson Reuters Pharma, update of May 27, 2014).

**BAN-2401** (Eisai, Tokyo under license from Bioartic Neuroscience, Stockholm, Sweden) is a humanized version of the mouse monoclonal antibody mAb158 that targets the large soluble amyloid product (LSAP; protofibril Aβ [PFAβ]). Eisai started Phase II trials in December 2012 in the US and in February 2013 in Europe (Thomson Reuters Pharma, update of April 17, 2014).

**Crenezumab** (MABT-5102A; RG-7412; Genentech, South San Francisco, CA, Roche Holding under license from AC Immune, Lausanne, Switzerland) is an anti-Aβ humanized monoclonal antibody as a conformation-specific, passive immunotherapy for the potential i.v or s.c. treatment of AD [648]. A Phase II clinical trial (n = 372) was initiated in April 2011 in the US, Canada and Europe. In December 2013 a Phase II trial began in PSEN1 E280A mutation carriers in Colombia in a preclinical stage of AD. At the Annual Meeting of the Alzheimer’s Association in Copenhagen, July 12–17, 2014 results from a Phase II study in 431 mild to moderate Alzheimer’s disease patients were presented. Mild Alzheimer patients showed 35.4% reduction of cognitive decline and a 19.6% reduction of global functional decline, both statistically significant, after treatment for 18 months, whereas moderate Alzheimer patients did not. This is reminiscent of the results with solanezumab of 2013, where also mild Alzheimer patients only responded to antibody treatment (Thomson Reuters Pharma, update of July 18, 2014).

**GSK-933776A** (GSK) is a monoclonal antibody for the i.v. treatment of AD and age-related macular degeneration. A Phase II age-related macular degeneration trial (n = 162) started in the US in August 2011. Data on the Phase I study were published [649] (Thomson Reuters Pharma, update of April 17, 2014).

The human polyclonal IgG antibody preparation known as Intravenous Immunoglobulin (IVIG) has been under study as a potential treatment for AD since 2002 [650]. The brain bioavailability of human intravenous immunoglobulin and its transport through the murine blood-brain barrier was investigated [651]. Low-dose human IVIG treatment improved synaptic plasticity and cognitive function through C3a-mediated induction of the CREB/CEBP pathway, while the levels of Aβ in the brain were not significantly affected [652]. IVIG treatment protected 3xTg AD mice from memory deficit and Aβ pathology [653]. IVIG treatment exerted antioxidant and neuroprotective effects in preclinical models of AD [910]. The mechanistic effects of IVIG in neuroinflammatory diseases were described [911]. Aβ concentration and structure influenced the transport and immunomodulatory effects of IVIG [654]. Longitudinal effects of IVIG on the AD cerebrospinal fluid proteome were described [655]. IVIG is beneficial in the therapy of AD by inducing efflux of Aβ from the brain through the low-density lipoprotein receptor-related protein-1 (LRP1) in the blood-CSF barrier (BCB) [912].

**Octagam** (Octapharma, Lachen, Switzerland) is a 10% liquid intravenous immunoglobulin launched for the treatment of primary immunodeficiency. The results of the first Phase II study in AD patients was presented in Lancet Neurology [656]. A second Phase II trial was initiated in Germany in January 2013 (Thomson Reuters Pharma, update of July 16, 2014).

**Privigen** (CSL Behring, King of Prussia, PA) is a launched 10% liquid intravenous immunoglobulin stabilized with proline for the treatment of primary immunodeficiency and possibly AD. Intravenous immunoglobulin shifted microglial activation state toward anti-inflammatory activity and reversed Aβ-mediated LTP inhibition (Thomson Reuters Pharma, update of September 19, 2013).

**Ponezumab** (PF-04360365, RN-1219; Pfizer) is a humanized IgG2 monoclonal antibody specific against the C-terminus of Aβ1–40 in preclinical evaluation for the treatment of primary immunodeficiency and possibly AD. Intravenous immunoglobulin shifted microglial activation state toward anti-inflammatory activity and reversed Aβ-mediated LTP inhibition (Thomson Reuters Pharma, update of May 16, 2014).

**Aducanumab** (NI-101, BIIB-037, BART; Biogen Idec, Weston, MA under license from Neuroimmune Therapeutics, Zurich, Switzerland) is a recombinant chimeric human IgG1 mAb targeted against Aβ. A Phase I clinical trial (n = 40) in patients with mild to moderate AD started in the US in July 2011 (Thomson Reuters Pharma, update of June 13, 2014).

**BI-1034020** (Boehringer Ingelheim user license from Ablynx, Gent, Belgium) is a nanobody therapeu-
tic, a naturally-occurring single chain antibody derived from *Camelidae*. Epitope structure and binding affinity of single chain llama anti-Aβ antibodies were studied by proteolytic excision affinity-mass spectrometry [661]. In October 2013 a Phase I single-center, partially randomized, single-blind, placebo-controlled, safety, tolerability, pharmacokinetic and pharmacodynamic study of single ascending doses of i.v. and s.c. nanobody was initiated in healthy volunteers (expected n = 80) in Germany (Thomson Reuters Pharma, update of May 23, 2014).

**LY-M002813** (Eli Lilly, Indianapolis, IN) is an antibody targeted against the N-terminal truncated pyroglutamate-3 isoform of Aβ for the potential s.c. or i.v. treatment of AD. A Phase I clinical trial in patients (expected n = 100) with MCI due to AD or mild to moderate AD was initiated in the US and Japan in May 2013. The antibody cleared Aβ plaques in AD mice without causing microhemorrhage [662] (Thomson Reuters Pharma, update of April 25, 2014).

**MEDI-1814** (AstraZeneca) is a monoclonal antibody for the potential treatment of AD via i.v. or s.c. formulations. In January 2014, a randomized, double-blind, placebo-controlled, parallel-assigned, Phase I trial was planned to be initiated in the US in elderly subjects (expected n = 121) with AD to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple ascending doses (Thomson Reuters Pharma, update of March 7, 2014).

**NEOD-001** (Onclave Therapeutics, Dublin, a wholly owned subsidiary of Prothera, formerly Neotope Biosciences following Prothera’s demerger from Elan) is a therapeutic humanized IgG1 kappa monoclonal antibody against serum amyloid A and AL amyloid, for the potential i.v. treatment of systemic amyloidosis, including AL amyloidosis (light-chain amyloidosis; primary amyloidosis) and AA amyloidosis (secondary amyloidosis) in Phase I clinical trials since April 2013 in the US. In February 2012 the drug was awarded Orphan status by the FDA for AA amyloidosis and AL amyloidosis (Thomson Reuters Pharma, update of May 7, 2014).

There are currently many antibodies for the potential treatment of AD and closely related diseases in preclinical evaluation (in alphabetical order):

**1E8** (CSIRO Preventive Health Flagship, Parkville, AU) is anti-Aβ monoclonal antibody targeting residues 17-22 of Aβ, of which the single chain antibody fragment (scFv) derivative was generated. The soluble 1E8 scFv bound to the central region of Aβ with an affinity of 55 nM and significantly reduced fibril formation of Aβ [663].

**9D5 antibody** (University of Göttingen/MBM ScienceBridge) targets pyro-Glu-Aβ peptide oligomers for the potential diagnosis and treatment of AD (Thomson Reuters Pharma, update of July 8, 2014).

**A-887755** (ABT-736; AbbVie, North Chicago, IL, a spin-out of Abbott Laboratories) is an Aβ, oligomer-selective, mouse monoclonal antibody. The humanized mAb version is ABT-736. Both were generated using a homogenous synthetic Aβ20-42 oligomer peptide (Thomson Reuters Pharma, update of May 14, 2014).

**Aglycosylated ponezumab** (InteliNeurosciences, New York, NY) is a IgG2 monoclonal antibody against Aβ employing its ANTISENILIN technology (Thomson Reuters Pharma, update of February 8, 2013).

**Aglycosylated murine ponezumab** (Pfizer, New York, NY, is a IgG2 monoclonal antibody against Aβ (Thomson Reuters Pharma, update of July 26, 2013).

**Antibody therapeutic program** (Alector, San Francisco, CA in collaboration with Adimab, Lebanon, NH) is developing leads for four major targets for the potential treatment of AD (Thomson Reuters Pharma, update of November 29, 2013).

**Antipyroglutamate-3 amyloid-β mAb** (ProBio-drug, Halle, Sachsen-Anhalt, Germany) is an IgG1 monoclonal antibody for the potential treatment of AD. The mAb significantly reduced total plaque deposition in AβPPsw/PS1dE9 transgenic mice [664]. A 500 mg dose of the antibody resulted in improvement in acquisition learning in the water T-maze test in AβPPsw/PS1dE9 transgenic mice. Note that oligomeric pyroglutamate Aβ is present in microglia and a subfraction of vessels in patients with AD, which has implications for immunotherapy [665] (Thomson Reuters Pharma, update of December 23, 2013).
tau protein is sufficient to initiate the spread of tau protein pathology [706]. Sources of extracellular tau and its signaling were described [707]. The prion-like properties of tau were described [913]. Phosphorylation of tau protein at sites Ser96 and Ser404 is one of the earliest events in AD and Down’s syndrome [709]. Mechanistic studies to elucidate the mechanism of tau aggregation were disclosed [710]. There is a growing consensus that sarkosyl-insoluble tau correlates with the pathological features of tauopathy [711]. Tau oligomers and fibrils induce activation of microglial cells causing neuroinflammation [712]. For the role of tau protein phosphatases, see the review [713]. The β2-adrenergic receptor, protein kinase A and c-jun N-terminal kinase signaling pathways were identified to mediate tau pathology [714]. The functional interrelationships of the glutamate system, Aβ peptides and tau protein were reviewed [715, 716]. It could be shown that mTOR regulates tau phosphorylation and degradation [717]. The synaptic accumulation of hyperphosphorylated tau oligomers is associated with dysfunction of the ubiquitin-proteasome system [718]. An overview on the ubiquitin-proteasome system versus the autophagy-lysosome system in the degradation of tau was published [719]. Intraneuronal tau aggregation precedes diffuse plaque deposition, but Aβ changes occur before increases of tau in cerebrospinal fluid [720]. Therapeutic strategies for tau mediated neurodegeneration were outlined [721]. For a novel trans-synaptic mechanism for tau protein transfer, see [722]. Tau promotes neurodegeneration through global chromatin relaxation [723]. For a comment, see [724]. Tau also has a critical physiological function in long-term depression in the hippocampus [725].

Drugs preventing tau, prion or α-synuclein aggregation

LMT-X (TRX-0237, TauRx Therapeutics, Singapore) is a potential follow-up compound and produg of Renterb (methylthioninium chloride, methylene blue, whose development was terminated in March 2013). In September 2012, a Phase III study for frontotemporal dementia began in 180 subjects for 12 months. In October 2012, two global Phase III studies were initiated for AD. The first study involves 833 patients with mild or moderate AD over 12 months, while the second study includes 500 patients with mild AD over 18 months. The clinical trials will be conducted in parallel and on a global basis including sites in Australia, Belgium, Canada, Finland, Germany, Italy, Russia, Spain,
Netherlands, Singapore, Malaysia, Taiwan, US and UK. For the review on tau-aggregation inhibitor therapy by Wischik et al., see [726] (Thomson Reuters Pharma, update of May 7, 2014). The structure was not communicated.

**ARC-100** (TP-287, NBT-287, abeotaxane; Cortice Biosciences, New York, NY, formerly Archer Biosciences under license from Tapestry Pharmaceuticals, Ankeny, IA, formerly NaPro BioTherapeutics) is a third-generation taxane with an ability to readily cross the blood-brain barrier for the potential i.v. treatment of taxane-resistant and taxane-naive cancers, paediatric brain cancer, AD, PSP, and corticobasal degeneration. The drug is in Phase II clinical trials for melanoma since February 2010, for glioblastoma since April 2010, for breast cancer since August 2011 and in Phase I for AD, neurodegenerative diseases and PSP since January 2013 in the US (Thomson Reuters Pharma, update of May 12, 2014). The complex structure was communicated.

There are many compounds inhibiting tau aggregation in preclinical evaluation (in alphabetical order):

- **Anle-138b** (University of Munich, Fig. 7) strongly inhibited formation of pathological oligomers in vitro and in vivo for both prion protein and α-synuclein [727]. (Thomson Reuters Pharma, update of July 10, 2014).
- **ASO-12** (Washington University, St. Louis, MO and Isis Pharmaceuticals, Carlsbad, CA) is a filamentous bacteriophage targeting from wild-type Aβ and tau aggregates for the potential treatment of AD [728] (Thomson Reuters Pharma, update of July 16, 2014).
- **Diaminohilazoles** (University of California Santa Barbara) modified tau phosphorylation and improved the tauopathy in mouse models [729].
- **Gold complexes** [Au(bpy)Cl2][PF6] (bpy = 2,2’-bipyridine) and [Au(dien)(Cl)2] (dien = diethyltriamine) (Renmin University of China, Beijing) inhibited the aggregation of prion neuropeptides [730].
- **NIPERAMCD-KT87**, a novel bis-imidazopyridine, significantly increased protein phosphatase 2A activity in the brains of AD rats [731].
- **Phtalocyanine tetrasulfonate** interfered with tau filament formation by targeting the protein into soluble oligomers [732].
- **Piperazine derivatives** inhibited PrPSc propagation in vitro. A lead structure increased the incubation time of scrapie infected mice [733].
- **PTI-51-CH3** (Proterotech, Kirkland, WA) targets tau protein for the potential treatment of PSP (Thomson Reuters Pharma, update of May 26, 2014). The structure was not communicated.
- **Synulcere** (PD-82; Proterotech, Kirkland, WA) is an α-synuclein aggregation inhibitor for the potential treatment of PD (Thomson Reuters Pharma, update of January 10, 2014).
- **T-22** (Conmms, Galveston, TX) is a tau oligomer-specific monoclonal antibody (TOMA), for the potential treatment of AD [734] (Thomson Reuters Pharma, update of January 22, 2014).
- **TAR DNA-binding protein-43** (TDP-43) associated NF-kappa B activation (TANA) inhibitors (ImStar Therapeutics, Vancouver, BC) are investigated for the potential treatment of neurodegenerative diseases including ALS, dementia, AD, and other neurodegenerative diseases (Thomson Reuters Pharma, update of April 22, 2014).
- **Tau aggregation inhibitors** (Exebryl-2; ProterTech, Kirkland, WA) are containing polyhydroxylated aromatic rings spaced by a linker region for the potential treatment of AD (Thomson Reuters Pharma, update of May 6, 2014). Structures were not communicated.
- **Tolcapone** and **Entacapone**, both catecho-O-methyltransferase inhibitors, acted as tau-derived hexapeptide (306)VQIVYK(311) aggregation inhibitors [735]. See also Part 2, Chapter 2.15. Drugs interacting with Catechol-O-methyltransferase.
- **Trifluoperazine** rescued human dopaminergic cells from wild-type α-synuclein-induced toxicity [736].
- **NPT-002** (NeuroPhage Pharmaceuticals, Cambridge, MA) is a filamentous bacteriophage targeting Aβ and tau aggregates for the potential treatment of AD (Thomson Reuters Pharma, update of July 15, 2013).
- A lead structure increased the incubation time of scrapie infected mice [733].
- **PTI-51-CH3** (Proterotech, Kirkland, WA) targets tau protein for the potential treatment of PSP (Thomson Reuters Pharma, update of May 26, 2014). The structure was not communicated.
inhibitors (Catholic University of Leuven), tau phosphorylation inhibitors (ProQnase), tidegulsib (Noscira, previously known as Neuropharma) and of TRx-0014 (methylthioninium chloride, methylene blue, Rember; TauRx Therapeutics; Fig. 15; [752–754–765]) were terminated.

Ligands interacting with tau and α-synuclein

A review on tau PET radiotracers was published very recently [766]. \(^{18}\)F-AV-1451 \(^{18}\)F-T807; Avid Radiopharmaceuticals, a subsidiary of Eli Lilly, following an acquisition from Siemens Medical Solution Molecular Imaging, Culver City, CA in April 2013; Fig. 7) is a tau-binding PET tracer for the diagnosis of AD in Phase II clinical trials in patients with AD and MCI in the US since December 2013. Early clinical PET imaging results were obtained with \(^{18}\)F-AV-1451 \(^{18}\)F-T807) [767, 768]. \(^{18}\)F-AV-1451 (1 μM) showed tau blocking and Aβ blocking up to 87 and 5%, respectively. In February 2014 a Phase I study was initiated in patients with tauopathies including AD, PSP, chronic traumatic encephalopathy, and frontotemporal dementia (Thomson Reuters Pharma, update of June 11, 2014). \(^{18}\)F-THK-523 (University of Melbourne) is an \(^{18}\)F-labeled arylquinoline derivative for the potential use in imaging tau deposition in neurofibrillary tangles in AD patients. By September 2012 a Phase I clinical trial was ongoing. In July 2013 clinical data were presented [771–774]. For the structure, see [7] (Thomson Reuters Pharma, update of June 4, 2014).

AC Immune (Lausanne, Switzerland in collaboration with Piramal Imaging, Berlin) is investigating tau-targeted PET imaging agents for the potential diagnosis of AD (Thomson Reuters Pharma, update of July 18, 2014).

Aminothienopyridazines are evaluated as imaging ligands for tau pathology [775]. BF-188 (Tohoku University; Fig. 7) is evaluated for fluorescence multispectral imaging of tau protein fibrils [776].

Roche is investigating probes for imaging neurofibrillary tangles for the potential diagnosis of AD. The 2-styrylindolium based fluorescent probes were inlicensed from the Technische Universität Darmstadt.
Immunization of P301L mutant mice with a twelve amino acid peptide of the human tau sequence (aa 395-406) together with CFA impeded the progression of neurofibrillary histopathology [789]. α-synuclein vaccination prevented the accumulation of PD-like pathologic inclusions in a rat model [790]. The immunogenicity of epitope vaccines targeting different B cell antigenic determinants of human α-synuclein was described [791].

**Antibodies against tau, superoxide dismutase 1, α-synuclein, and ApoE**

PRX-002 (formerly NEOD-002; Prothena, Dublin, Ireland, formerly Neotope Biosciences following Prothena’s demerger from Elan, and Roche) is an α-synuclein-targeted therapeutic monoclonal antibody for the potential i.v. treatment of PD and other synucleinopathies. In March 2014 a Phase I study was initiated in the US (Thomson Reuters Pharma, update of May 7, 2014).

**Anti-oligomeric monoclonal antibodies improved cognitive function by reducing Aβ deposition and tau pathology in 3xTg-AD mice [792].**

**Anti-tau antibodies** (Bristol-Myers Squibb and University of Pennsylvania, Philadelphia, PA) showed a significant improvement in an object recognition test in Tg4510 mice following systemic administration for one month (Thomson Reuters Pharma, update of December 26, 2013).

**ATS** (Washington University School of Medicine, St. Louis, MO) reduced somatodendritic tau load, p-tau immunoreactivity and silver stained positive neurons without affecting Aβ pathology in 3xTg-AD mice [915].

**Iij8.5, Iij9.3, and Iij9.4** (Washington University School of Medicine, St. Louis, MO) are human tau monoclonal antibodies that blocked tau aggregate seeding in vitro, markedly decreased tau pathology and improved cognition in vivo in P301S transgenic mice [793].

**Humanized anti-tau monoclonal antibodies** (AC Immune, Lausanne, Switzerland) had high specific affinity binding to pTau. One antibody was outlicensed to Genentech (Thomson Reuters Pharma, update of July 18, 2014).

**IPN-007** and **IPN-002** (Pierian, South San Francisco, CA, a subsidiary of Bristol-Myers Squibb) are monoclonal antibodies and tau protein modulators for the potential treatment of AD, frontotemporal dementia and PSP (Thomson Reuters Pharma, update of April 30, 2014).
MN-423 (Axon Neurosciences, Vienna, Austria) is a humanized anti-tau monoclonal antibody for the potential treatment of AD and related neurodegenerative tauopathies. By December 1998 the antibody had been discovered. In July 2014 the antibody was humanized (Thomson Reuters Pharma, update of July 23, 2014).

A rabbit monoclonal antibody site-specific for tau O-GlcNAcylated at serine 400 was disclosed by scientists from EMD Serono [794].

SOD1-targeting antibody (PREVENT-ALS; Amorfix Life Sciences, Mississauga, Ontario) is evaluated for the potential treatment of ALS (Thomson Reuters Pharma, update of July 17, 2014).

A tau oligomer-specific antibody was presented by the team of Professor Kayed at the University of Texas Medical branch at Galveston for the potential treatment of neurodegenerative tauopathies including TBI [734, 795] (Thomson Reuters Pharma, update of November 25, 2013).

Tau-targeted antibody therapy (Prothena, formerly Neotope Biosciences, Dublin, Ireland, previously a subsidiary of Elan, South San Francisco, CA) is a monoclonal antibody targeted to tau (Thomson Reuters Pharma, update of June 18, 2013).

Teijin Pharma (Tokyo) is investigating a program of mAbs targeting against phosphorylated tau protein for the potential treatment of AD (Thomson Reuters Pharma, update of March 21, 2014).

TNT-Ah (Panorama Research, Sunnyvale, CA) is a tau N-terminal antibody delivered through AAV-gene therapy for the potential treatment of neurodegenerative diseases (Thomson Reuters Pharma, update of March 15, 2014).

TOC-1 (Intelect Neurosciences, New York under license from Northwestern University, Evanston, IL) is a tau-oligomer-targeting monoclonal antibody [916–918]. It proved to be a valuable tool for assessing disease progression in the tTG4510 mouse model of tauopathy [919] (Thomson Reuters Pharma, update of November 15, 2013).

University of Iowa scientists are investigating phosphorylated tau targeted monoclonal antibodies, the clone 9G3 targeting tyrosine-18 phosphorylated human tau protein for the potential treatment of AD (Thomson Reuters Pharma, update of August 2, 2013).

VHH-TauA2 (Hoffmann-La Roche, Basel, Switzerland) is an anti-tau camel single-domain antibody and tau kinase inhibitor for the diagnosis of AD. VHH-K3VQ is an anti-amyloid-β camel single-domain antibody investigated as a diagnostic agent (Thomson Reuters Pharma, update of July 25, 2014).

Several monoclonal anti-apoE antibodies were elucidated [796], see also [797]. Excellent papers on passive immunization targeting pathological phospho-tau protein were published: 2012: [798], 2013: [799–802], 2014: [803]. Also approaches for the immunotherapy for α-synucleinopathies were discussed [804, 805].

**STEM CELLS**

Substantial progress was achieved in research of stem cells for the potential treatment of AD in 2012: [806–809], 2013: [810–815] and 2014: [816–819].

Medial ganglionic eminence-like cells derived from human embryonic stem cells corrected learning and memory deficits [820]. Embryonic stem cell-based modeling of tau pathology was described [821].

Induced pluripotent stem cells may be useful tools for disease modeling and drug discovery in AD [822] or neurodegenerative diseases [823, 824]. For a 3D AD culture model in induced pluripotent stem cell-derived neurons, see [825].

Placenta-derived mesenchymal stem cells improved memory dysfunction in an Aβ1–42 infused mouse model of AD [826]. Mesenchymal stem cells increased hippocampal neurogenesis [827], enhanced autophagy and increased Aβ clearance in AD disease models [828]. Intracerebral transplantation of adipose-derived mesenchymal stem cells accelerated neuropathological deficits in AD mice [829]. Bone marrow-derived mesenchymal stem cells contributed to the reduction of Aβ deposits [830] and improved memory in rat models of AD [831]. Systemic transplantation of human umbilical cord derived mesenchymal stem cells improved impaired cognition in AβPP/PS1/tau triple transgenic mice [832].

Neural stem cell transplantation improved spatial learning and memory via neuronal regeneration in AβPP/PS1/tau triple transgenic mice [833]. Neural stem cell therapy improved memory in a mouse model of AD [834].

Mesenchymal bone marrow-derived stem cell therapy (Stemedica Cell Technologies, San Diego, CA) is being developed for the intravenous treatment of ischemic stroke in Phase III since February 2011 in the US (n = 35). The study was completed in February 2013. In February 2014, a Phase III trial for the treatment of myocardial infarction was initiated in Kazakhstan (Thomson Reuters Pharma, update of February 24, 2014).
Autologous fat-derived stem cell therapy (RNL-Astromed; K-STEMCELL, previously RNL Bio, Seoul) is evaluated for the treatment of facial hemiatrophy in South Korea in June 2013 (Thomson Reuters Pharma, update of August 20, 2013).

Bone marrow-derived neurotrophic factor-producing mesenchymal stem cells (NurOwn, MSC-NTF; BrainStorm Cell Therapeutics, New York, NY) are adult mesenchymal stem cells secreting neurotrophic factors (GDNF and BDNF) investigated as a potential treatment of PD, sciatica, and MS. A Phase III clinical trial in ALS patients started in June 2011 in Israel. The trial was fast-tracked by the Israeli Ministry of Health to a Phase IIa dose-escalating trial, which was initiated in December 2012 (Thomson Reuters Pharma, update of February 26, 2014).

NGN-9076 (Neural stem cell therapy, NeuroGener-ation, Los Angeles, CA) is in a Phase II clinical trial in the US since May 2007 for the potential treatment of PD (Thomson Reuters Pharma, update of January 13, 2014).

NSI-566RSC (NSI-566, Neuralstem, Rockville, MD) are human neural stem cells (hNSCs) including spinal cord stem cells for the potential injectable treatment of ALS, stroke, HD, and AD. NSI-566 entered a Phase II ALS trial in September 2013 in the US. In recent papers, it was demonstrated that transplantation of fetal-derived human neural stem cells improved cognitive deficits in rats as was assessed by two separate cognitive tasks [835–837] (Thomson Reuters Pharma, update of May 29, 2014).

Purified human neural stem cell therapy (HuCNS-SC; StemCells, Palo Alto, CA, formerly CytoTherapeutics under license from NeuroSperes, Calgary, Alberta) is a proprietary transplantable human neural stem cell therapy for the potential treatment of spinal cord injury, age-related macular degeneration and AD. Human neural stem cells induced functional myelination in mice [838] and in the human brain [839]. Phase II clinical trials for spinal cord injury were initiated in the US and Canada in December 2011 and in Europe in May 2012. StemCells announced in September 2013 dosing of the first high-dose patient in a Phase II clinical trial in dry age-related macular degeneration in the US (Thomson Reuters Pharma, update of May 30, 2014).

Sargramostim (Immunex, Seattle, WA, now Amgen, Thousand Oaks, CA) launched in 1991 and now marketed by Genzyme (Cambridge, MA) is a yeast-derived recombinant granulocyte-macrophage colony-stimulation factor, which stimulates proliferation and differentiation of hematopoietic progenitor cells. In March 2011, a randomized, double-blind, parallel-assigned, pilot, safety/efficacy Phase II trial was initiated in patients (expected n = 40) with AD in the US (Thomson Reuters Pharma, update of June 13, 2014).

ASTOPC-1 (GRNOPC-1; Asterias Biotherapeutics, Menlo Park, CA, a subsidiary of BioTime, Alameda, CA, from an asset acquisition from Geron, Menlo Park, CA) is a preparation of oligodendrocyte precursor cells differentiated from a human embryonic stem cell line that produce neurotrophic factors and remyelinate axons for the potential injectable treatment of spinal cord injury in Phase I clinical trials since January 2013 in the US (Thomson Reuters Pharma, update of June 13, 2014).

Choroid plexus cell therapy (NeuropinCell, NiCell; Living Cell Technologies, Sydney, and Osaka Pharmaceuticals, Tokyo) is an alginate-microencapsulated porcine choroid plexus cell product for the potential treatment of neurodegenerative diseases including HD and PD and dementia. Choroid plexus implants rescued AD-like pathologies by modulating Aβ degradation [840]. The preparation is in Phase I clinical trials for the treatment of PD in New Zealand since June 2013 (Thomson Reuters Pharma, update of April 1, 2014).

Neurostem-AD (Medipost, Seoul) is an umbilical cord blood-derived mesenchymal stem cell therapy, which regenerates nerve cells. A Phase I trial has been initiated in February 2011 in patients (expected n = 9) with dementia of Alzheimer-type in South Korea. Multiple low-dose infusions (or intravenous administration) of human umbilical cord blood cells improved cognitive impairments and reduced Aβ-associated neuropathology in AD mice [841, 842] (Thomson Reuters Pharma, update of May 6, 2014).

NGN-9077 (Neural stem cell therapy; NeuroGener-ation, Los Angeles, CA) is in Phase I clinical trials in the US since May 2007 for the potential treatment of multiple system atrophy and Shy Drager syndrome (Thomson Reuters Pharma, update of January 15, 2014).

There are several stem cell preparations in preclinical evaluation (in alphabetical order):

Allopregnanolone (University of Southern California, Los Angeles, CA) is a potent and highly efficacious proliferative agent in vitro and in vivo of both rodent and human neural stem cells [843–846]. For recent reviews on allopregnanolone, see [847–849] (Thomson Reuters Pharma, update of December 4, 2013).
Induced multipotent neural stem cell therapy (University of South Australia, Adelaide) are developed by reprogramming mammalian fibroblasts using undisclosed small molecules for the potential treatment of neurodegenerative diseases (Thomson Reuters Pharma, update of January 7, 2014).

Marrow-derived multipotent adult progenitor cell therapy (McLean Hospital, Belmont, MA) are engineered to express α-secretase cleaved AβPP fragment (sAβPPs) for the potential i.v. treatment of neurodegenerative diseases (Thomson Reuters Pharma, update of January 10, 2014).

Neural stem cells (University College of London) can differentiate into retinal neurons to aid in the integration of cells into retina for the potential treatment of eye diseases including glaucoma (Thomson Reuters Pharma, update of November 29, 2012).

NGN-9078 (Neural stem cell therapy; NeuroGenesis, Los Angeles, CA) is in preclinical evaluation for the potential treatment of AD. Transplantation of neuronal cells into the brain was shown to improve and delay the symptoms of AD in animal models (Thomson Reuters Pharma, update of January 15, 2014).

NGN-9079 (Neural stem cell therapy; NeuroGenesis, Los Angeles, CA) is in preclinical evaluation for the potential treatment of AD. Transplantation of neuronal cells into the brain was shown to improve and delay the symptoms of AD in animal models (Thomson Reuters Pharma, update of January 15, 2014).

NWL-NSC (neural stem-like cells; New World Laboratories, Laval, Québec) are autologous stem cells derived from somatic cells using a way of “reprogramming” without any genetic engineering for the potential treatment of neurological diseases including spinal cord injury, TBI, PD, MS, AD, stroke, ischemia, and injury (Thomson Reuters Pharma, update of January 28, 2013).

Valproic acid can induce neurogenesis of neural progenitor/stem cells both in vitro and in vivo via multiple signaling pathways [850]. It reduced neuritic plaque formation in AβPPsw/PSEN2/PS1A246E transgenic mice [851]. It attenuated neuronal loss in the brain of AβPP/PS1 double transgenic AD mice model [852] and alleviated memory deficits in a transgenic mouse model of AD [853]. It is a useful mood stabilizer in AD patients.

Xcel-hNu-001 (San Diego Regenerative Medicine Institute) constitutes human pluripotent embryonic stem cell derived neuronal progenitors and neurons for the potential treatment of neurological diseases including motor neuron disease, spinal cord injury, AD, PD, and ALS (Thomson Reuters Pharma, update of July 21, 2014).

ZY-1 (Shanghai Jiao Tong University, Fig. 8) is an α4β2 nicotinic acetylcholine receptor agonist, which promoted proliferation and migration of adult hippocampal neural stem/progenitor cells [854, 855].

The development of the brain-derived stem cell therapy (Celprogen in collaboration with the Indiana University School of Medicine) and stem cell differentiation inducers (Samaritan) was terminated.

MISCELLANEOUS

Aβ fibrinogen interaction inhibitor RU-505 (The Rockefeller University, New York, NY; Fig. 8) restored the Aβ-induced altered fibrin clot formation and improved cognitive impairment in mouse models of AD [856].
ATF4 (Activating transcription factor 4) inhibitors (Columbia University, New York, NY) are evaluated for the potential treatment of AD (Thomson Reuters Pharma, update of November 26, 2013). Structures were not communicated.

Carbamazepine, an autophagy enhancer, alleviated memory deficits and cerebral Aβ pathology in a mouse model of AD [857].

Complement factor inhibitors (Annexon, Palo Alto, CA) are investigated for the potential treatment AD (Thomson Reuters Pharma, update of March 8, 2013). Structures were not communicated. Annexon also evaluates fully humanized antibodies against specific components of the complement system for the potential treatment of neurodegenerative diseases (Thomson Reuters Pharma, update of July 24, 2014).

Heat Shock Factor 1 activators (Duke University, Durham, NC; one example in Fig. 8) are investigated for the potential treatment of neurodegenerative disorders such as AD, PD, and HD [858, 859].

JRP-900 (an autophagy inducer, Prous Institute for Biomedical Research, Barcelona) is investigated for the potential treatment of neurodegenerative disease including AD, ALS, HD, and PD (Thomson Reuters Pharma, update of January 22, 2014). The structure was not communicated. For reviews on autophagy in AD and tauopathies, see [719, 860–863], in neurodegenerative disorders, see [864].

Klotho modulators (Boston University) are compounds, which upregulate the expression of the anti-aging protein Klotho for the potential treatment of MS, AD, and symptoms of aging including cognitive decline [865] (Thomson Reuters Pharma, update of January 31, 2013). Structures were not communicated. Cerebrospinal fluid Klotho concentrations are lower in AD patients [866]. The neuroprotective effect of Klotho is mediated via regulation of members of the redox system [920].

Low-dose therapy Levetiracetam (AgeneBio, Carmel, IN under license from John Hopkins University, Baltimore, MD) is investigated for the potential treatment of aMCI in Phase II clinical trials since December 2009 in 144 aMCI patients in the US (for the structure, see [7]). By November 2013, positive Phase IIa results were reported. At that time the FDA granted a pre-IND meeting in the first quarter of 2014 for a phase II/III trial. Reduction of hippocampal hyperactivity in aMCI patients by using a low dose of levetiracetam improved cognition [867] (Thomson Reuters Pharma, update of June 4, 2014).

miRNA mimetics (University of Gottingen and MBM ScienceBridge GmbH) are investigated for the potential diagnosis and treatment of memory impairment. For a review of the research status of the regulation of miRNA on BACE-1 see [921] (Thomson Reuters Pharma, update of July 8, 2014).

MT-007 (Socratech, Rochester, NY) is a low-density lipoprotein receptor related protein cluster IV mutant (LRFIV) with glycine replacing aspartic acid residue 3674. In C57BC/6 mice LRFIVD3674G (20 mg/kg i.v. for 5 days) reduced Aβ1-42 in brain to significantly lower levels compared with wild-type LRFIV (Thomson Reuters Pharma, update of November 26, 2013).

MTD-TFAM (Gencia, Charlottesville, VI) is a recombinant human mitochondrial transcription factor A modified with a mitochondrial transduction domain that transports the product across membranes into mitochondria for the potential treatment of mitochondrial diseases, including inherited mitochondrial respiratory chain disease and neurodegenerative diseases such as PD, AD, and ALS (Thomson Reuters Pharma, update of March 24, 2014).

Proteostasis modulators (AlzProtect (Loos, Nord-Pas-de-Calais, France) are investigated for the potential treatment of neurological diseases, including HD, PD, ALS, frontotemporal lobar dementia, and AD (Thomson Reuters Pharma, update of November 6, 2013).

Recombinant TGF-β agonists (Palo Alto Institute for Research and Education, CA) are investigated for the potential treatment of AD (Thomson Reuters Pharma, update of April 7, 2014). Structures were not communicated.

XN-001 (an enhancer of the function of the dihydropyrimidinase-related protein 2, Xonovo, Wilmington, DE in collaboration with the Oklahoma Medical Research Foundation, Oklahoma City, OK) is the lead from a program of small molecule synthetic derivatives of lanthionine ketimine for the potential oral treatment of neurodegenerative diseases including AD. XN-001 decreased microglial inflammatory cytokines and treated all three hallmarks of AD in experimental triple transgenic mice by reducing Aβ peptide burden, reducing phospho-tau, and relieving cognitive decline (Thomson Reuters Pharma, update of December 26, 2013).

CONCLUSION

No AD medication or cognitive enhancer was launched in 2013. FDA approved the Aβ imaging agent 18F-flutemetamol (18F-Vizamyl, GE Healthcare) in October 2013. EMA and FDA approved the Aβ imag-
ing agent 18F-florbetaben (Neuraceq, Piramal) in February and March 2014, respectively.

Currently there are three Phase III AD trials of disease modifying drugs underway, of the monoclonal antibodies against Aβ solanezumab (Lilly) and gantenerumab (Roche) and of LMTX-TRX-0237, TauRx Therapeutics), a tau aggregation inhibitor. There are two Phase III clinical trials of an Aβ PET imaging agent 18F-NAV4094 (Naveidea) and of the vesicular monoamine transporter type 2 (VMAT2) PET ligand 18F-florobenzine (Avid Radiopharmaceuticals, Lilly) ongoing.

Seven Phase II clinical trials of disease modifying drugs, of monoclonal antibodies against Aβ BAN-2401, crenezumab, GS-93777A, lv, octagam, ponezumab, and of vaccines against Aβ AFFITOPE-AD-02 and CAD-106 are underway. This applies also for the three Phase II clinical trials of small molecules preventing Aβ aggregation or inhibiting formation of transhyretin amyloid fibrils, as doxycycline hyclate (see [7]), ELND-005 (see [7]), or preventing tau aggregation as PBT-2 (see [7]).

Concerning drugs for the palliative treatment of AD four Phase III compounds are currently frontrunners, ARC-029 (voltage-gated channel blocker), DP-b99 (a calcium and zinc chelator), SK-PC-B70M (a natural product, see [7]) and TRI-102-ADD-001 (a nootropic) followed by 28 Phase II compounds (excluding stem cell preparations), apanatelone (a gene expression stimulator), BN-82541, Min01 (see [7]), MTP-131 (see [7]), and VP-20629 (antioxidants), circadin (see [7]), (+)-clausenamide, KD-501 (see [7]), PPL (see [7]), resveratrol (see [7]), RPh-b201 (see [7]), sodium oligomannuramate, STA-1 and VR-040 (see [7], natural products), LND-101001, N-251a (see [7]), PXT-964, TPM-189 (see [7]), VI-1121 (see [7], nortriptics), AM-111 (see [7]), davucetide, NK-001 (see [7]), and NNZ-2566 (peptides).

DISCLOSURE STATEMENT


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