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

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Abstract. Cognitive enhancers (nootropics) are drugs to treat cognition deficits in patients suffering from Alzheimer’s disease, schizophrenia, stroke, attention deficit hyperactivity disorder, or aging. Cognition refers to a capacity for information processing, applying knowledge, and changing preferences. It involves memory, attention, executive functions, perception, language, and psychomotor functions. The term nootropics was coined in 1972 when memory enhancing properties of piracetam were observed in clinical trials. In the meantime, hundreds of drugs have been evaluated in clinical trials or in preclinical experiments. To classify the compounds, a concept is proposed assigning drugs to 19 categories according to their mechanism(s) of action, in particular drugs interacting with receptors, enzymes, ion channels, nerve growth factors, re-uptake transporters, antioxidants, metal chelators, and disease modifying drugs, meaning small molecules, vaccines, and monoclonal antibodies interacting with amyloid-β and tau. For drugs, whose mechanism of action is not known, they are either classified according to structure, e.g., peptides, or their origin, e.g., natural products. The review covers the evolution of research in this field over the last 25 years.

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

INTRODUCTION

As of September 30, 2012, there are 26,788 entries in PubMed under the term cognitive enhancers, 26,781 entries under the term nootropic, and 245 entries under the term cognition enhancers. Scifinder lists 5,133 references under the research topic nootropic, 541 references under the term cognitive enhancer, and 9,853 references for cognition enhancers. The Thomson Reuters Pharma database lists 1,111 drugs as nootropic agents or cognition enhancers and gives zero results under the term cognitive enhancer. 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 Maître [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 interacting with Transcription Factors (Part 3)
11. Antioxidants (Part 3)
12. Metal Chelators (Part 3)
13. Natural Products (Part 3)
14. Nootropics (“Drugs without mechanism”) (Part 3)
15. Peptides (Part 3)
16. Drugs preventing amyloid-β aggregation (Part 3)
16.1. Ligands interacting with amyloid-β (Part 3)
16.2. Inhibitors of serum amyloid P component binding (Part 3)
16.3. Vaccines against amyloid-β (Part 3)
16.4. Antibodies against amyloid-β (Part 3)
17. Drugs interacting with tau (Part 3)
17.1. Small molecules preventing tau aggregation (Part 3)
17.2. Ligands interacting with tau (Part 3)
17.3. Vaccines against tau (Part 3)
17.4. Antibodies against tau (Part 3)
18. Stem Cells (Part 3)
19. Miscellaneous (Part 3)

In Part 1, drugs interacting with receptors were described [5]. In Part 2, drugs interacting with enzymes were described [1696]. Here, in Part 3, we give an overview on drugs interacting with targets 3 to 10 and compounds and preparations of categories 11 to 19.

Disease modifying drugs are aimed to counteract the progression of a disease. In particular for AD, many excellent reviews discuss this subject (in chronological order) [6–27].

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. A current hypothesis is that an extracellular insult to neurons could trigger the production of inflammatory cytokines by astrocytes and microglia [28]. Conversely, Aβ has been shown to induce the expression of interleukin (IL)-1β, tumor necrosis factor-α (TNF-α) and IL-6 in astrocytes and microglia in culture [29]. One genome-wide analysis in 691 subjects of mean age of 72.6 years showed that raised chemokine (C-C motif) receptor 2 (CCR2) expression was the most strongly associated transcript with lower Mini-Mental Status Exam scores and accelerated decline in score over a period of 9 years [30]. Decline in score over a period of 9 years [30]. The expression profiles of cytokines in the brains of Alzheimer’s disease patients were compared to the brains of non-demented patients [1697]. Also see 11. Antioxidants, because inflammation is tightly connected with the oxidative cascade.

TT-301 (MW01-6-189WH; MW-189; Transition Therapeutics, Toronto following its acquisition of neuroMedix under license from Northwestern University) is an inhibitor of macroglial cell activation and pro-inflammatory cytokine production for the potential i.v. treatment of CNS diseases including AD. Preclinical characterization of the suppression of brain proinflammatory cytokine upregulation was carried out [31]. A double-blind, randomized, placebo-controlled Phase I clinical trial in healthy male subjects (n = 16) started in the US in May 2011 (Thomson Reuters Pharma, update of September 14, 2012). The structure was not communicated.
**TT-302** (MW01-7-084WH, MW-084; Transition Therapeutics, Toronto; Fig. 1) is an inhibitor of pro-inflammatory cytokine production by activated glia for the potential oral treatment of CNS disorders including AD, traumatic brain injury and inflammatory diseases such as arthritis [32]. Phase I clinical trials are expected for 2012 (Thomson Reuters Pharma, update of September 29, 2012).

**Minozac** (MW01-2-151SRM, MW-151, Transition Therapeutics, Toronto following its acquisition of NeuroMedix, under license from Northwestern University) (Fig. 1) is an inhibitor of pro-inflammatory cytokine production by activated glia for the potential treatment of CNS diseases including AD, Parkinson’s disease (PD), multiple sclerosis, and traumatic brain injury [33–36] (Thomson Reuters Pharma, update of August 13, 2012).

**AD-16** (Guangzhou Institutes of Biomedicine and Health) is the thiophene analogue of Minozac. It reduced amyloid-β-induced spatial learning and memory impairment as potently as donepezil in an Alzheimer’s mouse model [1698]. (Thomson Reuters Pharma, update of October 19, 2012).

**SEN-1176** (Senexis, Cambridge, UK) (Fig. 1) is a pyrrole[3,2-c] [1,2,4]triazolo[1,5-a]pyrimidine, which suppresses Aβ42-induced macrophage production of nitric oxide, TNF-α, IL-1β, and IL-6 in a dose-dependent fashion, an activity profile consistent with a neuroinflammation inhibitor [1711] (Thomson Reuters Pharma, update of June 24, 2011).

**Infliximab** (Janssen Biotech, Horsham, PA), a launched monoclonal antibody against TNF-α, improved cognition after intrathecal administration in a woman with AD [38].

The University of Zurich is investigating an antibody against the interleukin-12 subunit p40 for the potential treatment of Alzheimer’s disease [1699] (Thomson Reuters Pharma, update of November 26, 2012).

The development of **REN-1189** (formerly CPI-1189; Centaur Pharmaceuticals), a TNF-α release inhibitor, was terminated. Also the development of **Semapimod** (CNI-1493; Cytokine PharmaSciences, CPSI, formerly Cytokine Networks), a cytokine inhibitor, which inhibited Aβ production, plaque formation, and cognitive deterioration in an animal model of AD was suspended [39, 40].
Gene therapy in AD, a potential for disease modification, was discussed [1715]. An interesting review on genes and the parsing of cognitive processes was communicated [42]. Bi-phasic change in brain-derived neurotrophic factor (BDNF) gene expression following antidepressant drug treatment was described [43, 44]. The modulation of Nur77 and Nor-1 expression by dopaminergic drugs was elucidated [45]. The regulation of GABA<sub>A</sub> receptor subunit expression by pharmacological agents was investigated [46]. Gene therapy in mouse models of Huntington’s disease (HD) was reviewed [47].

**Reperminogene perplasmid** (AMG-0001; DS-992; Collategene; AnGes MG, formerly MedGene Bioscience, Osaka, in collaboration with Daiichi Sankyo) is a hepatocyte growth factor (HGF) plasmid-based gene therapy for i.m. injection. It showed nootropic properties with a potential for the treatment of PD. In November 2011, a Phase III trial for peripheral arterial disease was expected to be initiated in 2012. In April 2012, the Phase III studies were still in preparation [48]. A long-term follow-up evaluation of results from the clinical trial TREAT-HGF was reported [49] (Thomson Reuters Pharma, update of September 19, 2012).

**RVX-208** (Rev解决ropix, 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 259 patients showed that after 12 weeks of treatment with 150mg/day, a positive effect on Aβ<sub>42</sub> was seen. A compilation of data on RVX-208 was published in *Drugs in R & D* [50]. The rationale for the SUSTAIN study (172 patients) and the ASSURE study (330 patients) was presented [51]. Preclinical evaluations were reported [52, 53] and clinical data were provided [54–56]. RVX-208 significantly increased high-density lipoprotein (HDL)-C (p = 0.001), the primary endpoint of the SUSTAIN trial, a Phase 2b clinical study. SUSTAIN also successfully met secondary endpoints, showed increases in levels of Apo-A1 (p = 0.002) and large HDL particles (p = 0.02), both believed to be important factors in enhancing reverse cholesterol transport activity. In July 2012, the company was planning to initiate a Phase II trial of RVX-208 in patients with mild cognitive impairment (MCI) in the second half of 2013 (Thomson Reuters Pharma, update of September 27, 2012).

There are several drugs interacting with gene expression in preclinical evaluation (in alphabetical order): AAV-CYP46A1 (INSERM in collaboration with sanofi) is an adenovirus-associated virus (AAV) gene therapy encoding cholesterol 24-hydroxylase (CYP46A1 gene) for the potential injectable treatment of AD. Reduced Aβ peptides, amyloid deposits, and trimeric oligomers were observed in APP23 mice. Significant improvements in cognitive function assessed by the Morris water maze were seen in Tau22 mice [57] (Thomson Reuters Pharma, update of June 6, 2012). See also Part 2, Chapter 2.12. Drugs interacting with cholesterol 24-hydroxylase (CYP46A1).

**AZ-AAV9** (RegenX Biosciences, Washington DC) is an AAV vector-9 that carries neuroprotective genes for the potential injectable treatment of AD (Thomson Reuters Pharma, update of July 27, 2012).

**HSD17B10** is a gene, which encodes HSD10, a mitochondrial multifunctional enzyme that plays a significant part in the metabolism of neuroactive steroids and the degradation of isoleucine. Elevated levels of HSD10 were observed in the hippocampi of AD patients [58].

**PRO-289** (Prosensa Therapeutics, Leiden, the Netherlands) is the lead from a series of single-stranded RNA-based antisense oligonucleotide-based therapeutics to inhibit the CTG trinucleotide repeat expansion of the huntingtin gene (HTT) by preventing the cellular production of aberrantly expanded HTT mRNA and mutant huntingtin protein (Thomson Reuters Pharma, update of February 10, 2012).

**SynCav** (Rafi Therapeutics, San Diego CA) is a gene therapy that upregulates synaptic driver Caveolin-1 to promote regeneration of neurons for the potential treatment of neurodegenerative diseases such as AD, PD, HD, and amyotrophic lateral sclerosis (ALS) (Thomson Reuters Pharma, update of August 10, 2012).

Intrahippocampal gene transfer of F-spondin, an activator of the reelin pathway, improved spatial learning/memory in the Morris water maze and increased the exploration of the novel object in the Novel Object Recognition test in wild-type mice [59].

**Inventiva** (Daix, Bourgogne, France) is investigating compounds that increase expression of a target gene under epigenetic control resulting in increased levels of a secreted neuronal protein for the potential treatment of Alzheimer’s disease. (Thomson Reuters Pharma, update of November 23, 2012). Structures were not communicated.

Neurologix under license from Keio University was investigating colivelin, a hybrid peptide composed of
activity-dependent neurotrophic factor [60–64] and a humanin derivative for the potential gene therapy of AD [65, 66]. The program was terminated. The development of LX-6171 (Lexicon Pharmaceuticals, formerly Lexicon Genetics), a small molecule inhibitor of the SLC6A gene and the LG617 receptor, was discontinued as well.

**DRUGS INTERACTING WITH HEAT SHOCK PROTEINS**

Binding of heat shock protein 90 (HsP90) to tau facilitates a conformational change that results in its phosphorylation by glycogen synthase kinase 3β (GSK-3β) and its aggregation into filamentous structures [67]. HsP90 regulates tau pathology through co-chaperone complexes [68].

HsP90 inhibitors, such as PU-H71, PU-3, PU24FCI (Fig. 2) and PU-DZ8 of the purine class of HsP90 inhibitors from the Memorial Sloan-Kettering Institute of Cancer Research, New York caused an elimination of aggregated tau [69–75].

**PU-H71** is in Phase I clinical trials since July 2011 (n = 40) in the US. The study was expected to be complete by July 2013 (Thomson Reuters Pharma, update of April 24, 2012).

ALS Biopharma (Doylestown, PA) is investigating small-molecule brain-penetrant modulators of Hsp70 for the potential treatment of neurological disorders including AD (Thomson Reuters Pharma update of January 17, 2012).

Conforma Therapeutics (San Diego, CA) presented a new class of Hsp90 inhibitors [76–78] and showed that E102 (structure not disclosed) promoted selective decrease of the P-tau species in a mouse model of tauopathy.

**KU-32** (University of Kansas, Fig. 2) is a novel-biocin derivative acting as an inhibitor of Hsp90 and an inducer of Hsp70 for the potential treatment of neurological diseases. In transgenic mice expressing human P301L-mutant tau KU-32 (10 mg/kg for 15 weeks) reduced cortical levels of CP13-labeled tau [1700]. (Thomson Reuters Pharma, update of May 31, 2012).

Lundbeck follows up another series of Hsp90 inhibitors (Thomson Reuters Pharma update of March 31, 2011). The structures were not disclosed.

![Fig. 2. Heat shock protein 90 inhibitors and a thyrotropin-releasing hormone analogue.](image-url)
Aβ accumulation decreased expression of the heat shock protein 70-interactive protein (CHIP), which functions as a tau ubiquitin ligase [79]. CHIP is a key molecular link between Aβ and tau pathologies. Increasing CHIP levels may have beneficial effects to decrease tau pathology, because CHIP can polyubiquitinate tau and may play a crucial role in preventing accumulation of phospho-tau and neurotubillary tangles. Heat shock protein 70 prevented both tau aggregation and the inhibitory effect of preexisting tau aggregates on fast axonal transport [80]. An exchange of Hsp70 for Hsp90 is involved in tau degradation [1701].

Excellent reviews on heat shock proteins were previously published [81, 82].

The development of AEG-33773 (Aegera Therapeutics), an allosteric modulator of Hsp90 leading to Hsp70 upregulation, was terminated.

### DRUGS INTERACTING WITH HORMONES

Sustained efforts went into the exploration of the cognition enhancing effects of thyrotropin-releasing hormone and its analogues since it had been recognized as an activator of brain cholinergic systems [83]. Pilot studies of intravenous thyrotropin-releasing hormone in AD were undertaken [84, 85]. Improvement of cognitive deficits in depressed patients were reported [86].

**Taltirelin** (Ceredist, TA-0910; Mitsubishi Tanabe Pharma) (Fig. 2), an orally active synthetic thyrotropin-releasing hormone analogue, was launched in Japan in 2000 for the treatment of neurodegenerative disease, in particular spinocerebellar degeneration [87–89]. The sales in 2011 were USD 226.8 million (Thomson Reuters Pharma, update of August 30, 2012).

KPS-0373 (Kissei under license from Shionogi) is a thyrotropin-releasing hormone derivative for the potential oral treatment of spinocerebellar ataxia in Phase II clinical trials in Japan (Thomson Reuters Pharma, update of July 31, 2012). The structure was not communicated.

**Leuprolide acetate implant** (VP-4896, Memryte; Curaxis Pharmaceuticals, Raleigh NC, formerly Voyager Pharmaceutical and DURECT) is a biodegradable implant formulation of the gonadotropin-releasing hormone agonist 1-9-leutinizing hormone-releasing factor-6D-leucine-9-(N-ethyl-L-prolinamide), a nonapeptide, for the treatment of AD in women. A Phase Ib clinical study plan is currently evaluated. The effects of treatment with leuprolide acetate depot on working memory in women were described [90]. Luteinizing hormone modulated the processing of amyloid-β protein precursor (AβPP) and Aβ deposition [91] and of cognition in transgenic mice [92]. Several reviews were published [93–96] (Thomson Reuters Pharma, update of August 24, 2012).

**Tesamorelin** (Egrifta; TH-9507; Theratechnologies, Quebec and US commercialization partner EMD Serono and licensee Sanofi) is a stabilized, truncated growth hormone releasing factor (GRF1-44; ThGRF1-44). In a controlled study of 152 adults (66 with MCI) participants self-administered daily subcutaneous injections of tesamorelin or placebo for 20 weeks, which had favorable effects on cognition in both adults with MCI and healthy older adults [97] (Thomson Reuters Pharma, update of August 15, 2012).

The development of azetirelin (YM-14673; Yamanouchi, now Astellas [98, 99]), of calcitriol (Neurocalc; Apollo Biopharmaceuticals, now MitoKor), of JTP-2942 (Japan Tobacco [100–102]), of montirelin (CG-3703; CNK-602A; NS-3; Grünenthal [103]), of protirelin (CG-3569; Grünenthal [104–106]), of posatirelin (RGH-2202; Gedeon Richter [107–109]), of protirelin (DN-1417; Takeda [110]), of thyrotropin-releasing hormone analogs (Roche), and of thyroliberin (RX-77368, Reckitt & Colman [111]) was terminated.

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

Dysregulation of Ca^{2+} homeostasis plays a crucial role in the pathogenesis of AD. In the pathogenesis of AD [1702]. Oligomeric Aβ proteins directly incorporated into neuronal membranes, formed cation-sensitive ion channels (“amyloid channels”) and caused disruption of calcium homeostasis [112, 113]. Aβ oligomers directly and dose-dependently modulated PQ-type calcium channels [114]. In triple transgenic AD mice, upregulated ryanodine receptor activity led to a reduction of long-term potentiation [115]. Mutations of presenilin can affect the intracellular calcium levels via the endoplasmic reticulum calcium stores [116]. The levels of the calcium-sensing enzyme hippocalcin were elevated in AD brains [117].

Interesting reviews were published [118–121].

Drug repositioning for the treatment of Alzheimer’s disease was described recently [1703].

**ARC-029** (Archer Pharmaceuticals, Roskamp Institute, Sarasota FL) is a blood-brain barrier crossing...
formulation of nilvadipine (Fig. 3), a blocker of L-type voltage-gated calcium channels. The drug has been approved for a multisite Phase III clinical trial enrolling more than 500 AD patients in Europe. In February 2012, the study was expected to begin in the second half of 2012 (Thomson Reuters Pharma, update of April 16, 2012).

Nilvadipine (FR-34235; Fujisawa; launched in Japan in 1989) was extensively characterized in vitro and in vivo for the potential treatment of AD. It facilitated the clearance of Aβ across the blood-brain barrier [122, 123]. It prevented the impairment of spatial memory induced by cerebral ischemia combined with Aβ in rats [124, 125]. It also antagonized Aβ vasoreactivity [126]. First positive clinical results on nilvadipine in AD patients were communicated. It was safe and provided short-term cognitive benefits in AD patients [127–131].

ARC-031 and ARC-031-SR (Archer Pharmaceuticals; sustained release formulation) is a non-calcium channel blocking and soluble Aβ reducing nilvadipine derivative in Phase I clinical trials (Thomson Reuters Pharma, update of January 3, 2012). The structure was not communicated.

RNS-60 (Revaliesio Corporation, Tacoma WA) acts on voltage-gated ion channels. It is formulated as an inhalant anti-inflammatory charge-stabilized nanosstructure. The company investigates also the potential treatment in AD and PD. A Phase I/IIa asthma trial began in May 2010. In October 2011, data from the multi-dose stage of the Phase I study were reported. RNS-60 showed a therapeutic benefit and was safe at all doses (Thomson Reuters Pharma, update of April 27, 2012). The structure was not communicated.

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ZSET-1446 (ST-101, Sonexa Therapeutics, San Diego CA under license from Zenyaku Kogyo) (Fig. 3) is in Phase II clinical trials for AD since February 2009. A second Phase II clinical trial for the treatment of essential tremor was initiated in the US in May 2011. It was recognized that ZSET-1446 (ST-101) targeted T-type voltage-gated calcium channels in mediating improved cognition in the CNS [132]. In vivo data were published previously [133, 134] (Thomson Reuters Pharma, update of July 17, 2012).

AD-N02 (Adamed, Mazowieckie, Poland) is a sodium channel blocker and dopamine/5-HT stabilizer for the potential treatment of schizophrenia and bipolar disorder (Thomson Reuters Pharma, update of August 22, 2012). The structure was not communicated.

Isradipine (Novartis, launched in 1997) is a L-type voltage-gated calcium channel blocker protecting MC65 neuroblastoma cells from AβPP
C-terminal fragment (AβPP-CTF)-induced neurotoxicity [135–137, 1704].

The development of many drugs interacting with ion channels was terminated (in alphabetical order); DMP-543 (Bristol-Myers Squibb; an inhibitor of M-type K+ channels), enecadin (PAION under license from Nippon Shinyaku; a sodium and calcium channel blocker), LB-101, LB-102, LB-217, LB-218, LB-253, LB-269, LB-301, and LB-302 (Life-like Biometric; modulators of two ionic channels, i.e., ionokines), linopirdine (DuP 996, Du Pont Merck, Bristol-Myers Squibb; an inhibitor of M-type K+ channels; despite promising EEG brain mapping data [138] and an increase of parietal regional cerebral blood flow in AD patients [139], the clinical results were disappointing [140], MEM-1003 (BAY-Z-4406, Memory Pharmaceuticals under license from Bayer; a L-type voltage-gated calcium channel [141]), nerispiridine (HP-184, Hoechst, now santen; an inhibitor of M-type K+ channel); nicardipine (YC-93, Yamanouchi [142]), nifedipine (BAY-A-1040, Adalat, Bayer [143]), nimodipine (BAY-E-9736, Nimotop, Bayer [144–145]), nitrendipine (BAY-E-5009, Bayotensin, Bayer; all L-type voltage-gated calcium channels [153, 154]), NP-34 (NP-04634; Noscria, formerly Neuropharma; a dual calcium channel blocker and acetylcholinesterase inhibitor [155], NS-649 (Neurosearch; a neuron-specific calcium channel blocker [156], NSD-761 (Neurosearch; a selective ion channel modulator); RGH-2716 (TDN-345; a nootropic neuroselective ion channel blocker; Takeda in collaboration with Gedeon Richter [157–159]), SNX-482 (R-type calcium channel blocker of Neurex, now Elan Pharmaceuticals [160–162]), SPF-017 (Sucamopo; selective type-2 chloride channel activator), tamo- larizine (NC-1100, calcium channel blocker, Nippon Chemipharm [163–165]), VRX-698 (Valent Pharmaceuticals International; a potassium channel opener), and XE-991 (Bristol-Myers Squibb; a KCNQ potassium channel blocker [166, 167]).

DRUGS INTERACTING WITH NERVE GROWTH FACTORS

The role of neurotrophic factors in AD was discussed [168] as a neurotrophic rationale for the therapy of neurodegenerative diseases [169]. The potential therapeutic use of BDNF, a key regulator for protein-synthesis dependent long-term potentiation and long-term memory, in neurological and psychiatric disorders was presented [170, 171], in particular for AD [172, 173]. Interestingly, genetic knockdown of BDNF in triple transgenic AD mice did not alter Aβ or tau pathology [174]. Nerve growth factor (NGF), cholinergic dependency in brain aging, MCI, and AD was discussed [175–181]. NGF treatment in dementia was described [182]. NGF and AD, new facts for an old hypotheses were communicated recently [183]. Hippocampal ProNGF signaling pathways and amyloid-β levels in mild cognitive impairment and Alzheimer’s disease were elucidated [1705]. It was claimed that NGF promoted long-term memory formation by activating poly(ADP-ribose) polymerase-1 (PARP-1) [184].

NeuroAid (MLC-601; Danqi Plantan Jiaonang; Molacq Pte Ltd, Singapore) is a BDNF stimulator derived from Radix Astragali, Radix Salviae Miltiorrhizae, Radix Paeoniae Rubra, Rhizoma Chuanxiong, Radix Angelicae Sinensis, Carthamus Tinctorius, Prunus Persica, Radix Polygalae, Rhizoma Acori Tatarinowii, Batbus Martensii, Hirudo, Eupolyphaga Sea Stereophaga, Calculus Bovis Synthetic or Arti- factus and Corna Saigeae Tataricarum, for the potential oral prevention of stroke including cerebral infarction and ischemic stroke and for the potential treatment of traumatic brain injury in a randomized, double-blind, placebo-controlled, multicenter, Phase III trial (n = 1100) since November 2007 in Singapore and the Philippines. The study was expected to be completed in 2012 (Thomson Reuters Pharma, update of October 3, 2012).

CERE-110 (AAV2-NGF; NeuroRescue AD; Ceregene, San Diego CA) is an AAV2 vector based gene delivery system containing cDNA for NGF. A Phase II clinical trial in mild-to-moderate AD patients (n = 50) started in May 2009 in the US. The therapeutic potential of CERE-110 was described in detail [185, 186] (Thomson Reuters Pharma, update of July 20, 2012).

GM-607 (Genervon Biopharmaceuticals, Pasadena CA) is a motoneuromorphotypic factor analogue for the potential treatment of ischemic stroke, spinal cord injuries, ALS, AD, HD, and PD. By April 2011, a Phase II ischemic stroke trial was initiated. By February 2012, further Phase II IND applications were being prepared for spinal cord injuries, ALS, PD, and AD (Thomson Reuters Pharma, update of August 28, 2012).

MIM-D3 (Mimetogen Pharmaceuticals, Quebec, Fig. 3) is a small molecule NGF peptidomimetic for the treatment of AD and dry eye (xerophthalmia). A Phase II trial for dry eye was initiated in November 2010 [187] (Thomson Reuters Pharma, update of May 17, 2012).
PYM-50028 (Cogane, PS8, P63; Phytopharm, UK) (Fig. 3), a steroidal saponin, stimulated BDNF release and may be beneficial for the treatment of PD, AD, glaucoma, and ALS. PYM-50028 reversed neuronal damage induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in a mouse model of PD [188]. In July 2011, FDA granted PYM-50028 orphan drug status for ALS. In November 2010, recruitment of patients (n = 400) began in the randomized, double-blind, proof-of-concept, placebo-controlled, dose-ranging Phase II study CONFIDENT-PD (Thomson Reuters Pharma, update of August 16, 2012).

T-817MA (Toyama Chemical, Fujifilm Holding) (Fig. 3) is a neurotrophic small molecule in Phase II clinical trials for AD in the US since April 2008. T-817MA attenuated cognitive impairments in P301L tau transgenic mice [189], prevented memory deficits caused by i.c.v. Aβ administration [190, 191], and attenuated Aβ-induced neurotoxicity [192] (Thomson Reuters Pharma, update of July 30, 2012).

NoG-0202 (ECB-AD, ECT-AD, NoGene A’s, Denmark) is an encapsulated cell bio delivery system to deliver cells expressing NGF. A Phase Ib trial started in December 2007 in Sweden. First clinical data were presented in July 2011. In January 2012, the trial was expected to be completed in 2012 [193] (Thomson Reuters Pharma, update of January 17, 2012).

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

- **AL-209** (ADNF-9, S:AL Allon Therapeutics, Vancouver): an activity-dependent neurotrophic factor derived from a nine amino acid sequence peptide and tubulin-binding agent that stimulated PARP-1 for the potential treatment of CNS and ocular disorders (Thomson Reuters Pharma, update of March 6, 2012).

- **AL-309** (Allon Therapeutics, Vancouver): an analogue of AL-209 and PARP stimulator for oral, intranasal and s.c. administration. By October 2012 preclinical development had been completed (Thomson Reuters Pharma, update of October 17, 2012).

- **AMBS-001** (CNS-001): Amarantus BioSciences, Sunnyvale CA, formerly CNS Protein Therapeutics having acquired the relevant IP from Prescient Neuropharma) is a program of therapeutics based on mesencephalic astrocyte-derived neurotrophic factor [194], which promoted the survival of dopaminergic neurons for the potential treatment of PD, AD, and brain injury. It also protected the heart from ischemic damage [195] (Thomson Reuters Pharma, update of October 2, 2012).

**Catecholamine derivatives** (Emory University, Atlanta, GA) acted like BDNF to activate the tyrosine kinase B (TrkB) receptor. They have a potential for the treatment of neurological diseases such as ALS, PD, and AD (Thomson Reuters Pharma, update of July 27, 2012). Structures were not communicated.

- **CB-1**, **CB-2**, and **CB-3** (Molcode, Tartu, Estonia) are BDNF mimetics, which activated the TrkB receptor leading to its phosphorylation (Thomson Reuters Pharma, update of December 27, 2011). The structures were not communicated.

- **7,8-Dihydroxy-flavone**, a TrkB receptor agonist and BDNF mimic, reversed memory deficits in a mouse model of AD [196]. The compound and derivatives thereof are also evaluated at Emory University in collaboration with the University of Wisconsin [197–199] (Thomson Reuters Pharma, update of August 10, 2012).

- **FC29 peptide** (University of Queensland, Brisbane, Australia) is a fragment of the p75 neuregulin receptor that inhibited p75NTR-mediated neuronal death via regulation of the Trk receptor function for the potential treatment of AD, PD, and motor neuron disease (Thomson Reuters Pharma, update of May 17, 2012).

- **Gambose amine and gambogic amide** (Emory University, Atlanta GA), TrkA receptor agonists with robust neurotrophic activity, prevented neuronal cell death [200] (Thomson Reuters Pharma, update of August 28, 2012).

- **Gedunin** (Emory University, Atlanta GA) and its derivatives including deoxygedunin are TrkB receptor agonists for the potential treatment of PD, HD, AD, HIV-related dementia, ALS, stroke, and multiple sclerosis [201] (Thomson Reuters Pharma, update of April 26, 2012).

- **JRP-655** (Prous Institute for Biomedical Research, Barcelona) is a BDNF secretagogue and neuroplasticity modulator (Thomson Reuters Pharma, update of September 5, 2012). The structure was not communicated.

- **4-methylcatechol**, which increased BDNF content and stimulated BDNF mRNA expression and synthesis, effectively improved spatial learning and memory in rats [202, 203].

- **NeuroAID II** (MLC-901, Molac Pu Ltd., Singapore), a BDNF stimulator, is a derivative of NeuroAID for the potential treatment of global ischemia in preclinical development (Thomson Reuters Pharma, update of September 2, 2011).

- **ND-602** (Neurodyn, Charlottetown, Canada) is a neuroprotective progranulin (PC cell-growth factor).
expressing lentiviral vector for the potential treatment of PD, AD, and ALS. ND-602 was found to increase activity of neprilysin and significantly reduced Aβ and plaque burden in the hippocampus and entorhinal cortex of Tg2576 mice (Thomson Reuters, update of May 25, 2012).

The development of many drugs interacting with neurotrophic factors was terminated. The most advanced drug, xaliproden (SR-57746A, Xaprina; sanofi), a 5-HT 1A agonist and stimulator of endogenous neurotrophin synthesis, did not meet the cognition endpoints in Phase III trials in AD patients, which applies also to paliredon (SR-57667B; with a biphenyl instead of the β-naphyl in xaliproden; sanofi, [204]).

The lessons learnt from the xaliproden clinical trials were discussed [205]. The biological characterization was reviewed [206].

Also the development of other drugs interacting with neurotrophic factors (in alphabetical order) was terminated: ABS-200 (American Bio- genetic Sciences), ADNF-14 (NIH, activity-dependent neurotrophic factor-14), AGT-120, and AGT-140 (ArmaGen Technologies); AK-30-NGF (a monoclonal antibody as carrier for the delivery of NGF; Alkermes), arundic acid (MK-0724, ONO-2506, Arocye, Ono Pharmaceuticals [207–210]), beta NGF (tethered to a molecular shuttle; Apollo Life Sciences), CEP-427 (a neurotrophic factor enhancing small molecule; Cephalon, now Teva), colenuronamide (MCC-257, Mitsubishi Tanabe Pharma), CX-438 (Cortex Pharmaceuticals), dekafin-1 (a fibroblast growth factor receptor, agonist and tyrosine kinase modulator; Enkam Pharmaceuticals); dFGF (dimerized fibroblast growth factor, Massachusetts Institute of Technology (MIT)/ViaCell Inc.); GDF-1 (Creative Biomolecules, now Curis; a growth and differentiation factor-1 agonist), glial maturation factor (Rhone-Poulenc/Regeneron), huM-13 (a humanized monoclonal antibody that binds to the TrkA receptor, Lay Line Genomics), inosine (an NGF, Alters Pharmaceuticals, formerly Boston Life Sciences (BLSI), under license from the Children’s Hospital of Boston), KP-66, KP-447, and KP-546 (Krenitsky), leterpinim (AIT-082; SPI-205, Neotrofin, Spectrum Pharmaceuticals, formerly NeoTherapeutics), which induced the expression of NGF, neurotrophin-3, and of basic fibroblast growth factor [211–216], LMH1A-31 (a p75 neurotrophin receptor ligand; Elan), nerve growth factor agonists (Chiron), neuregulin-2 (cerebellum-derived growth factor, NRG2; Acorda Therapeutics under license from CelNeS and Harvard University), NGF therapy (Lay Line Genomics), NP-901 (Nocira), NS-521 (NeuroSearch), p75 NGF receptor antagonist (Circadian Technologies under license from the Walter & Eliza Hall Institute), NT-3 (Genentech and StemCells), ReN-1820 (ReNeuron under license from the University of Bristol), ST-857 (acetyl-L-carnitine arginine amide; Sigma-Tau [217–219]), T-588 (Toyama [220–227]), and troefinex (a peptide neurotrophic factor; Protarga).

**DRUGS INTERACTING WITH RE-UPTAKE TRANSPORTERS (PSYCHOSTIMULANTS)**

Psychostimulants exert behavioral-calming and cognition-enhancing actions in the treatment of ADHD [228]. Cognition-enhancing doses of psychostimulants exert regionally restricted actions elevating extracellular catecholamine levels and enhancing neural signal processing preferentially in the prefrontal cortex. Additional evidence suggests a prominent role of prefrontal cortex D2 receptors in the behavioral and electrophysiological actions of low-dose psychostimulants [229, 230]. Excellent reviews on attention-modulating effects of cognitive enhancers were published [231–236]. An analysis of student use (and abuse) of cognitive enhancers was presented [237]. A review on glicine transporter type 1 (GlyT1) inhibitors was disclosed [238].

Methylphenidate (Ritalin, Ciba, now Novartis, launched 1956) is a psychostimulant drug, which increased the levels of dopamine and noradrenaline in the brain through re-uptake inhibition of the monoamine transporters [239]. Methylphenidate preferentially increased catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive functions [240]. Cognition-enhancing doses of methylphenidate preferentially increased prefrontal cortex neuronal responsiveness [241]. Methylphenidate decreased the amount of glucose needed by the brain to perform a cognitive task [242]. The improvement of memory functions by methylphenidate (and modafinil) in healthy individuals was described [243].

Most of these experiments were made with the mixture of erythro and three stereoisomers. The active principle of methylphenidate is the (S)-(+)-3-phenylpyridine hydrochloride (Dexmethyllphenidate, Ritadex; Novartis Pharma under license from Celgene launched 2002) (Fig. 4), also available as an extended-release oral formulation Focalin XR [244]. The spheroidal oral drug absorption system dexamethyllphenidate was described [245] (Thomson Reuters Pharma, update of July 27, 2012).
Modafinil (Provigil, Lafon Laboratories, later Cephalon, now Teva, launched 1998) is an inhibitor of dopamine, noradrenaline, and serotonin re-uptake and an α1 adrenoceptor agonist [246]. Modafinil showed improvement of cognition and attention in patients with chronic schizophrenia ADHD [247, 248], in particular in the first episode of psychosis [249, 250]. The neuronal mechanism by which modafinil affects cognitive and emotional function in schizophrenic patients was reviewed [251]. Experiments using BOLD functional magnetic resonance imaging (fMRI) in healthy volunteers showed that modafinil enhanced the efficiency of prefrontal cortical cognitive information processing, while dampening reactivity to threatening stimuli in the amygdala, the brain area implicated in anxiety [252]. Modafinil improved attention in well-rested individuals [243]. Modafinil reliably enhanced performance on several cognitive tests of planning.
and working memory, but did not improve learning and delayed recall performance in healthy volunteers [253]. It may be useful in the treatment of substance abuse [254]. It improved working memory and sustained attention in cocaine users [255].

The active principle of modafinil is the (R)-enantiomer Armodafinil (Navigil; CEP-10955; Cephalon, now Teva launched 2009) (Fig. 4). The sales of armodafinil in 2011 amounted to USD 266 mil (Thomson Reuters Pharma, update of September 21, 2012).

Atomoxetine (tomoxetine, Strattera, LY-139603; Lilly; launched 2003) (Fig. 4) is a selective noradrenaline re-uptake inhibitor for the treatment of ADHD in children and adults [256]. Atomoxetine inhibited noradrenaline and serotonin transporters with Ki values of 39, 3,830, and 34 nM, respectively [257]. Atomoxetine improved response inhibition in ADHD patients and in healthy volunteers via increased activation in the right frontal gyrus measured via fMRI [258, 259]. Sales in 2011 were USD 620 million (Thomson Reuters Pharma, update of September 26, 2012).

Lisdexamfetamine (Vyvanse; Shire Pharmaceuticals and New River Pharmaceuticals, launched 2007) (Fig. 4) is a drug for the treatment of ADHD in children, adolescents, and adults [260]. Lisdexamfetamine itself is inactive and acts as a prodrug to dextroamphetamine upon cleavage of the lysine portion of the molecule. Dextroamphetamine inhibited noradrenaline, serotonin and dopamine transporters with respective Ki values of 2.6 and 48 nM, respectively [257]. Atomoxetine improved most of the tested cognitive functions in preclinical evaluation (in alphabetical order):

- AM-285 (Cyclocreatine, CinCY; Lumos Pharma, Austin TX based on University of Cincinnati technology) (Fig. 4) is evaluated for the potential treatment of creatine transporter deficiency, an X-linked autism spectrum disorder characterized by severe cognitive impairment [268]. In June 2012, the FDA awarded cyclocreatine Orphan designation for the treatment of creatine transporter deficiency (Thomson Reuters Pharma, update of August 24, 2012).
- AS-1522489-00 (Astellas Pharma) is a glycine transporter-1 inhibitor, a 1,2,4-triazole derivative, of which only the (S)-enantiomer is biologically active [269, 270] (Thomson Reuters Pharma, update of January 27, 2012). The structure was not communicated.
- Lu-AA42202 (Lundbeck) (Fig. 4) is a triple dopamine, noradrenaline, and serotonin re-uptake inhibitor for the potential treatment of major depressive disorders and ADHD (Thomson Reuters Pharma, update of December 1, 2010).
- MLR-1017 (mesocarb, sydnocarb, sidnocarb, Melier Pharmaceuticals, Exton, PA) (Fig. 4) is a dopamine transporter inhibitor for the potential treatment of ADHD and levodopa-induced side effects in PD. The drug was previously launched in Russia [271, 272] (Thomson Reuters Pharma, update of April 12, 2012).
- PD-2005 (P2D Bioscience, Cincinnati, OH, identical with AHN 2-005, National Institute of Drug Abuse and US Naval Medical Research Center) (Fig. 4) is an inhibitor of the dopamine transporter for the potential treatment of ADHD and for cognitive impairments in traumatic brain injury. It dose-dependently improved performance of rats in a delayed-alternation task of spatial working memory [273] (Thomson Reuters Pharma, update of June 12, 2012).
- RO-4543338 (Roche) is a well-tolerated glycine transporter inhibitor, which facilitated drug cue extinction [274, 275]. The structure was not communicated.

Selective Serotonin Re-uptake Inhibitors (SSRIs)
There are several drugs interacting with re-uptake transporters in preclinical evaluation (in alphabetical order):

- Selective Serotonin Re-uptake Inhibitors (SSRIs) showed cognitive enhancing effects [276]. Patients treated with citalopram showed significant improvements on a cognitive subscale. Paroxetine and fluoxetine improved most of the tested cognitive functions in a study of 242 depressed patients during one year [277]. Other studies with citalopram, fluoxetine, sertraline, and zimelidine did not report improvement of memory and/or reaction time in demented patients [278].
- Thiethylperazine (Torecan) (Fig. 4), a drug approved by the FDA to relieve nausea and vomiting,
Fig. 5. VMAT2 and DA-reuptake PET ligands.

is an activator of ABCC1 transporters. In a mouse model of AD expressing the ABCC1 transporter, a markedly reduced load of Aβ was measured. Deficiency of ABCC1 transporter substantially increased cerebral Aβ levels [279] (Thomson Reuters Pharma, update of April 26, 2012).

The development of ASP-2535 (Astellas; a glycine transporter-1 inhibitor [280]), coluracetam (BCI-540, MKC-231; BrainCells Inc. under license from Mitsubishi Tanabe Pharma; an enhancer of high-affinity choline uptake and K⁺-induced release of acetylcholine [281–288]), CP-101 (CogniPharm, an i.v. formulation of modafinil), D-serine re-uptake inhibitors (Memory Pharmaceuticals, now Roche), flufenoxina (FAES Farma; a dual serotonin and noradrenaline re-uptake inhibitor), glycine transporter-1 inhibitors (Helicon Therapeutics), JNJ-17305600 (NFPS, NPS Allelix; a dual serotonin and noradrenaline re-uptake inhibitor), SCH-900435 (Org-25935; Organon, Schering-Plough, now Merck, a glycine transporter-1 inhibitor [289]), PD-2007 (P2D Bioscience, a dopamine transporter inhibitor), SCH-900435 (Org-25935; Organon, Schering-Plough, now Merck, a glycine transporter-1 inhibitor), SSR-103800 (290–292) and SSR-504734 (both sanofi; both glycine transporter-1 inhibitors [293–297]), teuniloxazine (sufloxazine, Lucelan, Metatone, Y-8894, Yoshitomi, Mitsubishi Pharma, a noradrenaline uptake inhibitor [298],[299–301]), and tesofensine (NS-2330, NeuroSearch, a monoamine re-uptake inhibitors of serotonin, dopamine, and noradrenaline [302]) was terminated. The development of tesofensine for the once-daily oral treatment of obesity in Phase II trials was also suspended [303].

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 [304]. Positron emission tomography (PET) ligands for the VMAT2 have become valuable diagnostic tools.

(+)-(11C)-dihydrotetrabenazine (DTBZ) (Fig. 5) allows the determination of the striatal monoaminergic presynaptic terminal density. In a study enrolling 20 patients with dementia with Lewy bodies (DLB), 25 AD patients, 7 patients with frontotemporal dementia, and 19 elderly controls clinicians could accurately differentiate between the different forms of dementia [305–307]. The uptake of (+)-(11C)-DTBZ in the stria-
In May 2012, an open-label, single-blind, Phase II/III study was initiated [312]. The whole body biodistribution was studied [317]. In patients with undiagnosed movement disorders (n=150) in the US to assess the safety and efficacy of florbenazine in differentiating PD. At that time, the study was scheduled to complete in September 2014. For the synthesis, see [309]; for the binding characteristics in rat striatum and hypothalamus homogenates (Kd = 0.19 and 0.25 nM, respectively), see [310, 311]. The whole body biodistribution was studied [312]. 

18F-AV-133 was used for noninvasive assessment of the dopaminergic system was unchanged compared to controls. The striatal uptake in DLB and PD patients was significantly decreased [308]. 18F-Florbenazine ([18F]AV-133; [18F]-FP-DTBZ; Avid Radiopharmaceuticals, Philadelphia PA, a subsidiary of Lilly, under license from University of Michigan) (Fig. 5) is in Phase III clinical evaluation. In May 2012, an open-label, single-blind, Phase II/III study (NCT01550484; [18F]-AV-133-B04) was initiated in patients with undiagnosed movement disorders (n=150) in the US to assess the safety and efficacy of florbenazine in differentiating PD. At that time, the study was scheduled to complete in September 2014. For the synthesis, see [309]; for the binding characteristics in rat striatum and hypothalamus homogenates (Kd = 0.19 and 0.25 nM, respectively), see [310, 311]. The whole body biodistribution was studied [312]. 

18F-AV-133 was used for noninvasive assessment of the vesicular monoamine transporter type 2 in 17 PD patients and 6 healthy controls. VMAT2 binding potential was decreased by 81% in the posterior putamen, 70% in the anterior putamen, and 48% in the caudate nucleus of PD patients [313]. This ligand is a valid measure of dopaminergic neuron integrity. The in vivo assessment in patients with DLB and AD was reported [314]. The optimal scanning time window was elucidated [315]. For PET imaging in a MPTP-induced mouse model of PD, see [316] (Thomson Reuters Pharma, update of August 7, 2012).

11C-β-CFT and 18F-β-CFT (Fig. 5) proved to be valuable PET ligands due to their high affinity interaction with dopamine re-uptake sites. AD patients showed a reduction of 11C-β-CFT in putamen and caudate of about 20%. Thus the putamen and the caudate nucleus were equally affected in contrast to PD, which showed predominantly putaminal reduction [317]. In PD, the mean uptake of 18F-β-CFT in the contralateral putamen was reduced to 31% and in the ipsilateral putamen to 45%. In the caudate nucleus, the uptake was reduced contralaterally to 67% and ipsilaterally to 77% [318]. For an exhaustive review, see [319].

123I-Ioflupane ([123I]-FP-CIT; GE Healthcare) (Fig. 5) is a SPECT ligand launched in 2000. It is the ligand of choice to differentiate between AD and DLB patients [320, 321]. It is valuable for the diagnosis of Parkinsonian syndromes [322]. SERT dependent 123I-Ioflupane uptake allows a more comprehensive assessment of neurochemical disturbances in degenerative Parkinsonism [323–325] (Thomson Reuters Pharma, update of August 14, 2012).

**DRUGS INTERACTING WITH TRANSCRIPTION FACTORS**

- cAMP response element-binding (CREB) protein and the discovery of cognitive enhancers was reviewed [326–328]. CREB phosphorylation as a mechanistic marker in the development of memory enhancing AD therapeutics was described [329]. The current knowledge of key calcium signal-regulated transcription factors, namely CREB, nuclear factor of activated T-cells, and downstream regulatory element antagonist modulator (DREAM) and memory formation was summarized [330]. Aβ disrupted activity-dependent gene transcription required for memory through the CREB-regulated transcription co-activators CRTC1 [331]. The GABAA receptor antagonist SG5742 improved spatial memory and reduced protein binding to CREB2 in the hippocampus [332] (see Part 1, Chapter 1.10.2 GABAA receptors). CREB antisense oligonucleotide administration into the dorsal hippocampal CA3 region impaired long- but not short-term spatial memory in mice [333]. The lack of DREAM protein enhanced learning and memory and slowed brain aging [334].

**SRF/MYOCD inhibitors** (Socratech LLC, Rochester NY) are small molecule inhibitors against serum response factor and myocardin, which are interactive transcription factors in vascular smooth muscle cells for the potential treatment of AD [335]. For a review on the imbalance of vascular molecules in AD, see [336] (Thomson Reuters Pharma, update of February 15, 2012). Structures were not communicated.

The development of CREB modulators (Helicon Therapeutics) and EPAC inhibitors (exchange protein directly activated by cAMP; a guanine nucleotide-exchange factor, Scottish Biomedical [337]) was terminated.

**ANTIOXIDANTS**

Soluble Aβ oligomers localize to mitochondria and interfere with their normal functioning causing an overproduction of reactive oxygen species (ROS), inhibiting respiration and ATP production and damaging the structure of mitochondria [338–340]. Some authors, however, claim that the early impairments of mitochondrial dysfunction and oxidative stress may precede Aβ overproduction and deposition [341–343]. Excellent reviews were presented over years [344–347]. Possibilities of intervention of antioxidant pathways in AD were discussed [348, 349].
Also see Chapter 3. Cytokines, as inflammation is tightly connected with the oxidative cascade.

Over the years, clinicians have explored treatment of AD patients with antioxidants. Free radicals can be scavenged by dietary means. Compounds such as acetyl-L-carnitine, curcumin [350], Gingko biloba extracts such as EGb 711, (R)-α-lipoic acid, melatonin, morin, trolox, vitamin C [351], and vitamin E [352–355] were tested in clinical trials in AD patients. The results were disappointing [356–372]. As a consequence of a landmark study, clinicians even advise AD patients not to take large doses of vitamin E or α-lipoic acid [373].

Many clinical trials were also carried out with synthetic antioxidants such as edaravone (MCI-186, Mitsubishi [374],[375–377]), idebenone (CV-2619, Avan, Catena, Noben, Sovrima, Takeda [378–380]), and the derivatives of 21-amino steroids (Upjohn’s lasaroids, such as tirilazad or U-74006F; U-74389G; U-74500A, U-75412E, U-78518F; and U-83836E [381–384]). None of these compounds produced statistically significant therapeutic benefits for AD patients.

MitoQ (redox mixture of mitoquinone and mitoquinol; Antipodean Pharmaceuticals, Menlo Park CA, under license from the University of Otago; Fig. 6 shows the oxidized form) is a brain penetrating mitochondria-targeting antioxidant [385–388]. It selectively blocked mitochondrial oxidative damage and prevented cell death [389–394]. It is evaluated in Phase II clinical trials for the treatment of PD and liver damage. Clinical trials for the treatment of Friedreich’s ataxia and sunburn were abandoned (Thomson Reuters Pharma, update of June 18, 2012).

A potential follow-up compound is MitoVitE (Fig. 6) [395, 396]. The development of MitoPBN (Antipodean Pharmaceuticals, Menlo Park CA) (Fig. 6) consisting of the spin trapping agent α-phenyl-N-tert.-butyl-nitrone [397, 398] conjugated to triphenyl-phosphonium bromide was terminated [399] (Thomson Reuters Pharma, update of June 18, 2012).

MTP-131 (Bendavia, SS-31, Szeto-Schiller peptide; Stealth Peptides Inc., Newton Centre MA) (Fig. 7) is a cell-permeable mitochondria-targeting antioxidant tetrapeptide (NH$_2$-D-Arg-Dmt-Lys-Phe-NH$_2$), which is in Phase II clinical trials for ischemia reperfusion injury since September, 2010 (EMBRACE–STEMI trial). It will further be investigated for the treatment of eye, neurological, mitochondrial, and metabolic...

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. The prevention of Aβ induced neurotoxicity by indole-3-propionic acid was described [404]. The rationale behind the selection of OXIGON as a potential disease-modifying therapy for Alzheimer’s disease was presented [1706]. Preliminary data from a multiple-dose Phase Ib trial for AD were reported in October 2010. It appears that ViroPharma wants to pursue the drug for the indication Friedreich’s ataxia only (Thomson Reuters Pharma, update of August 17, 2012).

There are several antioxidants in preclinical evaluation (in alphabetical order): Catalytic manganoporphyrine antioxidants, such as AEOL-10113, AEOL-10150, AEOL-10201 and AEOL-11207 (Aeolus Pharmaceuticals, Mission Viejo CA; Fig. 7) may be promising for the treatment of PD and ALS [405–407] and ischemic stroke [408–412] (Thomson Reuters Pharma, update of April 23, 2012). CNB-001 (The Salk Institute for Biological Studies) (Fig. 7) is a curcumin derivative for potential treatment of traumatic brain injury and stroke (Thomson Reuters Pharma, update of November 9, 2011).

DL-3-n-butylphthalide (NBP, Hebei, China) is a natural antioxidant extracted from seeds of Apium and a powerful free radical scavenger [413]. It protected dopamine neurons in a rotenone model for PD [414]. FRP-0924 (gemifloxacin, Neuron BioPharma, Granada, Spain) is an antioxidant and neuroprotectant for the potential treatment of neurodegenerative diseases including AD. FRP-924 crossed the blood-brain barrier and prevented neuronal death. As fluoroquinolones are generally well tolerated with most side effects being mild and serious adverse effects being rare, it is expected that the drug will enter Phase II rapidly (Thomson Reuters Pharma, update of August 14, 2012).

IAC (Cerebricon, Finland and Medestea Research, Torino, Italy) (Fig. 8) is a novel radical scavenger react-
ing with most carbon-, nitrogen-, and oxygen-centered radicals of biological interest [415–418]. Daily treatment with IAC (3–30 mg/kg i.p.) decreased mortality, enhanced cognitive functions in the water maze, and reduced the Aβ plaque burden in hAβPP transgenic mice [419].

**Lipid soluble antioxidants** (OXIS International, Beverley Hills CA) mimic the activity of the body’s natural cell membrane-protecting antioxidant vitamin E for the potential treatment of cardiovascular diseases, diabetes, AD, and PD (Thomson Reuters Pharma, update of June 12, 2012). The structures were not communicated.

Lipocrine and Memoquin, dual acetylcholinesterase inhibitors and antioxidants (University of Bologna), were described in Part 2, Chapter 2.1.1.3. (formulae in Part 2 in Fig. 6).

**NPS-0155** (Neuron BioPharma, Granada, Spain) is an antioxidant and neuroprotective compound for the potential treatment of AD and other neurodegenerative diseases (Thomson Reuters Pharma, update of April 27, 2012). The structure was not communicated.

**PAN-811** (3-AP; NSC-663249; OCX-191; Triapine, Panacea Pharmaceuticals, Gaithersburg MD) (Fig. 8) is a ribonucleotide reductase inhibitor, calcium ion chelator, and radical scavenger for the potential treatment of AD and ischemia [420, 421] (Thomson Reuters Pharma, update of February 25, 2011).

**S-52** (Shanghai Institute of Materia Medica) (Fig. 8) is a sinomenine derivative, an active natural product from the Chinese herb *Sinomenium acutum*. It is a scavenger of free radicals. It attenuated the toxicity of Aβ to energy metabolism, mitochondrial membrane structure, and key enzymes in the electron transport chain [422].

There are numerous preclinical reports of drugs and natural products, which, in addition to their radical scavenging properties, also prevented Aβ-induced neurotoxicity, such as penoniflorin [423], 2,2′-pyridoin [424], quetiapine [425], stemazole (Fig. 8) [426], and zeatin (Fig. 8) [427].

Dual free radical scavengers and Aβ binding ligands were described [428, 429].

The development of many antioxidants was terminated (in alphabetical order) of **AN-808** (Athena Neurosciences, now Elan Pharmaceuticals), **AO-2** and **AO-3 antioxidants** (Antoxis), **CNSB-002** (AM-36; Relevare; AMRAD, formerly Zenyth Therapeutics [430]) [431, 432], **CPI-1189** (Centaur [433, 434]), **disufenton sodium** (Cerovive, NXY-059, AstraZeneca, which was in Phase III clinical trials for the treatment of acute ischemic stroke [435–445]), **FR-210575** (Fuji-sawa [446]), **MDL-101002** (Hoechst Marion Rousell, now sanofi [447, 448]), and **raxofelast** (IRFI-016, Biomedica Foscama Industria [449–452]).

**METAL CHELATORS**

The metallobiology of AD was investigated in great detail over the last fifteen years. Excellent reviews were...

DP-109 (D-Pharm, Rehovot, Israel) (Fig. 9) is an i.v. prodrug of the calcium and zinc chelator BAPTA for the potential treatment of stroke and traumatic brain injury. It is in Phase III clinical trials for stroke since October 2009. First reports on clinical results were communicated [486–488]. Also preclinical data were disclosed [489–491] (Thomson Reuters Pharma, update of February 3, 2012).

PBT-2 (Praja Biotechnology, Parkville, Australia) (Fig. 9) is an oral zinc ionophore metal-protein attenuating compound that reduced levels of soluble Aβ in AD patients (n = 78), started in December 2006 with daily doses of 50 or 250 mg or placebo over three months, was completed in January 2008. A significant reduction of Aβ42 levels in the cerebrospinal fluid (CSF) was seen in the 250 mg group. This dose also significantly improved executive function performance in the category fluency and the trail making cognitive tests compared to placebo [493, 494]. In January 2012, the FDA approved an IND to initiate a randomized, multicenter, double-blind, placebo-controlled, parallel-group, safety, tolerability, and efficacy Phase IIa trial in early- to mid-stage HD patients (n = 100) in the US and Australia. In April 2012, the first patient was dosed in this trial. By June 2012 the trial had been initiated in Australia. Data are expected in the second half of 2013. The compound was extensively characterized in preclinical studies [495–497] (Thomson Reuters Pharma, update of October 2, 2012). See also Chapter 17.1. Small molecules preventing tau aggregation.

AEN-100 (Synthetic Biologics, formerly Adeona Pharmaceuticals, Ann Arbor, MI) is a once-daily, gastroretentive, sustained-release, oral tablet formulation of zinc acetate for the potential treatment of ALS and AD. By November 2011, a Phase I study for ALS patients was underway (Thomson Reuters Pharma, update of September 19, 2012).

Other metal chelators are currently in preclinical evaluation (in alphabetical order):

Aom-0937 (Hangzhou Adamerck Pharmlabs, China) is a prodrug of DP-109 (Thomson Reuters Pharma, update of July 28, 2011). The structure was not communicated.

DP-460 (D-Pharm, Rehovot Israel) (Fig. 9) is a membrane active chelator derivative of the calcium-specific chelator BAPTA that modulates copper and zinc homeostasis to inhibit oxygen radicals and plaque formation. It is in preclinical evaluation for the potential oral treatment of AD and ALS (Thomson Reuters Pharma, update of November 1, 2011). It appears that DP-460 was preferred to DP-109 [498]. Both compounds have been evaluated as neuroprotectants in a transgenic mouse model of ALS [499] (Thomson Reuters Pharma, update of August 7, 2012).

Deferoxamine (SAN-121; Sanomune, a subsidiary of DiaMedica under license from HealthPartners Research Foundation, Winnipeg, Canada) (Fig. 10) is a nasally-delivered iron chelator improving performance in a radial arm water maze in P3301L tau transgenic mice [500] (Thomson Reuters Pharma, update of December 23, 2011).

HLA20A (Technion Haifa) (Fig. 10) is a combination of an 8-hydroxy-quinoline metal chelator, which was carbamoylated at the 8-hydroxy function to interact with acetycholinesesterase as in rivastigmine [501, 502]. See Part 2, Chapter 2.1.1.10. Dual acetylcholinesesterase inhibitors and metal chelators.

PA-1637 (Pahumed, France) is an Aβ plaque production-inhibiting copper chelating agent (Thomson Reuters Pharma, update of May 28, 2012). The structure was not communicated.

PBT-3 and PBT-4 (Praja Biotechnology, Parkville, Australia) are non-8-hydroxyquinoline metal protein attenuating compounds, potential follow-ups of PBT-2. (For both Thomson Reuters Pharma, update of November 2, 2011). The structures were not communicated.

Triazole-pyridine derivatives as inhibitors of metal-induced Aβ aggregation were described [503].

VAR-10200 (HLA-20; Varel, West Chester, PA) (Fig. 10) combines the iron-chelating properties of 8-hydroxyquinoline with the MAO-B inhibitor for the potential treatment of age-related macular degeneration [501] (Thomson Reuters Pharma, update of February 24, 2012). See Part 2, Chapter 2.26. Drugs interacting with Monoamine Oxidase.

VAR-10300 (M-30; Varel, West Chester, PA, Technion and the Weizmann Institute) (Fig. 10) combines the iron-chelating properties of 8-hydroxyquinoline with the MAO-B inhibitor for the potential treatment of age-related macular degeneration [501] (Thomson Reuters Pharma, update of September 24, 2012). See also Part 2, Chapter 2.26. Drugs interacting with Monoamine Oxidase.
Adeona Pharmaceuticals, formerly Pipex under license from the University of Michigan; the iron chelator VAR-10100/VK-28 [523–526] and VK-11 and VK-12 (Prana Biotechnology).

**NATURAL PRODUCTS**

Excellent reviews on naturally occurring phytochemicals for the prevention and treatment of AD have
been presented [527–532]. An overview on "natural substances and AD: from preclinical studies to evidence based medicine" was published recently [533]. 

Mentat (BR-16A; Himalaya Drug Co.) is a standardized mixture of herbal extracts, which has been launched in India and the US (as MindCare) in November 2000 for the treatment of cognitive deficits (Thomson Reuters Pharma, update of November 6, 2000).

YY-280 (Yucrid; Yeyu, South Korea) is a combination therapy of ticlopide and EGB-761 (tannin, a Ginkgo biloba extract) administered as a tablet for the treatment of apoplexy and myocardial infarction. The drug was registered in Korea in May 2008 [534] (Thomson Reuters Pharma, update of April 11, 2012).

SK-PC-B70M (SK Chemicals Life Science, South Korea) is derived from the dried root of Pulsatella koreana (baekduong). A randomized, double-blind, placebo-controlled Phase III clinical trial for the treatment of mild-to-moderate AD patients \(n = 256\) was initiated in November 2010 in South Korea. SK-PC-B70M improved scopolamine-induced impairments of memory consolidation in rats [535, 536]. It had antioxidant activity and reduced A\(_{\beta}\) levels in the brains of Tg2576 mice [537, 538]. It alleviated the neurologic symptoms in G93A-SOD1 ALS mice [538] (Thomson Reuters Pharma, update of February 28, 2012).

Circadin (KI-1001, NSC-56423; Neurim Pharmaceuticals, Tel Aviv) is an oral controlled-release formulation of melatonin (i.e., melatonin acetamide) and was launched in 2007 for the treatment of primary insomnia. A Phase II clinical trial was initiated in Israel in patients with MCI \(n = 50\) in October 2007. Another Phase II clinical trial was initiated in the US, UK, and Israel in patients with mild-to-moderate AD \(n = 140\) treated with an acetylcholinesterase inhibitor to evaluate the effects of add-on Circadin (2 mg) on decline in cognitive skills, global functioning, and daytime somnolence in September 2009 (Thomson Reuters Pharma, update of September 26, 2012).

KD-501 (Kwang Dong Pharmaceutical Co., Seoul) is an extract from the Scrophulariae radix. The drug is in Phase II clinical trials for AD since March 2009 (Thomson Reuters Pharma, update of February 11, 2012).

PTX-200 (Phytrix, Munich, Germany) is a plant-derived neuroprotectant for the potential treatment of PD. A Phase IIa clinical evaluation in the UK was successfully completed (Thomson Reuters Pharma, update of February 1, 2012).

Resveratrol is a natural phyto compound, which activated Sirtuin-1 [539–541]. It reduced A\(_{\beta}\) accumulation [543–548]. It remodeled soluble oligomers and fibrils of A\(_{\beta}\) into off-pathway conformers [549]. Resveratrol is not a direct activator of SIRT1 enzyme activity [550]. Resveratrol improved memory deficits in mice fed a high-fat diet [551]. Subchronic oral toxicity and cardiovascular safety pharmacology studies were carried out [552]. The biosynthesis of resveratrol in yeast and in mammalian cells was achieved [553]. The Georgetown University Medical Center in Washington DC started at Phase II, randomized, double-blind, placebo-controlled study in patients with mild-to-moderate AD \(n = 120\) in the US in May 2012 (NCT01504854). A novel application in HD was discussed recently [554]. See also in Part 2, Chapter 2.40, Drugs interacting with Sirtuin, formula in Part 2, Fig. 23 (Thomson Reuters Pharma, update of June 22, 2012).

RPh-201 (Regenera Pharma, Rehovot, Israel) is a subcutaneous formulation of an agent derived from a traditional medicinal plant. A Phase IIa randomized, double-blind, placebo-controlled trial in healthy volunteers and adults with AD \(n = 56\) started in January 2012 in Canada. A topical formulation is currently evaluated in a Phase II study in patients with chronic ulcerated wounds \(n = 15\) in Israel (both Thomson Reuters Pharma, update of January 31, 2012).

VR-040 (apomorphine as dry powder inhaled formulation, Vectura, Chippenham, UK) is being developed in Phase II clinical trials for the potential treatment of PD since June 2006 (Thomson Reuters Pharma, update of October 3, 2012).

Exebryl-I (ProtoTech, Kirkland, WA and Chinese licensee Tasty Pharmaceuticals) is a synthetic compound with molecular weight of about 300 Da, one of the components of an Amazonian vine Uncaria tomentosa extract, which reduced aggregation of both A\(_{\beta}\) and tau. A Phase I clinical trial for AD was initiated in July 2008 (Thomson Reuters Pharma, update of June 8, 2012).

Taiši (Beijing SL Pharmaceutical under license from Xuanwu Hospital of Capital Medical University), a capsule formulation of a stilbene analogue isolated from an unspecified organism, is in clinical studies in China since February 2011 (Thomson Reuters Pharma, update of June 29, 2012).
There are many natural products in preclinical evaluation as potential drugs for the treatment of AD (in alphabetical order).

**Alpha-mangostin,** a polyphenolic xanthone derivative from mangosteen, concentration-dependently attenuated neurotoxicity induced by Aβ1-40 or Aβ1-42 oligomers (EC50 = 3.89 nM and 4.14 nM, respectively) [555].

**Anatabine** (Star Scientific, Glen Allen VI through its subsidiary Rock Creek Pharmaceuticals in collaboration with the Roskamp Institute) reduced Aβ when applied to cells [556] (Thomson Reuters Pharma, update of January 3, 2012).

**Andrographis paniculata leaves extract** showed cerebroprotective and nootropic activities in rats [557].

**Apomorphine** is an inhibitor of Aβ fibril formation [558]. Apomorphine treatment of AD mice promoted Aβ degradation [559]. Roles of apomorphine for regulated α-cleavage, autophagy, and antioxidation were discussed [560].

**AX-00111** (Axonal Consultoria Tecnologica Ltda, Sao Paulo Brazil) is a plant-derived compound for the potential treatment of AD (Thomson Reuters Pharma, update of June 1, 2012).

**Axona** (Accera Inc., Broomfield, CO) is a new medical food therapy for AD patients [561, 562]. It contains the proprietary formulation of medium-chain triglycerides, mostly caprylic triglyceride. The rationale for the use of Axona is based on the finding that the cerebral hypometabolism (i.e., impaired glucose metabolism) is an early sign of AD. Medium-chain triglycerides are metabolized in the liver resulting in the production of the ketone body beta-hydroxybutyrate, which is transported to the brain to provide an alternative fuel source for cerebral metabolism [563, 564]. See also [565].

**Bacopa monnieri** has shown memory free recall enhancing effects in adult humans [566]. Neuroprotective effects in experimental models of dementia were described [567].

**Baiacalin** (5,6,7-trihydroxyflavone) protected cortical neurons from Aβ25-35-induced toxicity [568] and in a one dose pre-treatment at 5 and 10 mg/kg i.p. attenuated Aβ23-35-induced amnesia in mice in a step-through passive avoidance paradigm. Post-treatment for 7 or 13 days (10-15 mg/kg i.p.) also attenuated Aβ25-35-induced amnesia [569]. Baiacalin prevented the production of hydrogen peroxide and oxidative stress induced by Aβ aggregation in SH-SY5Y cells [570]. Apigenin (4′,5,7-trihydroxyflavone), baiacalin, and norlithydroguaiaretic acid were potent inhibitors of liposome permeabilization by Aβ42 oligomers [571]. Baiacalin inhibited the formation of α-synuclein oligomers within living cells and prevented Aβ peptide fibrilization and oligomerization [572].

**Beta-asarone** improved cognitive functions in rats after injection of Aβ into the hippocampus [573] probably via JNK signaling and modulation of bcl-2 family proteins [574] and attenuation of neuronal apoptosis [575, 1708].

**BV-7003** (Bioved Pharmaceuticals) is a natural product for the potential treatment of memory loss (Thomson Reuters Pharma, update of September 11, 2012). The structure was not communicated.

**Cabernet Sauvignon** attenuated Aβ neuropathology in a mouse model of AD [579].

**Carvacrol** showed cognition enhancing activity in two rat models of dementia [580].

**Catechins** showed potent anti-amyloidogenic and fibril destabilizing effects in vitro [581–583].

**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 [584].

**Celastrus paniculatus** seeds showed nootropic activity [585].

**Chelserythrine** showed promising cholinesterase inhibition, good inhibition of amyloid-β aggregation and the ability to disaggregate preformed amyloid-β aggregates [1709].

**Cinnamon extract** reduced Aβ oligomerization and corrected cognitive impairment in animal models of AD [586].

**Coumarins** are naturally occurring β-secretase inhibitors [587] and acetycholinesterase inhibitors [588].

**Cryptotanshinone** (CTS), an active component of the medicinal herb Salvia miltiorrhiza, inhibited Aβ aggregation and protected SH-SY5Y cells from damage by Aβ [589]. It upregulated α-secretase by activation PI3K pathway in cortical neurons [590].

**Curcumin** showed potent anti-amyloidogenic effects for AD Aβ fibrils in vitro and in vivo [591–605]. Clinical trials in AD patients showed disappointing results [590, 600, 606]. A novel nanoparticle formulation of curcumin (NanoCurc) was developed at the Indiana University School of Medicine [607]. For curcumin-decorated nanoliposomes see [608]. Structure-activity relationships of Aβ aggregation inhibitors based on the curcumin scaffold were presented [609–611].
DL-3-n-butylphthalide (NB Pharmaceuticals, Hebei China) is a natural antioxidant extracted from seeds of *Apium* and a powerful free radical scavenger [413]. It protected dopamine neurons in a rotenone model for PD [414].

**DX-9386** is a traditional Chinese medicinal prescription, which improved thymectomy-induced impairment of learning behaviors in mice [612]. It protected dopamine neurons in a rotenone gated preformed fibrils, and inhibited Aβ$_{42}$-induced cytotoxicity [613].

(-)-Epigallocatechin-3-gallate (EGCG; Sunphenon) present in green tea reduced Aβ-mediated cognitive impairment presumably via flavonoid-mediated presenilin-1 phosphorylation, which reduced Aβ production [614–616]. EGCG prevented lipopolysaccharide-induced elevation of Aβ generation [617]. EGCG remodeled mature α-synuclein and Aβ fibrils and reduced cellular toxicity [618]. The cell signaling pathways and iron chelation were described [582, 619–624]. Also ERK and NF-κB pathways are involved [617]. The structural properties of EGCG-induced, nontoxic AD Aβ oligomers were described [625]. EGCG functions through estrogen receptor mediated activation of ADAM10 in the promotion of non-amyloidogenic processing of AβPP [626, 627]). A special formulation of EGCG in nanolipidic particles to improve its bioavailability was presented [628]. See also Part 1, Chapter 1.9. Drugs interacting with estrogen receptors and Part 1, Fig. 10.

**ESP-102** a standardized combined extract of *Angelica gigas*, *Saussurea chinesis*, and *Schizandra chinensis*, significantly improved scopolamine-induced memory impairment in mice [629]. Aβ$_{42}$-induced memory impairment in mice [630].

An aqueous extract of *Eucommia ulmoides* Oliv. Bark (EUE) showed beneficial effects on learning and memory impairments in mice [631].

**Flavonoids** in AD and neuroinflammation were discussed in depth [621, 632–635]. Some act as acetylcholinesterase inhibitors [636]. Biflavonoids were superior to monoflavonoids in inhibiting Aβ toxicity [637].

**Fortasyn Connect** is a multi-nutrient diet comprising docosahexaenoic acid (DHA), eicosapentenoic acid, uridine-mono-phosphate, choline, phospholipids, folic acid, vitamins B6, B12, C, and E and selenium. It reduced AD-like pathology in young adult AβPP/APPf/Ps1s$_{12}$ mice [638].

**Fulvic acid** inhibited aggregation and promoted disassembly of tau fibrils associated with AD [639].

Gallic acid from grape seed polyphenol extract may be useful for the treatment of AD [583].

**Garlic extract** attenuated the cytotoxicity of Aβ on undifferentiated PC12 cells [640] and suppressed lipoperoxidation induced by Aβ in PC12 cells [641]. It protected against Aβ$_{42}$-induced apoptosis [642]. Garlic extract inhibited Aβ fibril formation and defibrillated Aβ preformed fibrils [643]. Aged garlic extract ameliorated the early cognitive deficits in Tg2576 mice [644, 645]. A review on the "aged garlic extract" was published [646].

**Gastrodin** protected primary cultured rat hippocampal neurons against amyloid-β peptide-induced neurotoxicity via ERK1/2-Nrf2 pathway [1710].

**Ginger root extracts** (Zingiber officinale, Cognition Therapeutics) effects inhibition of Aβ$_{42}$ aggregation (Thomson Reuters Pharma, update of May 23, 2012).

**Ginger biloba** (EGb 761, Tanakan, Tanamin) treatment prevented age-related spatial memory deficits in a transgenic mouse model of AD [647]. It enhanced adult hippocampal neurogenesis and phosphorylation of CREB [648]. For reviews on *Ginkgo biloba* extract and CNS functions, see [649, 650]. For results of clinical studies, see (in chronological order) [651–665].

**Grape-derived polyphenolics** from *Vitis vinifera* grape seeds attenuated cognitive deterioration in a mouse model of AD [666]. Ultrastructural alterations of AD paired helical filaments by grape seed-derived polyphenols was studied [667].

**Guanosine** protected human neuroblastoma cells from oxidative stress and toxicity induced by Aβ peptide oligomers [668].

**Hederacolchidide-E** from *Pulsatilla kororana* showed cognition-enhancing and neuroprotective effects by reversing scopolamine-induced cognitive impairments in rats. It increased viability of human neuroblastoma SK-N-SH cells incubated with Aβ$_{42}$ [536].

**Heme** prevented Aβ$_{42}$ aggregation and its cytotoxicity [669].

**Hopeahainol A** attenuated memory deficits by targeting amyloid β in APP/PS1 transgenic mice [1711].

**ISH-971** (Ocean University of China, Shandong) is a marine sulfated eligosaccharide for the potential treatment of AD [670]. (Thomson Reuters Pharma, update of November 7, 2011).

**HX-106** (HX-106N; ViroMed Co., Seoul) is a natural product inhibiting acetylcholinesterase for the potential treatment of AD (Thomson Reuters Pharma, update of June 13, 2012). The structure was not disclosed.
Hyperoside protected primary rat cortical neurons from neurotoxicity induced by Aβ via the P38/Akt/Bad/Bcl-2L1-regulated mitochondrial apoptotic pathway [671].

IB-10C179 (Instituto Biomar, Leon, Spain) is a compound derived from marine organisms which protected primary neurons from apoptosis and reduced free radical production (Thomson Reuters Pharma, update of March 7, 2012). The structure was not communicated.

Icariin is a flavonoid isolated from Epimedi herba. It inhibited Aβ(25-35)-induced expression of the secretion in rat hippocampus [672]. It attenuated Aβ-induced neurotoxicity by inhibition of tau protein hyperphosphorylation in PC12 cells [673]. It attenuated lipopoly saccharide-induced microglial activation and resultant death of neurons by inhibiting TAK1/IKK/NF-κB and JNK/p38 MAPK pathways [674]. It improved memory impairment in AD model mice and attenuated Aβ-induced neurite atrophy [675]. There seems to be a synergistic effect to improve learning and memory deficits in rats by co-administration of Icariin and Ruta graveolens saponins [676].

IDN-5706, a hyperforin derivative, decreased the content of acetylcholinesterase associated with different types of Aβ plaques in 7-month-old double AβPP69/71×PS1 transgenic mice after treatment with IDN 5706 for 10 weeks [677].

Kaempferol protected PC12 and T47D cells from Aβ toxicity [581, 678, 679]. Loganguin isolated from Coriaria officinalis showed cognitive-enhancing activity in scopolamine-induced amnestic mice [680].

Luteolin exerted ameliorating effects on Aβ-induced impairment of water maze performance and passive avoidance in rats [681–685].

Medical Food Cocktail consisting of the dietary supplements curcumin, piperine, epigallocatechin gallate, α-lipoic acid, N-acetylcysteine, B vitamins, vitamin C, and folate administered for 6 months to Tg2576 mice resulted in improvement of cognitive functioning [685].

Melatonin inhibited AD β-fibrillogenesis [686–689]. The neuro-protective activities of melatonin against the Aβ are not mediated by melatonin membrane receptors. The role of melatonin in AD-like neurodegeneration was described [690–693]. Melatonin facilitated short-term memory [694].

Menthol exerted a protective effect on Aβ-induced cognitive deficits in mice [695]. Morin stabilized Aβ1-42 protofibrils [696]. It inhibited the early stages of Aβ aggregation [697]. It attenuated tau hyperphosphorylation by inhibiting GSK-3β [698].

Myrcetin is a naturally occurring regulator of metal-induced Aβ aggregation and neurotoxicity [699, 700]. Naringin showed memory enhancing activity in mice [701].

NeurocentRX Pharma is investigating a natural product-based compound for the treatment of cognitive diseases (Thomson Reuters Pharma, update of February 17, 2012).

Nordihydroguaiaretic acid inhibited growth arising from direct Aβ protofibril association [599, 702, 703].

O4 (an orexin-related small molecule) was able to convert toxic Aβ oligomers to nontoxic β-sheet-rich amyloid fibrils [704].

Obovatol, a biphenolic compound isolated from Magnolia obovata, attenuated scopolamine-induced cognitive dysfunctions [705], improved cognitive functions in animal models of AD [706], and attenuated LPS-induced memory impairments in mice via inhibition of NF-κB signaling pathway [707, 708].

Oleuropein and derivatives from olives were recognized as tau aggregation inhibitors [709].

Oren-gedoku-to exerts its potential use for the treatment of AD as a weak, reversible inhibitor of indolamine-2,3-dioxygenase [710].

Oroxylin A is a flavonoid compound that is found in the root of Scutellaria baicalensis Georgii. It attenuated the memory impairment induced by transient bilateral common carotid artery occlusion in mice [711].

1,2,3,4,6-penta-O-galloyl-beta-D-glucopyranose is the active constituent of the traditional medicinal herb Paonia suffruticosa. It showed potent Aβ anti-aggregation effects in vitro and in vivo [712].

Piceatannol showed protective effects against Aβ-induced neuronal cell death [713].

Picrococcin, a flavonoid abundant in propolis, protected against Aβ-induced toxicity in neurons [714].

Polyphenol derivatives (Pharma Eight, Nagoya) probably interacted with Aβ through π–π stacking interactions via the aromatic amino acids of Aβ [715]. For a review, see [716] (Thomson Reuters Pharma, update of January 13, 2011).

Procyandins extracted from the lotus seedpod reversed memory impairment in cognitively impaired aged rats associated with decreased hippocampal CREB phosphorylation [717, 718].

Prosapis cineraria (L.) Drue (Leguminosae), a plant of the Thar Desert of India and Pakistan, is used traditionally by local people for the treatment of memory disorders and to arrest wandering of the mind.
The extract exerted significant nootropic activity in the Morris water maze test, which may be attributed to the inhibition of brain acetylcholinesterase [719].

- **Puerarin**, a phytoestrogen isolated from *Pueraria lobata*, attenuated Aβ-induced cognitive impairment [720–723, 1712].
- Quercetin-O-glucoside significantly reduced the generation of amyloid-β peptide [1713].
- Pycnogenol protected neurons from Aβ-induced apoptosis [724].
- Quercetin showed protective effects against Aβ42 in primary neurons [586, 725].
- Rosmarinic acid protected PC12 cells from Aβ-induced neurotoxicity [599, 726]. Subchronic administration of rosmarinic acid, a natural prolyl oligopeptidase inhibitor, enhanced cognitive performance [727].
- Rutin inhibited Aβ aggregation and cytotoxicity, attenuated oxidative stress, and decreased the production of nitric oxide and proinflammatory cytokines [728].
- Saffron from *Crocus sativus* had an inhibitory effect on Aβ aggregation [729, 730]. It was administered to 46 patients with probable AD in a 16-week double blind study (15 mg twice a day). Saffron was safe and effective [731]. A 22 week study corroborated the first results [732]. Saffron may be a source of novel acetylcholinesterase inhibitors [733].
- Salidroside showed neuroprotective effects against Aβ-induced oxidative stress in SH-SYSY human neural roblastoma cells [734].
- S-allyl-L-cysteine, the main constituent of garlic, protected against Aβ-induced apoptosis and attenuated caspase-3 activation, DNA fragmentation and PARP cleavage [648]. It exerted protective effects on Aβ-induced cell death in NGF-differentiated PC12 cells [735] and protected against Aβ-induced neurotoxicity in organotypic hippocampal cultures [736]. For a review on garlic extract and one of its active ingredients, S-allyl-L-cysteine, see [646].
- Silibinin, a flavonoid derived from *Silibum marianum*, prevented memory impairment induced by Aβ1-42 in the Y-maze and novel object recognition tests in mice [737].
- Sinapic acid is a phenylpropanoid compound with anti-inflammatory and neuroprotective effects in a mouse model of Aβ1-42 protein-induced AD [738].
- Souvenaid (Nutricia, Châlet-St-Denis, Switzerland) is a mix of nutrients including the omega-3 fatty acid docosahexanoic acid, 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 [739–741].
- **Substance P**, the tachykinin undecapeptide, protected cerebellar granule cells against Aβ-induced apoptosis [742].
- Syringin from the dried stem barks of *Fraxinus rhynchophylla* protected against Aβ-induced toxicity in neuronal cells [743].
- Tannic acid destabilized Aβ fibrils in vitro [744, 745]. It is a natural β-secretase inhibitor [746].
- α-Tocopherol quinone inhibited Aβ aggregation and cytotoxicity, disaggregated preformed fibrils and decreased the production of ROS, nitric oxide, and inflammatory cytokines [747].
- Thymol showed cognitive-enhancing activity in two rat models of dementia [580].
- Total coptis alkaloids produced a protective effect on Aβ1-25-induced learning and memory dysfunction in rats [748].
- Urosolic acid attenuated Aβ-induced apoptosis in a dose dependent manner [749].
- Vitamin A has anti-oligomerization effects on Aβ in vitro [750].
- Vitamin B12 deficiency is associated with cognitive impairment [1714]. Vitamin B12 supplements administered orally or parenterally at high dose (1 mg daily) were effective in correcting biochemical deficiency, but improved cognition only in patients with pre-existing vitamin B12 deficiency [1715].
- Vitamin D deficiency is associated with increased odds of cognitive impairment [1716–1718].
- *Withania somnifera* (also known as Ashwagandha, an Indian ginseng) is a nootropic agent promoting cognition including memory [751]). *W. somnifera* administered once daily over 30 days reversed behavioral deficits, plaque pathology, accumulation of Aβ peptides and oligomers in the brains of middle-aged and old ADPP/PS1 AD mice. Enhanced expression of low-density lipoprotein receptor-related protein (LRP) in brain microvessels and the Aβ degrading protease nephrilysin occurred 14–21 days after a substantial decrease in brain Aβ levels [752].
- Wuzi Yanzong Granule improved memory function in patients with MCI [753].
- Yokukansan (TJ-54), a traditional Japanese herbal medicine, was tested in clinics for potential anti-dementia effects [754]. Spatial memory in a rat model of early AD was improved [755].
- Zokumei-to (ZMT) attenuated Aβ25-35-induced memory impairment [756].

The Central Drug Research Institute (India) was developing bacosides A and B, which are saponin...
nootropic agents. The compounds were in Phase II clinical evaluation, but it appears that the development was terminated. Also the development of CBNU-06 (Chungbuk University), DCB-AD1 (Development Center for Biotechnology), dyshiberaine (Daichi Suntory Biomedical Research Co., a compound isolated from the Micronesian sponge Dysidea herbacea [757]), of the nordihydroguaiaretic acid derivative EM-4232 (Eromos Pharmaceutical LLC), HSS-808, HSS-818, HSS-838, HSS-848 and HSS-888 (HerbalScienceLLC Singapore; standardized turmeric curcuma longa extracts), of LHM-123 (Mazal Plant Pharmaceuticals), MDF-004 and MDF-005 (Neuron BioPharma), and of YY-1224 and YY-1824 (Ynyu; orally available terpene trilactones extracted from Ginkgo biloba [758]) 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.

LSL-001 (Laboratoire S. Lasnier, Etaules, France) is a nootropic compound in Phase II clinical trials since June 2011 for the potential treatment of AD (Thomson Reuters Pharma, update of June 5, 2012). The structure was not disclosed.

N-251 (Neurokos Inc., Palo Alto, CA) is a compound of an undisclosed mechanism of action for the potential treatment of AD. Phase II clinical trials started in May 2009 (Thomson Reuters Pharma, update of June 1, 2012). The structure of N-251 was not communicated.

PF-0049423 (Pfizer) is a neurorestorative compound for the potential treatment of neurological disorders including stroke recovery. In December 2010, a randomized, double-blind, placebo-controlled Phase II trial was initiated in the US and in South Korea (n = 240) (Thomson Reuters Pharma, update of August 13, 2012). The structure was not communicated.

TPM-189 (Teikoku Pharma USA, San Jose, CA) is a transdermal formulation of a small molecule therapeutic for the potential treatment of AD in Phase II development (Thomson Reuters Pharma, update of May 17, 2012). The structure was not communicated.

VI-1121 (VIVUS Inc., Mountain View, CA) is a nootropic agent in Phase II clinical trials (n = 50) since August 2011 in the US (NCT01428362) (Thomson Reuters Pharma, update of September 9, 2011). The structure of VI-1121 was not communicated.

ASP-0777 (Astellas Pharma) is in Phase I clinical trials since May 2009 (Thomson Reuters Pharma, update of September 19, 2012). The structure was not disclosed.

Lilly is developing a small molecule for the treatment of cognitive impairment in schizophrenia in Phase I clinical trials since July 2012. (Thomson Reuters Pharma, update of November 13, 2012). The structure was not disclosed.

RO-5508887 (Roche) is a nootropic agent in Phase I clinical trials in healthy male volunteers in France since October 2011 (Thomson Reuters Pharma, update of August 16, 2012). The structure was not disclosed.

SEP-363856 (Sunovion Pharmaceuticals, Marlborough MA and Sumitomo Chemical) is an orally active compound with novel mechanism of action for the treatment of schizophrenia. The drug is in Phase I in the US. (Thomson Reuters Pharma, update of November 5, 2012). The structure was not disclosed.

TAK-357 (Takeda) is a cognitive enhancer with unspecified drug target in Phase I clinical development (Thomson Reuters Pharma, update of July 30, 2012). The structure was not communicated.

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

AC-0523 (Neura, a subsidiary of Accera, Broomfield, CO) (Fig. 11) is indicated for the treatment of mitochondrial dysfunction-related HD (Thomson Reuters Pharma, update of February 15, 2012).

AFX-929 (Afecta Pharmaceuticals; Irvine, CA) is a nootropic agent in preclinical development (Thomson Reuters Pharma, update of November 10, 2011). The structure was not disclosed.

Alzheimer’s disease therapeutics (Berg Pharma, Nashville TN) are nootropic compounds for the potential treatment of AD (Thomson Reuters Pharma, update of April 17, 2012). The structures were not disclosed.

Alzheimer’s disease therapeutics (Berg Pharma, Nashville TN) are nootropic agents for the potential treatment of AD (Thomson Reuters Pharma, update of April 17, 2012). The structures were not disclosed.

Alzheimer’s disease therapeutics (Berg Pharma, Nashville TN) are nootropic agents for the potential treatment of AD (Thomson Reuters Pharma, update of August 16, 2012). The structures were not disclosed.

Alzheimer’s disease therapeutics (Berg Pharma, Nashville TN) are nootropic agents for the potential treatment of AD (Thomson Reuters Pharma, update of August 16, 2012). The structures were not disclosed.

Alzheimer’s disease therapeutic program (Reyon Pharmaceuticals, Seoul) is a therapeutic program for the potential treatment of AD (Thomson Reuters Pharma, update of May 17, 2012). The structures were not disclosed.

Alzheimer’s disease therapeutic program (Reyon Pharmaceuticals, Seoul) is a therapeutic program for the potential treatment of AD (Thomson Reuters Pharma, update of May 17, 2012). The structures were not disclosed.

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Alzheimer’s disease therapeutic program (Reyon Pharmaceuticals, Seoul) is a therapeutic program for the potential treatment of AD (Thomson Reuters Pharma, update of May 17, 2012). The structures were not disclosed.
in preclinical development (All three drugs in Thomson Reuters Pharma, update of August 19, 2011). The structures were not disclosed.

**CPC-001** (Chase Pharmaceuticals, Washington, DC) is a compound for the palliative treatment of AD (Thomson Reuters Pharma, update of July 12, 2012). The structure was not disclosed.

**CWF-0804** (JW Pharmaceutical Corp., Choongwae Holdings, Seoul) is a nootropic agent in development for the Korean and Japanese markets (Thomson Reuters Pharma, update of May 11, 2012). The structure was not disclosed.

**D-130** (Envoy Therapeutics, Jupiter, FL) is a compound targeting the cortex region of the brain using bacTRAP technology for the potential treatment of cognition deficits (Thomson Reuters Pharma, update of June 1, 2012). The structure was not disclosed.

**D-180** (Envoy Therapeutics, Jupiter, FL) is a compound targeting the striatum region of the brain using bacTRAP technology for the potential oral treatment of PD (Thomson Reuters Pharma, update of September 12, 2012). The structure was not disclosed.

**GSK-2647544** (GSK) is a neuroprotectant for the potential treatment of Alzheimer’s disease. In October 2012, a single-blind, randomized, placebo-controlled, Phase I trial was expected to begin later that month in Australia in healthy male subjects (expected n = 16). At that time, the trial was expected to complete in April 2013 (Thomson Reuters Pharma, update of November 20, 2012). The structure was not disclosed.

**J-147** (Salk Institute for Biological Studies) (Fig. 11) is a drug that improved memory in normal rodents and prevented cognitive decline in transgenic mice of AD (Thomson Reuters Pharma, update of December 22, 2011).

**JAY 2.22-33** (Medical College of Georgia) (Fig. 11) significantly reduced Aβ toxicity and improved cognitive performances in transgenic AD mice [759].

**JWB1-84-1** (Medical College of Georgia) (Fig. 11) is a tertiary amine analogue of choline from the laboratory of the late Prof. Jerry J. Buccafusco. It produced a dose-dependent decrease in the number of errors made by well-trained AD-transgenic mice in the radial arm water maze test [759, 760].

**KD-901** (Kwang Dong Pharmaceutical Co., Seoul) is a nootropic drug in preclinical evaluation (Thomson Reuters Pharma, update of March 1, 2011). The structure was not disclosed.

**KU-046** (Kareus Therapeutics and Connexios Life Sciences, Atlanta, GA) is a combination drug, which demonstrated significant improvement of cognition (Thomson Reuters Pharma, update of May 29, 2012). The structure was not disclosed.

**LNK-3186 and LNK-3248** (AstraZeneca after its acquisition of Link Medicine Corp., Waltham, MA) are nootropic compounds (For both Thomson Reuters
Pharma, update of July 13, 2012). The structures were not disclosed.

Maltolyl p-coumarate attenuated cognitive deficits in rats treated with scopolamine or with Aβ25-35 (761).

MeN061061-1 (Lijin International Pharmaceutical, Hong Kong) is a small molecule neuroprotectant (Thomson Reuters Pharma, update of June 26, 2012). The structure was not disclosed.

MPP-26 (Met P Pharma, formerly Mattern Pharmaceuticals, Emmetten, Switzerland) is an intranasal gel formulation of pregrenolone for the potential enhancement of memory (Thomson Reuters Pharma, update of January 27, 2012).

NNZ-2591 (Neuren Pharmaceuticals, Auckland, NZ) (Fig. 11) is an orally active neuroprotectant didepiperazine derivative for the treatment of brain injury and PD [762] (Thomson Reuters Pharma, update of August 31, 2012).

NXD-9062 (Nymox Pharmaceutical Corp., Quebec) is a neuroprotectant for the potential treatment of AD (Thomson Reuters Pharma, update of February 22, 2012). The structure was not disclosed.

NXT-182 (Inception Sciences Inc., San Diego) is a novel small molecule neuroprotectant for the potential treatment of CNS disorders, including Alzheimer’s disease, Parkinson’s disease and age-related cognitive decline (Thomson Reuters Pharma, update of October 29, 2012). The structure was not disclosed.

OG-635 (Oryzon Genomics, Barcelona) is a nootropic agent for the potential treatment of AD and PD (Thomson Reuters Pharma, update of May 31, 2012). The structure was not disclosed.

Pentylentetrazole (Balance Therapeutics, Hillsborough, CA) is investigated for the potential treatment of cognitive impairment in Down’s syndrome (Thomson Reuters Pharma, update of September 4, 2012).

PNB-03, PNB-04, and PNB-05 (PharmaNeuroBoost NV, Limburg, Belgium) are nootropic agents for the potential treatment of PD (PNB-03), AD (PNB-04), and obsessive compulsive disorders (PNB-05) (Thomson Reuters Pharma, update of February 1, 2012). The structures were not communicated.

PTI-125 (Pain Therapeutics Inc., Austin, TX) reduced Aβ-related AD pathogenesis by targeting filamin A [763] (Thomson Reuters Pharma, update of August 3, 2012). The structure was not communicated.

RP-4000 (Reviva Pharmaceuticals, San Jose, CA) is a small molecule nootropic agent (Thomson Reuters Pharma, update of December 27, 2011). The structure was not communicated.

SEL-103 (Selvita Life Sciences Solutions, Krakow, Poland and Orion, Espoo, FL) is a program investigating small molecule nootropic agents (Thomson Reuters Pharma, update of July 4, 2012). Structures were not communicated.

SL1-42R (SK Biopharmaceuticals, formerly SK Life Science, Fair Lawn, NJ) is a small molecule nootropic agent (Thomson Reuters Pharma, update of March 19, 2012). The structure was not communicated.

TYP-1 (NOBEL ILAC, Istanbul, Turkey) is a small molecule neuroprotectant (Thomson Reuters Pharma, update of July 30, 2011). The structure was not communicated.

The development of ABHO-08-01 (BTG-1640; Abiogen under license from British Technology Group, BTG), ADS-8703 (Adamas Pharmaceuticals), AIP-002 (American Home Products, Wyeth, now Pfizer), AIT-034 ( Spectrum Pharmaceuticals, formerly NeoTherapeutics), Alzheimer’s disease therapeutics (DuPont/Scios), ALE-26015 (Astellix Pharm-Eco LP), aloracept (Hoechst, now sanofi), Alzene (Bar Ilan University and Iova), AQW-051 (Novartis; Phase II trials for treatment of schizophrenia and PD are ongoing), ASP-2355 and ASP-2905 (Astellas), AVN-397 (Aventive Pharmaceuticals, in Phase II trials for the treatment of anxiety), AWD-23-39 (Alzneimittelwerke Dresden, elbion), AZD-2858 (AstraZeneca), BCE-001 (4-chloro-phenoxy-acetic acid-1,3-bis(dimethylamin)-2-propylester [764–766]), BD-1054 (Russian Academy of Medical Science), BGC-20-0406 (RS-0406; SEN-1269 [767]), BMS-181168 (Bristol-Myers Squibb [768–770]), BW-394-U (Immune Network under license from BTG), CM-2433 (Cenomed, a subsidiary of Abraxis BioScience in collaboration with Medical College of Georgia), CX-417, CX-423 and CX-438 (Cortex Pharmaceuticals), DW-514 and DW-0811 (Daewon Pharm), DWJ-209 (Daewoong Pharmaceutical Co.), of the coumarin derivative ensaculin (KA-672; Dr. Willmar Schwabe [771–777]), ETX-6765 (eTherapeutics), F-94517 (Pierre Fabre), gedocarnil (Bayer Schering Pharma), GM-1416 (GlaxoSmithKline), GR-105 (Howard University and Ivax); HMR-2420 (Hoechst Marion Roussel, now Sanofi-Aventis), HSB-13 (EncephRx, a spin-out of the Southern Methodist University and the University of Texas [1719]), HTC-867 (Wyeth, now Pfizer), IQ-200 and IQ-201 (Immune Network under license from
the University of British Columbia), JNJ-39393406 (Janssen Pharmaceuticals), LX-104 (Laxdale, Amarin Corp.), of the MBARC program (EnVivo Pharmaceuticals), MK-0249 (Merck & Co), MK-5757 (Merck & Co), MG-19649 (Molecular Geriatrics, now Applied Neuro Solutions), MP-100 (Addiction Therapeutics), MR-708 (Medea Research), NDD-094 (Novartis [778]), NeoEA-1001 (neoCodex), nooglutil (Russian Academy of Medical Sciences [779]), NSA-789 (Wyeth, now Pfizer), OF-5858 and OF-6145 (All Russian Research Institute of Pharmaceutical Chemistry), Oligostropin (HF-0420; Loyola University of Chicago), Org 31433 (Organon Bioscienes, now MSD OSS BV), PF-05297909 (Pfizer), Prisotinol (CGS-5649B; Ciba-Geigy, Novartis [780–783]), pro- caine hydrochloride (Samaritan Pharmaceuticals), PRX-4001 and PRX-4006 (Proximagen), R-641 and Ro-40-1641 (both Roche), RU-47067 and RU-52583 (Roussel-Uclaf, now sanofi), sabeluzole (Janssen Pharmaceutica NV, Johnson & Johnson [784–789]), sil- con (Roussel-Uclaf, now sanofi), SN-104 (Sention), SNK-882 (Sanwa Kagaku Kenkyusho), SPP1-339 (SPI-339, NEO-339; Spectrum Pharmaceuticals, formerly NeoThera- peutics), SRA-997 (Novartis), ST-587 (Boehringer Ingelheim), T-9021 and T-9022 (QRxPharma), TAK- 065 (Takeda), tenilsetam (Hoechst Marion Roussel, now sanofi [791, 792]), trifusal (Grupo Uricha), V-0191 (Pierre Fabre) and of Z-4105 (Zambon) were terminated.

**PEPTIDES**

**Cerebrolysin** (Ebewe Pharmaceuticals, Vienna, Austria, launched, available in 1 ml, 5 ml, and 10 ml ampoules and in vials of 30 ml and 50 ml for intramuscular or intravenous injection or intravenous infusion) is “derived through a biotechnological procedure from highly purified porcine brain proteins and is comprised of free amino acids and biologically active, short chain peptides” [793]. Cerebrolysin acted as a presynaptic GABA<sub>a</sub> receptor agonist [794]. The nootropic effects of cerebrolysin were investigated in depth [795–799]. Cerebrolysin protected neurons from ischemia-induced loss of microtubule-associated protein 2 [800]. Effects of cerebrolysin on Aβ deposition in transgenic mice were studied extensively [801–807].

The pharmacology of neurotrophic treatment with cerebrolysin was reviewed [808]. Clinical data were published (in chronological order) [793, 809–823].

First clinical results of a combination treatment of cerebrolysin and donepezil were reported [824]. Data of cerebrolysin in AD were compiled [825]. The safety profile of cerebrolysin in dementia and stroke trials was described [826].

**Cortexin** (Geropharm, St. Petersburg, Russia) is a launched polypeptide with neuroprotective, nootropic and antioxidant properties, for the intra-muscular treatment of central nervous system injury caused by cerebrovascular accidents, encephalitis, encephalopathies, epilepsy and trauma (Thomson Reuters Pharma, update of October 05, 2012). The structure was not communicated.

**Davunetide** (intranasal, AL-108, NAP, Allon Therapeutics, Vancouver) is an 8-amino acid peptide (NAPVSIQP) derived from the activity-dependent neuroprotective protein. A Phase III clinical trial was initiated for the treatment of patients with progressive supranuclear palsy in December 2010. A Phase II clinical trial in AD patients started in January 2007 (Thomson Reuters Pharma, update of July 17, 2012). Allon Therapeutics is also developing injectable intravenous and subcutaneous formulations of davunetide.

There are numerous publications on the extensive preclinical characterization of davunetide describing protection of the brain against ischemic injury in rats [827], inhibition of the aggregation of Aβ [828], decrease of anxiety-like behavior in aging mice [829], reduction of the severity of traumatic head injury [830], reduction of accumulation of Aβ and tau hyperphosphorylation [831–833], stimulation of microtubule assembly [834, 835], enhancement of cognitive behavior in transgenic mice [836], and improvement in motor function and reduction of α-synuclein inclusions in mice overexpressing α-synuclein [837]. Reviews on davunetide were published [838–847]. The effects of davunetide on cognition and functional capacity in schizophrenia were described [848] (Thomson Reuters Pharma, update of September 21, 2012).

**AM-111** (XG-102, D-JNKI-1; Auris Medical and Xigen, a spin off from the Centre Hospitalier Universitaire Vaudois and the University of Lausanne) is an injectable protease-resistant peptidic derivative of the JNK-inhibiting protein IB-1 for the i.v. treatment of acute sensorineural hearing loss, stroke, and AD [849–852]. A Phase IIb trial for acute sensorineural hearing loss was initiated in January 2009 (n = 210) and results are expected in autumn of 2012. Auris Medical
is also investigating a topical gel formulation of AM-111 (Thomson Reuters Pharma, update of August 31, 2012).

**Etanercept** (ENBREL, NK-001; Neurokine Pharmaceuticals, Vancouver) is a recombinant fusion protein of 934 amino acids (mol. weight: 150 kDa) composed of a dimer of the extracellular portion of human TNFR-2 fused to the Cc fragment of human IgG1 [853, 854]. A rapid cognitive improvement following perispiral etanercept administration to 15 probable-AD patients treated once weekly for 6 months was reported [855–857]. See also the commentary [858]. In December 2010, the drug was in Phase II development for the potential treatment of neurocognitive impairment following coronary artery bypass graft surgery (Thomson Reuters Pharma, update of July 9, 2012).

**FGL** (ENKAM Pharmaceuticals, Copenhagen, Denmark) is a peptide neural cell adhesion molecule mimetic for the potential treatment of AD and stroke. In December 2011, clinical studies including three Phase I studies, one proof-of-concept Phase IIa study in AD, and a pilot study in patients recovering from stroke was planned to begin in 2012 (Thomson Reuters Pharma, update of April 23, 2012). Enkam was previously developing FGLL, a peptide neural cell adhesion molecule mimetic, for the potential intranasal treatment of AD and stroke. In May 2005, the drug was shown to be safe and well tolerated in a Phase I study for AD. By December 2011, the drug was no longer being developed due to the lack of flexibility for the route of administration.

**Glypromate** (Gly-Pro-Glu) is naturally cleaved from the N-terminal sequence of IGF-1 and displayed neuroprotective actions in vitro and in vivo [859–861]. It protected against Aβ-induced somatostatin depletion in rat cortex [862, 863].

**NNZ-2566** (Neuren Pharmaceuticals, Auckland, NZ) (Fig. 11) 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 traumatic brain injury, Rett syndrome, PD, and AD [864–867]. Excellent synthetic organic chemistry was described [868–871]. In November 2012 the IND was filed for a Phase II trial. At that time an application was submitted to the Texas Children’s Hospital IRB and enrollment was expected to begin pending approval by the FDA and the Texas Children’s Hospital IRB (Thomson Reuters Pharma, update of November 23, 2012) (Thomson Reuters Pharma, update of August 31, 2012). Neuren is also developing a formulation for intravenous infusion.

There are many peptides in preclinical evaluation for the potential treatment of AD (in alphabetical order):

**AL-408** (Allon Therapeutics, Vancouver) is the orally active D-amino acid derivative of davunetide (AL-108) and an active element of the PARP-1 activating activity-dependent neuroprotective protein (Thomson Reuters Pharma, update of November 9, 2011).

**Alzimag** (IMAGENIUM, Paris, France) is a peptide for the potential treatment of AD (Thomson Reuters Pharma, update of December 22, 2011). The structure of the compound were not communicated.

**C3bot peptides** (Charité Medical School Berlin and Hannover Medical School) are short neuron-specific neurotogenic peptides derived from the C3 exoenzyme of Clostridium botulinum, which transiently activated RhoA for the potential treatment of neurodegenerative disorders including AD, PD, Huntington’s chorea, spinal cord and traumatic brain injury [872–875] (Thomson Reuters Pharma, update of June 7, 2012). COG-112, COG-133, and COG-1410 (Cognosci Inc., Research Triangle Park, NC) are apoE-mimetic peptides that showed consistent reduction of both Aβ deposition and of tau hyperphosphorylation in three tau transgenic mouse models and in two AβPP transgenic mouse models [876, 877] (Thomson Reuters Pharma, update of June 5, 2012 for COG-112 and of September 11, 2012 for COG-133 and COG-1410).

**G-79** (BN-201; Biovare, Barcelona) is a peptide for the potential treatment of multiple sclerosis, ALS, AD, PD, and glaucoma (Thomson Reuters Pharma, update of July 4, 2012).

**KIBRA pathway modulators** (Amnestic Inc., a wholly owned subsidiary of SYGNIS Pharma, Heidelberg, Germany) offer a new genetic link to cognition that may benefit patients suffering from AD. For the association of KIBRA and late onset AD, see [878]; for enhancement of cognition in anxiety disorders [879] (Thomson Reuters Pharma, update of August 14, 2012).

**Leptin** reduced the accumulation of Aβ and phosphorylated tau in rabbit organotypic slices [880–882]. The company Neurotez (Bridgewater, NJ) is investigating leptin as an Aβ synthesis inhibitor for the potential treatment of AD. The company planned to file an IND in 2012. Effects of leptin on memory processing were described [883–885]. Leptin induced proliferation of neuronal progenitor cells [886] (Thomson Reuters Pharma, update of August 24, 2012).
MT-007 (MT-007-LRP1V, recombinant LRP fragments; Socratech LLC, Rochester NY) is produced by stable transfected baby hamster kidney cells expressing LRP-IV. The preparation improved cerebral blood flow, learning and memory in a mouse model of AD (Thomson Reuters Pharma, update of April 23, 2012).

Netrin-1 (BioMarin Pharmaceuticals, Novato, CA, under license from the Buck Institute) interacted with AβPP and regulated Aβ production [887, 888]. Netrin-1 increased soluble AβPPs and decreased Aβ1-40 and Aβ1-42 levels in a 320 mouse model of AD. An intranasal delivery is planned (Thomson Reuters Pharma, update of July 20, 2012).

NNZ-4921 and NNZ-4945 (NRP-2945, an 11-mer; CunoNZ under license from Neuren Pharmaceuticals, Auckland, NZ) are neuronal regeneration peptides for the potential treatment of multiple sclerosis and motor neuron disease, respectively [889] (Thomson Reuters Pharma, updates of June 18, 2012 and September 7, 2012, respectively).

NRG-101 (Mind-NRG, Geneva, Switzerland under license from ProteoSys, Mainz, Germany) is an injectable neuregulin peptide for the potential treatment of PD, AD, and schizophrenia (Thomson Reuters Pharma, update of July 6, 2012).

NT-1 and NT-2 (Neurotez, Bridgewater, NJ) are small peptides, which block the interaction between mutant presenilin and cytoplasmic linker protein 170 (CLIP-170) that is linked to increased Aβ levels (Both Thomson Reuters Pharma, update of June 6, 2012).

NX-210 (Neuronax, Saint Beauzire, France) is the lead compound of a series of peptides for the potential treatment of spinal cord injury and other neurological disorders, such as stroke, AD, PD, and traumatic brain injury (Thomson Reuters Pharma, update of June 29, 2012). The structure was not communicated.

Pepticlere (DP-68 and DP-74; ProteoTech, Kirkland, WA) is the name of small molecule nasal sprays, 6- to 9-mer peptides that inhibit Aβ fibril formation (Thomson Reuters Pharma, update of August 22, 2012). The structures were not disclosed.

PP-0301 (Hybio Pharmaceutical, Guangdong, China) is a polypeptide for the potential treatment AD (Thomson Reuters Pharma, update of September 20, 2011).

RAP-310 (Rapid Pharmaceuticals, Zug, Switzerland) is a small stabilized receptor active peptide targeting the CCR5 receptor for the potential treatment of AD (Thomson Reuters Pharma, update of October 1, 2012). The structure was not communicated.

RG-01, RG-09, and RG-018 (ReGen Therapeutics, London) are neuroprotectant peptides from colostrinin (vide infra) for the potential treatment of neurodegenerative diseases including AD (Thomson Reuters Pharma, update of June 27, 2012). The structures were not communicated.

SX-AZD1 (Serometrix, Pittsford, NY) is a peptide mimetic interacting with APOE4 (Thomson Reuters Pharma, update of July 29, 2011). The structure was not communicated.

XD4 is a heptapeptide isolated from a Ph.D.-C7 library through phage display that rescued memory deficits in AD transgenic mice by significantly inhibiting Aβ42-induced cytotoxicity, increasing microglial phagocytosis of Aβ, and decreasing Aβ-induced generation of ROS and nitric oxide [890].

Colostrinin (ReGen Therapeutics, London) is a polypeptide complex isolated from ovine colostrum containing a high proportion of proline (25%) and hydrophobic amino acids (40%). It is composed of peptides of molecular mass up to 3,000Da. It reduced aggregation of Aβ [891, 892] and alleviated Aβ-induced toxicity [893]. It facilitated learning and memory in rats [894] and chicks [895]. Effects on gene expression were described [896]. Clinical results were presented (in chronological order) [897–901]. Reviews on colostrinin were published [902, 903].

The development of colostrinin for the treatment of AD patients was discontinued. The compound was launched as a nutraceutical in Australia in July 2007 (Thomson Reuters Pharma, update of May 17, 2011).

The development of ANA-1 and ANA-5 (Alzhyme Pty; phage peptides, which bind to Aβ to inhibit its generation of hydrogen peroxide [904], adrenomedullin peptides (National Institutes of Health), AS-602704 (Merck Serono under license from Axonys), C-AVP, (4-9) (Yakult Central Institute for Microbiological Research), ebiratide (Hoe-427; Hoechst, now sanofi; an ACTH (6-9) derivative [905–907], gilatide (a nonapeptide of Axonyx under license from Thomas Jefferson University), metallothionein (Neurosciences Victoria and the University of Tasmania [908, 909]) and of noopept (GVS-111, SGS-111; DVD-111; Sagens Pharmaceuticals under license from the Russian Academy of Sciences; a nootropic dipeptide analogue of picacetam [910–920]) was terminated. The development of NC-1900 (Nippon Chemiphar, the active fragment analog of arginine vasopressin [921–925], PR-21C (Pharmaxon; a polysialylated form of the neural cell adhesion molecule) and of RGX-100 and RGX-200 (RemeGenInc, Inc., Cortica Neuroscience; Aβ production-inhibiting BR12-derived peptides for the intranasal administration to AD patients [926–933]).
was discontinued. The development of SEM-606 (University of Manchester) and of TKP-1001 (EUSA Pharma, formerly Tasliker under license from The Open University) was terminated.

**DRUGS PREVENTING AMYLOID-β AGGREGATION**

Plasma Aβ levels can be linked directly to specific cognitive changes that constitute the conversion from MCI to AD [934–939]. The relationship between atrophy and Aβ deposition in AD was investigated thoroughly [940–942]. A review of the literature correlating Alzheimer disease neuropathologic changes with cognitive status was provided [947]. The molecular and neuropathological mechanisms of amyloid-β and cognition in Alzheimer’s disease were outlined [1720]. A rapid decline of memory in healthy older adults with high amyloid-β load was described [1721], which was more important than ApoE genotype [1722]. Cognitive decline in adults with high amyloid-β load was evaluated [1723]. Aβ assemblies mediated rapid disruption of synaptic plasticity and memory [943]. The topic “Aβ toxicity in Alzheimer’s disease” was reviewed [944, 945]. A critical review on the amyloid cascade hypothesis was published [946]. Although Aβ plaques may play a key role in AD pathogenesis, the severity of cognitive impairment correlates best with the burden of neurofibrillary tangles [947]. The key interactions of apolipoprotein E and Aβ pathology were reviewed [948].

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) 1996: [949], 1998: [950, 951], 1999: [952–956], 2001: [957], 2002: [958–960], 2005: [961, 962], 2006: [963], 2007: [964, 965], 2009: [495, 966–968], 2010: [969–971], 2011: [972, 973], 2012: [974–976].

**Tafamidis** (PF-06291826, Fx-1006, Vyndaquel, Pfizer following its acquisition of FoldRx Pharmaceuticals under license from the Scripps Research Institute) (Fig. 12) is a small-molecule transthyretin stabilizer for the oral treatment of transthyretin familial amyloid polyneuropathy [977–980]. The drug was approved by EMA in November 2011 was launched in Europe in March 2012 [1724]. In June 2012, the FDA issued a complete response letter and requested the completion of a second efficacy study. For the identification of Aβ binding sites on transthyretin see [981]; for transthyretin amyloidosis see [982, 983] (Thomson Reuters Pharma, update of September 25, 2012).

**Eprodisate** (1,3-propanesulfonate diodium salt; NC-503, Fibrillex, Kciata; Celtic Therapeutics, St. Thomas VI under license from Bellus Health) (Fig. 12) is an orally active sulfated glycosaminoglycan mimetic designed to inhibit the formation and deposition of amyloid fibrils. A Phase III study was initiated in December 2010 for the treatment of renal disease in patients with AA amyloidosis [984–987] (Thomson Reuters Pharma, update of September 5, 2012).

**For ARC-029** (Archer Pharmaceuticals, Roskamp Institute, Sarasota, FL; Phase III clinical trials), see Chapter 7, Drugs interacting with Ion Channels (+ Receptors).

**For Davunetide** (intranasal of via i.v. or s.c. administration; Allon Therapeutics, Vancouver, Phase III clinical trials), see Chapter 15, Peptides.

**For APH-0703** (Aphios Corp., Woburn MA), a nanoparticle formulation of APPH-9601 in Phase II clinical trials since May 2010 (Thomson Reuters Pharma, update of July 5, 2012), see Part 2, Chapter 2.35, Drugs interacting with Protein Kinase C.

**Doxycycline hyclate** (Fondazione IRCCS Policlinico San Matteo, Pavia, Italy) is in a Phase II study (NCT01171859) in patients with transthyretin amyloidosis (n=40) since July 2010. At oral doses of 200 mg for three months, doxycycline produced a significantly lower decline in the ADAScog scores in 101 mild-to-moderate AD patients [988] (Thomson Reuters Pharma, update of April 27, 2012).

**ELND-005** (AZD-103; scyllo-inositol, scyllo-cyclohexanexehexol, Elan, Dublin, Ireland, and Ellipsis Neurotherapeutics, formerly Transition Therapeutics, Toronto, Canada) (Fig. 12) is an orally available inhibitor of Aβ peptide aggregation. Results of a Phase II dose-ranging, randomized, placebo-controlled study in 351 patients with mild-to-moderate AD treated for 78 weeks with either 250, 1,000, or 2,000 mg/day were reported. Patients with mild AD receiving 250 mg of ELND-005 had higher scores on the Neuropsychological Test Battery compared with placebo, which were significant. In contrast ADCS-ADL scores were not significant. The two higher doses were discontinued [989]. In August 2012, a Phase II study was initiated in bipolar disorder patients in the US. The study is expected to be completed in August 2014 (Thomson Reuters Pharma, update of September 14, 2012).

The endogenous brain inositols stabilized small aggregates of Aβ, which are non-toxic to NFG-differentiated PC-12 cells and primary human neuronal
Fig. 12. Drugs interacting with amyloid-β.
cultures [990]. In particular scyllo-inositol, when given orally to transgenic mice, reversed AD phenotype, improved impaired cognition, and altered cerebral Aβ pathology [991, 992]. Scyllo-inositol dose-dependently rescued long-term potentiation in mouse hippocampus from the inhibitory effects of soluble oligomers of cell-derived human Aβ [993, 994]. Elevated scyllo-inositol concentrations were found in patients with AD [995].

Syntheses of scyllo-inositol derivatives have been reported [996]. The synthesis of the PET ligand [18F]-1-deoxy-1-fluoro-scyllo-inositol was described [997]. A comparison of three amyloid assembly inhibitors, scyllo inositol, epigallocatechin gallate and the molecular tweezer CLR01 (vide infra) was published [998].

SOM-0226 (SOM Biotech SL, Barcelona) is a drug for the potential treatment of transthyretin amyloidosis in Phase II clinical development (Thomson Reuters Pharma, update of May 30, 2012). The structure was not communicated.

For AAD-2004 (GNT Pharma, Suwon, South Korea) in Phase I clinical trials (Thomson Reuters Pharma, update of May 4, 2012). See Part 2, Chapter 2.34. Drugs interacting with Prostaglandin D & E Synthases, Part 2, Fig. 22.

Beta amyloid modulator (Medipost, Seoul) is in Phase I clinical trials in South Korea since September 2011 for the potential treatment of AD (Thomson Reuters Pharma, update of May 7, 2012). The structure was not communicated.

BLU-8499 (formerly NRM-8499; Bellus Health, formerly Neurochem, Quebec) is a prodrug of tramiprosate (vide infra). 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. The data were reported in January 2011. It showed improved gastrointestinal tolerability and lower inter-individual variability of drug exposure compared to comparable doses of tramiprosate (Thomson Reuters Pharma, update of September 5, 2012).

DWP-09031 (presumed to be DWJ-301; Daewong Pharmaceutical Co. in collaboration with Medifron, both South Korea) inhibited the production and aggregation of Aβ. By January 2012, the Korean FDA had approved an IND for a Phase I trial. The randomized, double-blind, placebo-controlled study (NCT01522586) is planned in healthy male volunteers (n = 64) to assess the safety, pharmacokinetics and pharmacodynamics of DWP-09031 (Thomson Reuters Pharma, update of July 27, 2012). The structure was not disclosed.

For Exebryl-1 (ProteoTech, Kirkland, WA) and China licensee Tasly Pharmaceuticals; in Phase I clinical trials, Thomson Reuters Pharma, update of May 10, 2012), see Part 2, Chapter 2.1.1.2., Dual acetylcholinesterase and Aβ inhibitors.

Systebryl (ProteoTech, Kirkland, WA) is the lead of a series of small molecules including PTI-19 and PTI-51 for the potential treatment of systemic AA amyloidosis. In December 2011, Systebryl was in Phase I studies (Thomson Reuters Pharma, update of December 21, 2011). Structures were not communicated.

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

Alzheimer’s disease therapeutics (BioChromix Pharma AB, Solna, Sweden) are compounds, which achieved a significant reduction in plaque load and neurotrophic Aβ aggregates. (Thomson Reuters Pharma, update of August 24, 2012). The structures were not communicated.

Aβ oligomer cellular prion protein binding inhibitors (AstraZeneca under a sublicense from Axenion Therapeutics under license from Yale University) are interacting with the cellular prion protein, the high affinity receptor for Aβ oligomers [999–1003] (Thomson Reuters Pharma, update of August 17, 2012). No structures were disclosed.

Aβ protein inhibitors (Neurospore Therapies, San Diego CA) are peptidomimetic compounds that interfere with Aβ aggregates (Thomson Reuters Pharma, update of July 16, 2012). Structures were not communicated.

Aβ/tau protein aggregation inhibitors (CNRS, FIST SA, Paris, France) are investigated for the potential treatment of AD (Thomson Reuters Pharma, update of August 24, 2012). Structures were not communicated.

Amyloid-derived diffusible ligands are investigated by Merz Frankfurt, Germany under license from Acumen Pharmaceuticals (Thomson Reuters Pharma, update of June 12, 2012). The structures of the compounds were not communicated.

ARN-4261 (New York University and Aria Neurosciences, Hamden CT) (Fig. 12) and ARN-2966 (Fig. 12) are inhibitors of Aβ aggregation. ARN-2966 reduced Aβ deposition and memory deficit in transgenic mice. Following treatment a significant 25% reduction in Aβ plaque load was noted compared with
mice that received a vehicle control. The data demonstrated that ARN-2966 was biostable and well tolerated in transgenic mice with blood-brain barrier penetration after both oral and intravenous dosing (Thomson Reuters Pharma, update of August 28, 2012).

AVCRI-104P4 (University of Barcelona) (Fig. 12) inhibited Aβ aggregation including acetylcholinesterase- and self-induced Aβ aggregation, β-secretase, acetylcholinesterase, and butyrylcholinesterase (Thomson Reuters Pharma, update of September 28, 2012).

AVN-457, AVN-458 and AVN-492 (Aviscuro Pharmaceuticals, San Francisco) are nootropic agents for the potential treatment of cognitive disorders (Thomson Reuters Pharma, update of October 22, 2012). The structures were not disclosed.

AZP-2006 (AlzProtect, Loos, France in collaboration with INSERM and the University of Lille II) is an AβPP modulator of undisclosed structure (Thomson Reuters Pharma, update of July 4, 2012).

Beta-amyloid aggregation inhibitors (Medisyn Technologies, Minnetonka, MN / Mount Sinai School of Medicine) demonstrated significant Aβ-lowering and anti-aggregation activity in vitro. Two compounds also reduced the amount of Aβ in mouse brain in vivo (Thomson Reuters Pharma, update of June 21, 2012). Structures were not communicated.

Beta-amyloid aggregation inhibitors (Snowdon Inc., Vancouver) are expected to enter Phase I trials in 2012 (Thomson Reuters Pharma, update of August 19, 2011). The structures of the compounds were not communicated.

Beta amyloid beta sheet formation inhibitors (AC Immune, Lausanne, Switzerland) are small molecules, which inhibited the aggregation of Aβ to oligomeric and fibrillar species for the potential treatment of AD and glaucoma [1004]. Two 3-aminoopyrazole moieties carrying additional aryl substituents were connected via a linker. The concept of 3-aminoopyrazoles with a donor-acceptor-donor hydrogen bond pattern complementary to that of the β-sheet of Aβ·S was first investigated by Schrader and colleagues [1005–1013] (Thomson Reuters Pharma, update of September 24, 2012).

Beta-amyloid inhibitor (Icogenex, Seattle, WA) is a small molecule therapeutic that normalizes the production of Aβ (Thomson Reuters Pharma, update of June 26, 2012). The structure was not disclosed.

Beta-amyloid inhibitor (Star Scientific, Glen Allen VI through its subsidiary Rock Creek Pharmaceuticals in collaboration with the Roskamp Institute) reduced Aβ when applied to cells (Thomson Reuters Pharma, update of January 3, 2012). The structure was not disclosed.

Beta-amyloid modulators (Crossbeta Biosciences, Utrecht, The Netherlands) are small molecules, which target Aβ oligomers and misfolded proteins (Thomson Reuters Pharma, update of August 24, 2012). Structures were not communicated.

Beta-amyloid precursor protein modulators (Alzcor Pharmaceuticals, Arlington, MA) are investigated for the potential treatment of AD (Thomson Reuters Pharma, update of July 27, 2011). Structures were not disclosed.

BMS-869780 (Bristol-Myers Squibb) (Fig. 12) reduced Aβ1-42 levels in transgenic mice at oral doses and displayed an IC50 value at Aβ1-42 in the low nM range. It was not hepatotoxic (Thomson Reuters Pharma, update of August 6, 2012).

BT2-EG4 (Johns Hopkins University and Georgetown University) is a benzothiazole aniline derivative and amyloid-β synthesis inhibitor for the potential treatment of Alzheimer’s disease (Thomson Reuters Pharma, update of October 30, 2012). The structure was not communicated.

C36 (Medisyn Technologies, Minnetonka, MN in collaboration with the Mount Sinai School of Medicine) is an Aβ1-40 and Aβ1-42 lowering small molecule for the potential treatment of AD (Thomson Reuters Pharma, update of December 6, 2011). The structure was not disclosed.

Captopril (SP-233; Samaritan Pharmaceuticals, Las Vegas, NV under license from Georgetown University) (Fig. 12), a spirostenol drug, blocked the oligomerization of Aβ1-42 exerting a direct effect on mitochondria [1014–1017] (Thomson Reuters Pharma, update of March 18, 2011).

Carvedilol is a launched unselctive α1, β1 and β2 blocker, which inhibited Aβ fibril formation [1018].

CLR01 (University of Duisburg-Essen, Rensselaer Polytechnic Institute, NY and UCLA) (Fig. 12) is a molecular tweezer, which binds to lysine residues with micromolar affinity and interferes with a combination of hydrophobic and electrostatic interactions that are important in the self-assembly of most amyloidogenic proteins including Aβ, tau, and α-synuclein [1007, 1018–1024].

CLR-097 (Clera Inc., Toronto) inhibited the process of Aβ plaque formation (Thomson Reuters Pharma, update of December 5, 2011). The structure was not disclosed.

Cotinine, a natural metabolite of nicotine, may be a potential new therapeutic agent against AD [1025]. It reduced amyloid-β aggregation and improved memory in Alzheimer’s disease mice [1725].

Daunomycin inhibited Aβ fibril formation [1018].
DBT-1339 (Medifon, Seoul and licensee Daewoong, South Korea) (Fig. 12) is the lead compound from Aβ protein deposition inhibitors (Thomson Reuters Pharma, update of June 1, 2012).

Enoxaparin (Enox, a low molecular weight heparin) lowered brain Aβ load in a mouse model of AD [1026]. It also improved cognition in APPsw/PS1dE9 mice [1027, 1028].

GAG/carbohydrate compounds (ProteoTech, Kirkland, WA) are glycosaminoglycan modulators for the potential treatment of AD (Thomson Reuters Pharma, update of June 7, 2012). Structures were not disclosed.

Galantamine inhibited Aβ aggregation and cytotoxicity [1029].

haw-AD-14 (Hawthorn, Madison, Mississippi under license from CoPlex) is an Aβ synthesis and tau phosphorylation inhibitor (Thomson Reuters Pharma, update of September 26, 2011). The structure was not disclosed.

HO-4160 (University of California at Davis) (Fig. 12) is a spin-labeled fluorene compound that specifically disrupted Aβ oligomers [1030].

Imipramine in part through inhibition of TNFα prevented cognitive decline and Aβ accumulation in a mouse model of AD [1031].

IPS-04001, IPS-04001 and IPS-04003 (InnoPharmaScreen, South Korea) is a specific inhibitor of Aβ peptide and VEGF-165 interaction. By June 2012, in vivo efficacy studies had shown a significantly enhanced effect on the memory of NSE-PS2/N141Ltransgenic mice (Thomson Reuters Pharma, update of July 16, 2012). The structure was not communicated.

KMS-88 series (Hammi Pharmaceutical, South Korea, the Korea Institute of Science and Technology and Seoul National University) (Fig. 12) is a series of aminostyryl-benzofuran derivatives inhibiting Aβ fibril formation [1032, 1033] (Thomson Reuters Pharma, update of September 12, 2012).

Minocycline is a second generation tetracycline that can effectively cross the blood-brain barrier. It improved cognitive impairment in AD models [1034]. It provided protection against Aβ25-35 induced alterations of the somatostatin signaling pathway [1035, 1036]. It reduced microglial activation [1037, 1038] and Aβ derived neuroinflammation [1039]. It recovered MTT-formazan exocytosis impaired by Aβ [1040]. It reduced the development of abnormal tau species in models of AD [1041–1043]. Minocycline protected PC12 cells against NMDA-induced injury via inhibiting 5-lipoxygenase activation [1044, 1045]. Minocycline improved negative symptoms in patients with early schizophrenia [1046]. See also Part 2, Chapter 2.2.5 Drugs interacting with 5-Lipoxygenase.

NPT-4003 (Neurupore Therapies, San Diego CA) is the lead of heterocyclic compounds that interfere with amyloid-β aggregates. Detailed data were presented at the ICAD Vancouver in July 2012 [1726]. (Thomson Reuters Pharma, update of July 16, 2012). The structure was not communicated.

Rifampicin inhibited Aβ aggregation and neurotoxicity [1047–1049]. In a clinical trial in 101 mild-to-moderate AD patients, statistically significant improvements in the ADAScog scores after treatment with 300 mg rifampicin for three months were found [988]. Rifampicin and caffeine caused an upregulation of LRPI [1050]. The brain efflux index of Aβ in rifampicin and caffeine treated mice was significantly higher (82% and 80%, respectively) than the brain efflux index of control mice (62%). It appears that a yet to be identified transporter/receptor plays a significant role in Aβ clearance, which is upregulated by rifampicin and caffeine.

Rolitetracycline is effective as inhibitor of Aβ fibril formation [1031].

SD-1002 (Synaptic Dynamics, Farmington CT) is a lysosomal modulator that reduced protein deposition of amyloid-β1-42 oligomers for the potential treatment of Alzheimer’s disease (Thomson Reuters Pharma, updates of October 22, 2012). The structure was not communicated.

SEN-1500 (Senessis, Cambridge, UK) (Fig. 12) and follow-up compound SEN-1576 (structure not disclosed) are small molecule Aβ aggregation inhibitors [1727] (Thomson Reuters Pharma, updates of March 23 and August 2, 2012, respectively).

Small molecule Aβ modulators (Ascenturon, a spin-out of Merck Serono, Geneva, Switzerland) are drugs for the potential treatment of AD (Thomson Reuters Pharma, update of October 3, 2012). Structures were not disclosed.

SP-08 (Samaritan Pharmaceuticals, Las Vegas, NV under license from Georgetown University) (Fig. 12) is an Aβ antagonist with neuroprotectant properties (Thomson Reuters Pharma, update of March 18, 2011).

TAK-070 (University of Tokyo under license from Takeda) is a β-secretase and Aβ aggregation inhibitor (Thomson Reuters Pharma, update of July 10, 2012). The structure was not communicated.

Tetracycline(s) showed anti-amyloidogenic activity in vitro [1051] and protected Caenorhabditis elegans from Aβ-induced toxicity by targeting oligomers [1052].
For VP-20629 (Indole-3-propionic acid; OX1; IN-OX1; OXIGON, ViroPharma, Exton PA, under license from Intellect Neurosciences under license from New York University and Mindset BioPharmaceuticals; Thomson Reuters Pharma, update of August 10, 2012), see Chapter 11. Antioxidants.

AGT-160 (ArmaGen Technologies, Santa Monica, CA) is a recombinant IgG fusion protein formed by the fusion of a single chain Fv antibody against Aβ plaque formation to the company’s human insulin receptor-targeting monoclonal antibody Trojan horse for transport across the blood-brain barrier for the potential detection and treatment of AD (Thomson Reuters Pharma, update of January 23, 2012). See also Part I. Chapter 1.16. Insulin receptors.

EDN-OL1 (Edun Biotechnology, St. Louis, Missouri under license from St. Louis University) is an antisense oligonucleotide targeting Aβ production, which improved memory and learning in three different AD mouse models. By February 2012, EDN-OL1 had demonstrated activity in patients with Down syndrome (Thomson Reuters Pharma, update of August 24, 2012).

NPT-001 (NeuroPhage Pharmaceuticals, Cambridge, MA) is a filamentous M13 bacteriophage that disrupted plaque aggregation through binding of Aβ. Direct binding of M13 bacteriophage to fibrils of aggregated Aβ was observed with high affinity of 4 nM. In an AD mouse model, Aβ plaques were reduced by 70% after a single intracranial administration (Thomson Reuters Pharma, update of July 16, 2012).

Spheron-based therapeutics (Nymox Pharmaceuticals Corp, Quebec) are compounds capable of blocking the transformation of human spherons into plaques [1053, 1054] (Thomson Reuters Pharma, update of February 22, 2012).

Aβ-aggregation inhibitor research programs were ongoing at Elan [1055], at GreatPharma [1056], at GSK [1057, 1058], at Johnson & Johnson [1059], at Pfizer [1060], at Pharmacia-Farmabitalia Carlo Erba [1061] and at Scios [1062].


Excellent papers on theoretical calculations on Aβ-aggregation inhibitors were published (in chronological order) 2006: [1130, 1131], 2008: [1066, 1132–1134], 2009: [1135–1137], 2011: [1138, 1139] [1140, 1141], 2012: [1142–1144].

The Phase III development of trimipramine (3-amino-1-propanesulfonic acid, homo-taurine, NC-531, Alzheimed, Cerebral; Bellus Health, former Neurochem), an orally available glycysaminoglycan mimic, was terminated in 2007 [1145–1151]. The compound was launched as a nutraceutical for memory protection [1152]. Also the development of ALS-499 and ALS-633 (Advanced Life Sciences, in collaboration with Argonne National Laboratory), amyloid beta aggregation inhibitor (Zyntia), amyloid oligomer specific antagonists (Treventis), amyloid protein deposition inhibitor (ProtoTech), AN-531 (Athena Neurosciences, now Elan Pharmaceuticals), AS-602704 (Ac-FPPFD-NH₂, Merck Serono[1153]), beta amyloid aggregation inhibitors (Novartis), beta amyloid synthesis inhibitors (BTG), CLR-01 (Clear Therapeutics, a spin-off from UCLIA), CT-500 (Creabilis Therapeutics), ID-1135 and ID-1567 (Bellus Health), lysosomal modulators (Synaptic dynamics), MPI-442090 and MPI-442091 (Myriad Genetics in collaboration with the Mayo Clinic), NC-503 and NC-531 (Neurochem; Bellus Health), NHT-0112 (Neuro-Hitech), NOX-A42 (Nexxon Pharma), NVP-AAM147 and NVP-AAM155 (Novartis), phenserine-based amyloid inhibitors (Message Pharmaceuticals), PPI-368, PPI-558 and PPI-1019 (Apoll; all Pracisc Pharmaceuticals [953, 957]), PPI-777 (ProtoTech), Reumacon (Meda under license from Conpharm), Ro-47-1816-001, Ro-65-7652-000, Ro-65-8564-001 and Ro-8815-001 (Roche), RS-1178 (BGC-20-1178), Senexis under license from BTG under license from Sankyo [1154], RS-0406 (BGC-20-0406), Senexis under license from BTG under license from Sankyo [1155–1158] and RS-0466 (Sankyo), RX-AD (Rimonyx Pharmaceuticals), SAN-61 and SAN-161 (Sanomone, a subsidiary of DaMedica), Senapinom (CNI-1493; Cytokine PharmaSciences, CPSI, formerly Cytokine Networks), a cytokine inhibitor, which inhibited Aβ production, plaque formation and cognitive deterioration in an animal model of AD [39, 40, 1729], SEN-304, SEN-606, SEN-1186, SEN-1203.
and SEN-1329 (Senexis), SIB-1848 (SIBIA Neurosciences, now Merck and Bristol-Myers Squibb), SKF-746532 (SmithKline Beecham, now GSK), synthetic anti-beta sheet peptides (Mayo Foundation), THIUR-24 (Thurs Corp.), transthyretin (Research Foundation of the State University of New York), and of VIP-SSM (University of Illinois) was terminated.

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. Considerable evidence suggests that Aβ deposition precedes decline in cognition [1159, 1160]. The development of PET amyloid-β imaging agents was described [1730].

11C-PiB (University Pittsburgh) (Fig. 13) had a Kᵢ = 1.4 nM for AD frontal cortex and Kᵢ = 4.7 nM for Aβ fibrils and did not bind to neurofibrillary tangles [1161]. The log P value is 1.2 [1162]. Patients with AD typically showed a marked 11C-PiB retention (with a significant 1.5 to 2-fold increase) in cortical areas known to contain large amounts of Aβ plaques [1163–1165]. 11C-PiB positivity in MCI indicated already advanced Aβ pathology [1166]. Significant correlations between 11C-PiB retention and CSF biomarkers were found in MCI patients [1167]. Clinical severity of AD measured by the Clinical Dementia Rating scale sums of boxes correlated with 11C-PiB uptake in PET [1168]. 11C-PiB imaging of human immunodeficiency virus-associated neurocognitive disorder was described [1169]. For a direct comparison of 11C-PiB, 18F-Florbetapir, 18F-Florbetaben, and 18F-Flutemetamol, see [1170] for a comparison between Pittsburgh Compound B and Florbetapir see [1731]. "From Alois to Amyvid" see [1734]. PET imaging was also carried out in a murine model of amyloid-β plaque deposition [1735].

FDA approved 18F-Florbetapir as a PET imaging agent to estimate Aβ neuritic plaque density in patients with cognitive impairment on April 6, 2012. Lilly launched the imaging agent in June 2012. The compound will be manufactured and distributed by Cardinal Health [1200] (Thomson Reuters Pharma, update of September 17, 2012). 18F-Florbetaben (18F-BAY 94-972; 18F-AV-1/ZK; Piramal Healthcare, Mumbai, India from an asset acquisition from Bayer under license from Avid Radiopharmaceuticals, Philadelphia, PA, a subsidiary of Eli Lilly, under license from the University of Pennsylvania) (Fig. 13) is a launched 18F PET imaging agent targeting Aβ. It had a Kᵢ of 2.87 nM, did not bind to tau, and can easily be labeled with 18F by an automated synthesis [1179–1187]. By March 2010, more than 700 patients were enrolled in a Phase III trial presumed to be the 18F-AV-45-A07 study. Several clinical papers appeared describing imaging with 18F-Florbetapir [1188–1195]. Correlations between 18F-Florbetapir and FDG images were reported [1196]. 18F-Florbetapir is useful to quantify brain amyloid load [1197]. For a direct comparison of 11C-PiB, 18F-Florbetapir, 18F-Florbetaben, and 18F-Flutemetamol, see [1170]; for a clinical comparison of 18F-Florbetapir and 18F-FDG PET in patients with AD and controls, see [1198]. A prospective cohort study was described [1199].

A longitudinal assessment of 18-month of cognitive decline in mild cognitive impairment and Alzheimer’s disease patients using florbetapir was communicated [1733]. “From Alois to Amyvid” see [1734]. PET imaging was also carried out in a murine model of amyloid-β plaque deposition [1735].

The clinical perspective of imaging with 18F-Florbetapir was described [1211]; for the impact of 18F-Florbetaben PET imaging on confidence in early diagnosis of AD, see [1212].
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Fig. 13. Radioligands for PET scans of amyloid-β.

18F-Flutemetamol (GE-067; GE Healthcare, Chalfont, UK and Universities of Pittsburgh and Uppsala) (Fig. 13) has a Kᵢ of 0.74 nM [1181]. Results of a Phase I study were reported [1213], as were results of a Phase II study [1214, 1215]. In December 2009, a Phase III trial sponsored by GE Healthcare was initiated in the US. By April 2010, Phase III trials were also underway in Europe. In April 2012, preliminary data from the two Phase III studies in terminally ill patients and young healthy subjects were reported. Data showed that the primary endpoint was met. Patients (who underwent brain autopsy) showed concordance between 18F-Flutemetamol PET images and AD-associated Aβ brain pathology and healthy subjects showed concordance with the known lack of brain Aβ. The association between in vivo 18F-Flutemetamol PET imaging and in vivo cerebral cortical histopathology was described [1216], as was a combination of biomarkers PET 18F-Flutemetamol and MRI [1217].

For a direct comparison of 11C-PiB, 18F-Florbetapir, 18F-Florbetaben, and 18F-Flutemetamol, see [1170]. Binary classification of 18F-Flutemetamol PET using machine learning was disclosed [1218]. The pharmacokinetics of 18F-Flutemetamol in wild-type rodents were reported [1219] (Thomson Reuters Pharma, update of October 3, 2012).

18F-AZD-4694 (Navidea Biopharmaceuticals, Dublin, Ohio, formerly Neoprobe Corporation under license from AstraZeneca) is an i.v. PET ligand for the potential imaging of Aβ depositions in AD in Phase II development [1220]. In December 2011, a Phase III program was planned to start in early 2013 (Thomson Reuters Pharma, update of September 21, 2012). The structure was not communicated. For syntheses of additional 18F-ligands of AstraZeneca see [1737].

BAY-1006578 (Bayer) is 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 April 30, 2012). The structure was not communicated. A potential follow up compound is BAY-1008472 [1221].

123I-MNI-168 (Institute for Neurodegenerative Disorders, IND, New Haven, CT) is a SPECT ligand to detect Aβ deposition in patients with AD. A Phase I clinical trial was initiated in the US in January 2009 (n = 34). In February 2011, the trial was terminated (Thomson Reuters Pharma, update of February 10, 2012). The structure was not communicated.
18F-MNI-558 (Molecular Neuroimaging in collaboration with the Institute for Neuro-degenerative Disorders, IND, New Haven, CT) is a PET agent that binds Aβ. The compound was in a Phase 0 trial in AD patients and in volunteers (n = 10) from October 2010 to July 2011 (Thomson Reuters Pharma, update of April 30, 2012). The structure was not communicated. 11C-BF-227 (Fig. 14) was used for amyloid PET imaging [1222-1225], for PET imaging of α-synuclein deposition [1226, 1227], and for in vivo detection of prion amyloid plaques [1228].

129I-DRM-106 (Fujifilm Pharma) (Fig. 14) is a radioiodinated imidazopyridine derivative for the potential use as SPECT imaging agent for Aβ for the diagnosis of AD (Thomson Reuters Pharma, update of September 21, 2011).

18F-Hexethal (Pfizer, under license from the University of Aberdeen), a barbiturate derivative, is an Aβ imaging agent (Thomson Reuters Pharma, update of September 24, 2012).

13C-SB-13 (Fig. 14) was evaluated first in post-mortem brain tissues [1229] and in AD patients [1230]. 18F-Florbetapir dimer (Avid Radiopharmaceuticals, Philadelphia, PA, Eli Lilly) is a PET imaging agent for the potential diagnosis of cerebral amyloid angiopathy [1231] (Thomson Reuters Pharma, update of May 8, 2012).

Dicyanovinylnaphtalenes were described for neuroimaging of Aβ [1232]. Also 18F-labeled benzothiazoles [1233] and 18F-labeled 2-pyridinylbenzoxazoles and 2-pyridinylbenzothiazoles were presented for PET imaging of Aβ plaques [1234].

The development of 11C-AZD-2184 and 11C-AZD-2995 (both AstraZeneca [1235-1237, 1738]) and 18F-FDDNP (Siemens Medical Solutions Molecular Imaging and UCL) (Fig. 14) was terminated. 18F-FDDNP was the first PET tracer used in vivo for detection of cerebral Aβ plaques in 2002 [1238]. 11C-FDDNP binds to Aβ and neurofibrillary tangles in AD, to prion plaques in Creutzfeldt-Jakob disease, to Aβ deposits in cerebral amyloid angiopathy, and to Lewy bodies in PD and DLB [1161]. It was used for measuring amyloid-β and tau levels in adults with Down’s syndrome [1739]. The ligand is still used for prediction of cognitive decline [1174, 1740]. Longitudinal imaging of AD pathology using 11C-PiB, 18F-FDDNP, and 18F-FDG PET was described [1239]. 11C-FDDNP PET allowed a prediction of cognitive decline based on hemispheric cortical surface maps [1240]. 11C-IMPY (Avid Radiopharmaceuticals, Philadelphia, PA, under license from University of Pennsylvania, Fig. 14) is a SPECT ligand for imaging studies [1241, 1242]. Its Kd is 15 nM [1243]. The safety and biodistribution was evaluated [1244]. The signal-to-noise ratio for plaque labeling is not as robust as that of 11C-PiB. 11C-PiB showed a S/N ratio of about 2.5, while 11C-IMPY displayed a ratio of 1.8–2.0, between 30 and 50 min after an i.v. injection [1181]. Its development was terminated.

The development of amyloid binding PET ligands (Aventis, fluoropregnated indolyl-phenyl-acetylenes (Avid Radio-pharmaceuticals), 11C-6-Me-BTA (University of Pittsburgh), and of 11F-SMIBR-W372 (Siemens Medical Solutions Molecular Imaging) was terminated.

Inhibitor of serum amyloid P component binding

The normal plasma protein serum amyloid P component (SAP) binds to fibrils in all types of Aβ deposits and contributes to the pathogenesis of amyloidosis [1245-1247].

Ro-63-8605 (CPHPC; Pentraxin Therapeutics, London under license from Roche) (Fig. 14) is a competitive inhibitor of serum amyloid P component binding to amyloid fibrils (IC50 = 0.9 μM). First results from in vivo mouse and human studies have been communicated [1245, 1248–1250]. In addition, Pentraxin Therapeutics and GSK are investigating a combination of CPHPC with a humanized antibody for the potential treatment of amyloidosis (Thomson Reuters Pharma, update of March 22, 2012).

Vaccines against amyloid-β

AN-1792 (AIP-001; Elian and American Home Products, later Wyeth, now Pfizer) was the first vaccine against AD in clinical trials. The antigen was synthetic Aβ42, which was administered with QS-21 from the Stimulon family of saponins purified from the bark of Quillaja sapomaria as adjuvant [1251, 1252]. Treatment of patients with AN-1792 plus adjuvant and the adjuvant alone as placebo was in a ratio of 4 : 1. 18 patients developed meningoencephalitis probably due to an inappropriate T cell activation and/or the proinflammatory Th1 type of adjuvant. The study was discontinued in March 2002 [1253]. Nevertheless, many important data could be collected. From 129 patients immunized with the drug, 25 were classified as antibody responders after 4.5 years. These patients showed significantly slower decline on the
disability assessment for dementia and a significant difference on a dependence scale compared to placebo-treated patients. Antibody responders also showed less of a decline in a memory test. The scientific harvest of this single clinical trial is listed in chronological order [1254–1286] (Thomson Reuters Pharma, update of August 24, 2012).

**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 aluminum hydroxide. The antibody response is focused exclusively on Aβ and did not show crossreactivity to AβPP [1287, 1288]. A European Phase II clinical trial in 420 patients in Austria, Germany, France, the Czech Republic, Slovakia, and Croatia started in April 2010 (Thomson Reuters Pharma, update of August 1, 2012).

**CAD-106** (Cytos Biotechnology, Zurich and Novartis) is an Aβ1-6 peptide linked to a Qβ virus-like particle for the s.c. treatment of patients with AD. One Phase IIa trial was initiated in July 2008 (n = 27), and a second Phase IIa trial was started in October 2008 (n = 30). The safety, tolerability, and antibody response of active Aβ immunotherapy with CAD-106 in patients with AD was published [1289]. For comments, see [1290, 1291]. It was found that 80% of the patients involved in the trial developed their own protective antibodies against Aβ without suffering any side-effects over the three years of the study. The researchers believe that the CAD106 vaccine is a tolerable treatment for patients with mild-to-moderate 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 [1276, 1292, 1293]. Preclinical results in transgenic mice were presented [1294] (Thomson Reuters Pharma, update of July 26, 2012).

**Vanutide cridificar** (ACC-001, PF-05236806; Janssen Alzheimer Immunotherapy, Dublin, Ireland acquiring Elan’s Alzheimer’s Immunotherapy Program and Pfizer) is a peptide fragment of Aβ conjugated to the mutated diphtheria toxin protein CRM197. The adjuvant is QS-21. In May 2007, a randomized, multicenter, double-blind, placebo-controlled, parallel assignment, safety/tolerability/immunogenicity Phase II trial in patients with mild-to-moderate AD (n = 56) began [1295]. In July 2009, Pfizer began a multicenter, randomized, unblinded, QS-21-adjuvanted, long-term, Phase II trial of vanutide cridificar (3, 10, and 30 microg, im) in patients (n = 160) in the US. At that time the estimated study completion date was September 2014. In August 2009, an additional study

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**Fig. 14. PET and SPECT ligands.**
was initiated in Japanese subjects ($n=32$) [1276] (Thomson Reuters Pharma, update of August 13, 2012).

ACI-24 (AC Immune, Lausanne, Switzerland) is an Aβ1-15 peptide to which on both ends two lysines were attached, which are tetrapalmitoylated on the e-nitrogens. The antigen is embedded in a liposome membrane. Adjuvant is a mixture of the lipids DMPC, DMPG, cholesterol, and MPLA in a ratio of 9:1:7:0.06, respectively [1296, 1297]. The drug restored memory defects of transgenic AD mice. The IgF subclasses of the antibodies generated from the vaccine were mostly IgG2b indicating a non-inflammatory Th2 isotype.

MIV AC Development) is a synthetic human Aβ peptide conjugated to an aluminum-containing adjuvant with or without ISCOMATRIX (an adjuvant containing saponin, cholesterol, and phospholipids) [1299]. Mild-to-moderate AD patients ($n=124$) received six injections/year of increasing doses of either placebo or V-950 in the presence or absence of varying concentrations of ISCOMATRIX in Phase I clinical trials in the US and Sweden over a four year period [1276] (Thomson Reuters Pharma, update of June 25, 2012).

V-950 (Merck, Whitehouse Station, NJ) is an N-terminal Aβ peptide conjugated to an aluminum-containing adjuvant with or without ISCOMATRIX (an adjuvant containing saponin, cholesterol, and phospholipids) [1299]. Mild-to-moderate AD patients ($n=124$) received six injections/year of increasing doses of either placebo or V-950 in the presence or absence of varying concentrations of ISCOMATRIX in Phase I clinical trials in the US and Sweden over a four year period [1276] (Thomson Reuters Pharma, update of February 24, 2012).

There are numerous vaccine preparations in preclinical evaluation (in alphabetical order):

- **ABVac00 and ABVac42** (Araclon Biotech, Zaragoza, Spain) are active therapeutic antibody vaccines awaiting approval for clinical trials [1741] (Thomson Reuters Pharma, update of June 25, 2012).

- **ADepVac** (Ichor Medical Systems, San Diego, CA) is in collaboration with the University of California at Irvine and the Institute for Molecular Medicine is a DNA vaccine using the TriGrid electroporation technology [1300] (Thomson Reuters Pharma, update of July 13, 2012).

- **ALZ-101** (Alzinova, Goteborg, Sweden, a spin-off of MIVAC Development) is a specific oligomer-directed therapeutic vaccine (Thomson Reuters Pharma, update of July 18, 2012).

- **ALZ-301** (Alzinova, Goteborg, Sweden, a spin-off of MIVAC Development) is an Aβ20 oligomer targeted replacement therapy (Thomson Reuters Pharma, update of July 18, 2012).

- **Alzheimer’s disease vaccine** (VLP Biotech, San Diego CA) is a vaccine that activates antibodies against Aβ protein (Thomson Reuters Pharma, update of May 3, 2012).

- **Amyloid-β 3-10 DNA vaccination** (China Medical University, Shenyang) suggested a potential new treatment for AD [1301–1305]. Active immunization with Ankyrin G, a neuronal cytoskeletal protein, with Freund’s adjuvant complete of arcAβ mice reduced Aβ pathology [1306].

- **BAN-2203** (BioArctic Neuroscience, Stockholm, Sweden) is an immunotherapeutic vaccine targeting Aβ prototibrils (Thomson Reuters Pharma, update of January 7, 2011).

- **BBS-1 BACE inhibitor mAb vaccine** (Navsars, Nes Ziona, IL 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 July 30, 2012).

- **C12** (Pharma Bio, Moscow, Russia) is a program of therapeutic vaccines comprised of synthetic peptide fragments of the α7 nicotinic acetylcholine receptor used to generate antibodies that block Aβ binding to neurons (Thomson Reuters Pharma, update of March 29, 2012).


- **MER-5101** (Mercia Pharma, Scarsdale, 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 (Thomson Reuters Pharma, update of January 27, 2012).

- **Mimovax** (MV-01; Affiris, Vienna AT) is an AFFITOPE-based vaccine targeting truncated and modified forms of Aβ (Thomson Reuters Pharma, update of April 2, 2012).
NU-700 (Nuron Biotech, Exton, PA under license from Vitruvian BioMedical under license from the University of Texas Southwestern Medical Center) is an adjuvant free, gene-base (DNA) Aβ1-42 vaccine for the potential treatment or prevention of AD (Thomson Reuters Pharma, update of May 22, 2012).

Recombinant adenovirus vector vaccine (Vaxin, Birmingham, AL in collaboration with AncC Bio, South Korea) elicited an immune response against Aβ using Crucell’s PER.C6 technology for the potential intranasal treatment of AD (Thomson Reuters Pharma, update of May 2, 2012).

RV-03 (Intelligent Neurosciences, New York, NY) is a peptide vaccine developed using the RECALL-VAX technology targeting both Aβ and a truncated delta tau protein (Thomson Reuters Pharma, update of August 21, 2012).

SeV-amyloid beta RNA vaccine (DNAVEC, Tsukuba, Japan) is an intranasal vaccine comprising a Sendai virus vector encoding the Aβ1-40 gene [1308] (Thomson Reuters Pharma, update of September 21, 2011).

Excellent papers on Aβ vaccines from universities were presented (in chronological order) 2000: [1309, 1310]; 2001: [1311]; 2004: Aβ1-42 gene vaccination [1312]; 2005: a synthetic universal Th cell pan HLA DR epitope, pan HLA DR-binding peptide (PADRE), in which the PADRE-Aβ1-15 sequence lacks the T cell epitope of Aβ1-15 [1313]; 2006: an Aβ1-42 derived in alum adjuvant [1314], an intranasal dendritic microrgenic Aβ1-15 vaccine [1315–1319]; 2007: an oral vaccination using a recombinant adeno-associated viral vector carrying Aβ1-42 cDNA (AAV/Aβ1) [1320], a transcutaneous administration of aggregated Aβ1-42 plus the adjuvant cholera toxin [1321], a mannan-Aβ133 conjugate [1322, 1323]; 2008: a DNA epitope vaccine that expresses epitopes of Aβ1-42 [1324]; 2009: K6 Aβ1-30-NH2 in alum adjuvant [1325], an Aβ1-33-MAP peptide to markedly reduce intracellular Aβ deposits [1326], K6Aβ1-30 for immunizations of old primates [1327]. Aβ1-42 vaccinations also reducing mouse tau pathology [1328]; 2010: an oral vaccination with GFP-Aβ [1329], immunization of aged beagle dogs with aggregated Aβ1-42 formulated in an alum adjuvant [1330], active immunization with Aβ1-42 emulsified in CFA containing Mycobacterium tuberculosis extract [1331], lowering of Aβ plaque burden by the sDM1 peptide, a 20 amino acid peptide bound by cytoines that binds tetramer forms of Aβ1-40 and Aβ1-42 amyloids [1332]; 2011: two novel anti-Aβ vaccines consisting of virus like particles [1333], the identification of the shortest Aβ peptide generating specific antibodies [1334]; 2012: preventive immunization of aged primates [1335].

Excellent reviews on Aβ vaccines have been provided (in chronological order) 2001: [1336, 1337]; 2002: [1257, 1338–1341]; 2003: [1342]; 2004: [1343], 2005: [1344–1346], 2006: [1347–1349], [1350], 2007: [1351–1355], 2008: [1356–1359], 2009: [1282, 1360–1363], 2010: [1364–1370], 2011: [1371, 1372–1374], and 2012: [23].

A clinical review of active and passive immunotherapeutic approaches in AD targeting Aβ was presented [1375, 1376].

The development of Aβ retroparticles (University of Heidelberg and Novartis [1377]), Abbild (Vironics), ACC-002 (Elan), AFFITOPE AD-01 (Affiris), Alzheimer's vaccine (Lundbeck under license from Pharmexa), Alzheimer’s vaccine (Mindset BioPharmaceuticals), Alzheimer's disease vaccines (University of South Florida and University of New Mexico), anti-amyloid-β vaccines (Wyeth, now Pfizer and Janssen Alzheimer Immunotherapy), DNA vaccine (University of Texas, Southwestern Medical Center), immunotherapy vaccine (Prana Biotechnology), KNX-Vaccine3A (Kinxsis under license from the University of California at Irvine), PEVIPRO (Pevion Biotech [1378]), PX-106 (Lundbeck/Pharmaexa), and RV-01 (Intelligent Neurosciences) was terminated.

Antibodies against amyloid-β

Bapineuzumab (AA8–001; Janssen Alzheimer Immunotherapy, Dublin, Ireland following the acquisition of Elan’s Alzheimer’s Immunotherapy Program and Pfizer) is a humanized monoclonal antibody raised against eight amino acids in the N-terminus of Aβ for the potential i.v. and s.c. treatment of AD. A Phase III clinical study started in December 2007. The Phase III program included two trials in ApoE4-positive patients (n = 800 in the US and EU) and two in ApoE4-negative patients (n = 1,250 in the US and EU) for 18 months each and three extension studies for both ApoE4 and non-ApoE4 arms with three doses, 0.5, 1, and 2 mg/kg. The highest dose had to be abandoned due to vasogenic edema safety concerns. One extension study started in July 2009 (n = 1,350), two additional extension studies in December 2009 in the EU and Australia (n = 800 and 1,000, respectively). Clinical results from the Phase I and Phase II studies were reported [1276, 1361, 1379–1382] as was a 11C-PiB PET assessment [1383] and the effects on CSF biomarkers [1384]. Reviews on bapineuzumab were published (in chronological order) [23, 1385–1392]. For the scientific basis see the Nature
125I-labeled 3D6, the mouse parent antibody of bapineuzumab, in transgenic mice was reported [1742].

In July 2012, Pfizer reported that the ’392 study in ApoE4 carriers did not meet its primary endpoints. Pfizer, Johnson & Johnson, and Elan announced that development of i.v. bapineuzumab was terminated (Thomson Reuters Pharma, update of September 18, 2012).

Solanezumab (LY-2022430; Lilly) is a mid-domain humanized monoclonal antibody selective for soluble Aβ. Three Phase III studies were initiated in patients with mild-to-moderate AD (n = 1,000) in May 2009, patients received 400 mg of solanezumab or placebo i.v. every 4 weeks for 80 weeks. First results were disclosed (in chronological order) [1276, 1394–1398]. Safety and biomarker effects of solanezumab in patients with AD was communicated [1399]. Solanezumab failed to meet the cognitive and functional primary endpoints of two Phase III AD trials. But it showed a significant reduction in cognitive decline in patients with mild AD. The open-label EXPEDITION-EXT extension trial, which is fully enrolled, will continue as planned (Thomson Reuters Pharma, update of September 18, 2012).

Gantenerumab (R-1450; Roche under license from MorphoSys) is a human anti-Aβ monoclonal antibody. A Phase II clinical trial in Canada (n = 360) was initiated in January 2011. Prodromal AD patients (NCT01224106) are to receive 105 or 225 mg administered by s.c. injection every 4 weeks for 104 weeks to evaluate effects on cognition and functioning, safety, and pharmacokinetics. In June 2012, the trial was expanded to a Phase II/III trial. The trial size will be increased from 360 to 770 participants. The mechanism of Aβ removal was described [1400, 1401]. An expert opinion was provided [1402] (Thomson Reuters Pharma, update of September 5, 2012).

Crenezumab (MABT-5102A; RG-7412; Genentech 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. A Phase II clinical trial (n = 372; NCT01397578) was initiated in April 2011. The first Alzheimer’s Prevention Initiative will study the effects of crenezumab in 300 people from a large family in Columbia with a rare genetic mutation that typically triggers AD symptoms around age of 45. It is a collaboration between the National Institutes of Health (NIH), Banner’s Alzheimer’s Institute, and Genentech over five years starting in 2013. Data and findings will be shared publicly after the study completion. The scientific basis for the selection of crenezumab was published recently [1403] (Thomson Reuters Pharma, update of September 5, 2012).

GSK-933776A (GSK) is a monoclonal antibody for the i.v. treatment of AD and age-related macular degeneration. A Phase II trial (n = 162) of age-related macular degeneration started in the US in August 2011 (Thomson Reuters Pharma, update of August 24, 2012).

The topic intravenous immunoglobulin as a treatment for AD, the rationale and current evidence was described in reviews [1404, 1405, 1743].

Immune globulin intravenous human (IVIg) launched as Gammmagard in the US and as Kiovig in Europe; Baxter International, Deerfield, IL) is a highly purified solvent/detergent-treated, sterile, freeze-dried preparation derived from human plasma for the treatment of primary immunodeficiency disease. This pool of human immunoglobulins obtained from healthy donors contains naturally occurring anti-Aβ antibodies. In a Phase II trial in 24 patients, the eight-person placebo group worsened, whereas the 16 treated patients improved moderately on both cognitive and quality-of-life measures over the first 6 months [1406–1408]. A Phase III clinical trial in AD patients enrolling 390 patients was initiated in September 2008. Trial completion is expected by the end of 2012 (NCT00818862, NCT00299988) [1276]. The first report of long-term (three-year) stabilization of AD symptoms with IVIG (Gammmagard, Baxter), including no decline on measures of cognition, memory, daily functioning, and mood, was reported in 2012 (Thomson Reuters Pharma, update of September 3, 2012).

Octagam (Octapharma, Lachen, Switzerland) is a 10% liquid intravenous immunoglobulin launched for the treatment of primary immunodeficiency. By December 2008, a double-blind, randomized, Phase II clinical trial (NCT 00812565) in 58 patients with AD had been initiated in the US. Clinical data were presented at the AAIC in Paris in July 2011 (Thomson Reuters Pharma, update of April 3, 2012).

Flebogamma DIF 10% (or 5%) (Grifols SA, Barcelona) is a 10% (or 5%) double inactivated and filtered immunoglobulin therapy for the treatment of primary immunodeficiency. Data were presented on a single-center, open-label, pilot study on the use of Flebogamma DIF 0.5 g/kg i.v., q2w for 6 months in AD.
patients (n = 4) (Thomson Reuters Pharma, update of March 23, 2012).

BAN-2401 (Eisai under license from Bioarctic Neuroscience, Stockholm, Sweden) is a humanized monoclonal antibody that targets the large soluble amyloid product (protofibril Ab). A Phase I trial in 80 patients with mild-to-moderate AD began in September 2010. Eisai plans to co-administer BAN-2401 with donepezil and memantine (Thomson Reuters Pharma, update of July 19, 2012).

NI-101 (BiBB-037, BART, Biogen Idec, Weston, MA under license from Neuroimmune Therapeutics, Zurich Switzerland) is a recombinant chimeric human IgG1 mAb targeted against Ab. 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 September 24, 2012).

PF-05236812 (AAB-003; Janssen Alzheimer Immunotherapy and Pfizer) is a humanized monoclonal antibody targeted to the 99 amino acid C-terminal fragment of Ab. In October 2010, a randomized, double-blind, placebo-controlled, adaptive, Phase I trial was initiated in patients with mild-to-moderate AD (n = 80) in the US [1411] (Thomson Reuters Pharma, update of August 16, 2012).

RN6G (Rinat Neuroscience Corp., New York, now Pfizer) is a humanized Ab antibody for the potential i.v. treatment of age-related macular degeneration in Phase I trial (n = 45) since April 2009 in the US. In April 2012, a randomized, double-blind, placebo-controlled, Phase II study was planned in patients with geographic atrophy secondary to age-related macular degeneration (expected n = 276) to assess the safety and efficacy of RN6G [1412] (Thomson Reuters Pharma, update of November 12, 2011).

SAR-228810 (sanofi) is an anti-Ab monoclonal antibody. A randomized, double-blind, placebo-controlled, Phase I trial in patients with mild-to-moderate AD (n = 48) was initiated in Sweden in January 2012. The study is scheduled to complete in December 2013 (Thomson Reuters Pharma, update of July 27, 2012).

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

AE10 (Prana Biotechnology, Parkville, Australia) is a monoclonal antibody targeting a proprietary pathological Ab target epitope (Thomson Reuters Pharma, update of November 2, 2011).

6F6 (GSK) is an anti-Ab monoclonal antibody for the potential treatment of age-related macular degeneration (Thomson Reuters Pharma, update of June 9, 2011).

9D5 (University of Göttingen, MBM Science-Bridge) targets pyro-Glu-Ab peptide oligomers for the potential diagnosis and treatment of AD [1413] (Thomson Reuters Pharma, update of August 7, 2011).

A-887755 (Abbott Laboratories) is an Ab, oligomer-selective, mouse monoclonal antibody generated using a homogenous, synthetic Ab oligomer peptide (Thomson Reuters Pharma, update of February 27, 2012).

A-992401 (Abbott Laboratories) is a mAb targeting the receptor for advanced glycation-end-products (Thomson Reuters Pharma, update of December 1, 2010).

Ab40-4-42 (Bosung Pharmaceutical, Seoul) is a biological therapeutic, which acted by inhibiting Ab aggregation and cytotoxicity (Thomson Reuters Pharma, update of May 14, 2012).

ACU-193 (Acumen Pharmaceuticals, Livermore, CA) is a monoclonal antibody against amyloid-derived diffusible ligands (Thomson Reuters Pharma, update of August 16, 2012).

AD-0802 (Bioarctic Neuroscience, Stockholm, Sweden) is a humanized mAb with affinity for binding to Ab protofibrils. It is a potential follow-up compound to BAN-2401 (vide supra) (Thomson Reuters Pharma, update of January 7, 2011).

AGT-160 (ArmaGen Technologies, Santa Monica, CA) is a recombinant IgG fusion protein formed by the fusion of a single chain Fv antibody against Ab plaque formation to the company’s human insulin receptor-targeting monoclonal antibody Trojan horse for the transport across the blood-brain barrier. A 1 mg/kg i.v. dose of AGT-160 was administered twice a week for 12 weeks to transgenic AD mice resulting in a 40% decrease in the brain concentration of Ab (Thomson Reuters Pharma, update of January 23, 2012). See also Part I. Chapter I.16. Drugs interacting with the insulin receptor.

ALZ-201 (Alzinoval, Goteborg, Sweden, a spin-off of MIVAC Development) is an oligomer-specific Ab monoclonal antibody (Thomson Reuters Pharma, update of July 20, 2012).

Amyloid precursor protein C-terminal fragment-targeted monoclonal antibodies (Ecole Polytechnique Fédérale de Lausanne, EPFL) is a monoclonal antibody targeted to the 99 amino acid C-terminal fragment of AbP (AbPP-C99) (Thomson Reuters Pharma, update of March 31, 2011).

Anti-amyloid beta antibodies (Kyowa Hakko Kirin under license from Immunos Pharma, OncoTherapy Science Inc.) are antibodies targeting Ab.
oligomers (Thomson Reuters Pharma, update of August 6, 2012).

**Brain-targeted BACE1 antibody** (Genentech, Roche Holding) is a bi-specific antibody against BACE1 and the transferrin receptor to allow transcytosis across the blood-brain barrier [1414, 1415] (Thomson Reuters Pharma, update of May 14, 2012). This technique was pioneered by Prof. William M. Pardridge of UCLA [1416–1422].

**CPIHPc+antibody** (Pentraxin, London and GSK) is a combination of CPIHPc, which lowers blood levels of serum amyloid P component (see Chapter 16.2) and a humanized antibody for the treatment of amyloidosis [1249] (Thomson Reuters Pharma, update of March 22, 2012).

**DILX-212** (Delexx Therapeutics, Zurich, Switzerland) is an anti-βAβ antibody fragment (Thomson Reuters Pharma, update of March 29, 2012).

**Fully human monoclonal antibodies** (Intrexon, Blacksburg VI after its acquisition of Immunologix) are targeting βAβ plaques for the potential treatment of AD (Thomson Reuters Pharma, update of June 13, 2012).

**IN-N01** (Intellect Neurosciences under license from Immuno-Biological Laboratories, IBL, New York, NY) is an antibody drug conjugate consisting of a βAβ-specific humanized mAb employing its ANTI-SENILIN technology, for the potential treatment of AD, glaucoma, age-related macular degeneration and traumatic brain injury. In September 2012, Intellect planned to conduct studies in combination with tau mAbs TOC-1 and TauC3 (Thomson Reuters Pharma, update of September 20, 2012).

**IN-N01-OX2** (Intellect Neurosciences, New York, NY) is a humanized IgG4 monoclonal antibody conjugated to melatonin developed using its CONJUMAB-
A technology for the potential treatment of age-related macular degeneration and Alzheimer’s disease (Thomson Reuters Pharma, update of October 2, 2012).

**L-pathomab** (LT-3015; Lpath Inc., San Diego, CA) is a systemic formulation of a humanized anti-lyso-phosphatic acid monoclonal antibody for the potential treatment of fibrosis, ocular inflammation, and CNS disorders including AD [1423] (Thomson Reuters Pharma, update of August 28, 2012).

**MDT-2007** (Medronic, Minneapolis, MN) is a humanized anti-βAβ monoclonal antibody, the humanized version of the mouse mAb 6E10 (Thomson Reuters Pharma, update of January 6, 2012).

**Nanobody therapeutics** (Ablynx, Gent Belgium and licensee Boehinger Ingelheim) are naturally-occurring single chain antibodies of Camelidae. In April 2012, a CTA was submitted to European regulatory authorities for a Phase I study (Thomson Reuters Pharma, update of August 23, 2012).

**NEOD-001** (Onclive Therapeutics, Dublin, Ireland and Neotope Biosciences, South San Francisco, CA and Elan) is a proprietary monoclonal antibody for the potential treatment of AL amyloidosis. In February 2012, the drug was awarded Orphan status by the FDA for AA amyloidosis and AL amyloidosis (Thomson Reuters Pharma, update of June 27, 2012).

**STC-103** (STC Biologics, Cambridge, MA) is a novel Fc fusion protein therapeutic for the potential treatment of AD (Thomson Reuters Pharma, update of August 10, 2012).

Excellent papers on βAβ antibodies from universities and basic research from companies were presented (in chronological order) 1996: [1424, 1429]; 2000: [1393]; 2005: [1426, 1427], 2006: [1428, 1429], 2007: [1430–1441], 2008: [1442–1447], 2009: [1448–1454], 2010: [1455–1460], 2011: [1461–1465], 2012: [1466, 1467, 1744].

Excellent reviews were provided (in chronological order) 2006: [1350], 2007: [1468–1470], 2008: [1356, 1358, 1471, 1472], 2009: [1360, 1361, 1473–1475], 2010: [1369]; 2011: [23, 1371, 1388, 1389, 1476–1478], 2012: [1479]. The challenge of adverse effects of immunotherapy for AD was addressed [1480].

A clinical review of active and passive immunother-apeutic approaches in AD targeting βAβ was presented [1375, 1376].

The development of 11A1 (a monoclonal antibody against the toxic conformer of βAβ; Tokyo Metropolitan Institute of Gerontology, Kyoto University and Immuno-Biological Laboratories), A-11 (βAβ deposition-inhibiting antibody, Kinexis under license from the University of California), AAB-002 (Janssen Alzheimer Immunotherapy and Pfizer), ABP-102 (Abiogen Pharma; a catalytic monoclonal antibody, an abzyme), ACU-5AS, ACU-0101979 and huC091 (Acumen Pharmaceuticals), anti-Aβeta monoclonal antibodies (Mapp Biopharmaceutical in collaboration with Johns Hopkins University), the anti-amyloid beta antibody therapy targeting specific forms of the βAβ parenchymal plaque (Sanofi under license from Rockefeller University), anticalin (Pires, an antibody against residues 16-26 of Aβ), AZD-3102 (AstraZeneca), hapineuzumab (AAAB-001; Janssen Alzheimer Immunno-therapy and Pfizer), beta amyloid deposition-inhibiting antibodies (amyloids, Kinexis), beta amyloid-targeting antibodies (Mindset Biopharmaceuticals), encapsulated scFv
A hallmark of the AD brain is the presence of inclusions within neurons that are comprised of fibrils formed from hyperphosphorylated microtubule-stabilizing protein tau (paired helical filaments and neurofibrillary tangles [1486–1489]). The formation of misfolded multimeric tau species is believed to contribute to the progressive neuron loss and cognitive impairments of AD [1490]. Tau suppression in a neurodegenerative mouse model improved memory function [1491]. The precise composition of the neurotoxic species Tau-P* is not defined yet [1486]. The formation of fibrils formed from hyperphosphorylated microtubule-interacting tau mediations of toxicity, and second, Aβ triggers progressively increased phosphorylation of tau compromising the binding of tau to microtubules leading to increasing dendritic tau levels [1501]. For a very instructive figure depicting these interactions, see [1502]. The synaptic accumulation of hyperphosphorylated tau oligomers is associated with dysfunction of the ubiquitin-proteasome system [1503].

A cascade of biomarkers was proposed: Aβ precedes tau-mediated neuronal injury; Aβ- and tau-mediated abnormalities precede neuroimaging biomarkers such as changes in hippocampal or ventricular volumetry measured by MRI; and all of these precede cognitive change marked by progressive deterioration in episodic memory and other cognitive domains such as executive functions abilities [1504–1506]. In a longitudinal study in 172 participants (AD: n = 41; MCI: n = 85; and normal controls: n = 46), the temporal relations among the four classes of biomarkers were examined. Results indicated that CSF Aβ effects on cognition change were substantially attenuated by CSF tau and measures of brain structure and function and CSF tau effects on cognitive change were attenuated by neuroimaging variables. Contrary to hypotheses, CSF Aβ and CSF tau were observed to have independent effects on neuroimaging and CSF tau had a direct effect on baseline cognition independent of brain structure and function [1507].

Small molecules preventing tau aggregation

**TRX-0014** (methylthioninium chloride, methylene blue, Rembser TauRx Therapeutics, Singapore, a spin-out from the University of Aberdeen) (Fig. 15) is a tau protein aggregation inhibitor. In August 2004, a placebo-controlled, dose-ranging Phase II trial was initiated in subjects (n = 275) with AD associated dementia in the UK. The doses were 30, 60, or 100 mg tid. In July 2007, a Phase II open-label continuation study of two doses of 30 or 60 mg tid gelatin capsules started for 52 weeks. The drug reduced cognitive decline by 81% over 1 year and no significant loss of cognitive function was seen over 19 months [1508, 1509]. In November 2010, the EC granted the drug Orphan status for frontotemporal dementia, progressive non-fluent aphasia and progressive supranuclear palsy. In February 2012, an open-label trial in patients with frontotemporal dementia was ongoing. For the preclinical characterization, see [1510–1516]. Only when levels of soluble tau protein were concomitantly

action with the postsynaptic density protein 95, an interaction required for Aβ toxicity and second, Aβ triggers progressively increased phosphorylation of tau compromising the binding of tau to microtubules leading to increasing dendritic tau levels [1501]. For a very instructive figure depicting these interactions, see [1502]. The synaptic accumulation of hyperphosphorylated tau oligomers is associated with dysfunction of the ubiquitin-proteasome system [1503].

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reduced by a very high concentration of methylene blue cognitive improvement was observed in a mouse model of human tauopathy [1517]. Methylene blue also inhibited the aggregation of Aβ [1518, 1519] (Thomson Reuters Pharma, update of September 10, 2012).

**LMT-X** (TauRx Therapeutics, Singapore) is a potential follow-up compound and produg of Rember. 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 will involve 833 patients with mild to moderate Alzheimer’s disease over 12 months, while the second study will include 500 patients with mild Alzheimer’s disease 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 (Thomson Reuters Pharma, update of November 21, 2012). The structure was not communicated.

**PBT-2** (Prama Biotec Technology, Parkville, Australia) (see Fig. 9) is an oral zinc ionophore metal-protein attenuating compound that reduced levels of soluble Aβ and tau hyperphosphorylation in a Phase IIa study in AD patients. (Thomson Reuters Pharma, update of October 2, 2012) See also Chapter 12. Metal Chelators.

Tidaglutin (NP-12, NP-031112; Nypta, Noscira, previously known as Neuropharma, Madrid) (Fig. 15) is a GSK-3β inhibitor in Phase II clinical trials for AD. Results from the 309-patient study were expected by October 2012. First positive results of a clinical pilot study were reported [1520] (Thomson Reuters Pharma, update of July 23, 2012). See also Part 2, Chapter 2.16. Drugs interacting with GSK-3β.

**BMS-241027** (Bristol-Myers Squibb) is a small molecule microtubule stabilizer aimed at preventing the production of abnormal tau protein. A randomized, double-blind, placebo-controlled Phase I study was initiated in patients with mild AD (expected n = 100) in the US and in Europe in March 2012 (Thomson Reuters Pharma, update of August 6, 2012). The structure was not communicated.

**PP2A stimulator** (Se-015, Ve-015; Velacor Therapeutics, Victoria, Australia) is a selenium derivative acting as protein phosphatase 2A (PP2A) stimulator resulting in dephosphorylation of Akt kinase and tau. By February 2011, a Phase I trial had been completed and the company received the approval to initiate a Phase IIa trial in AD patients in Australia (Thomson Reuters Pharma, update of February 10, 2011). The structure has not been communicated.

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

**Aβ/tau protein aggregation inhibitors** (CNRS, FIST S.A, Paris, France) are investigated for the potential treatment of AD (Thomson Reuters Pharma, update of August 24, 2012). The structures of the compounds were not communicated.

**Astemizole and Lansoprazole** have been found to selectively interact with tau polymers [1521].

**Berberine** attenuated tau hyperphosphorylation in HEK293 cells [1745].

**Bezafibrate** (Bezalip, Bezekol; Boehringer Mannheim, now Roche, co-marketing with Kissie Pharmaceuticals, launched 1977) (Fig. 15), a drug for the treatment of hyperlipidemia, is a pan-P90R agonist, which improved behavioral deficits and tau pathology in P301S mice exerting a preventive effect [1522].

**BLV-0703** (BLV-200703; Bioalvo, Lisbon, Portugal) (Fig. 15) is a tau aggregation inhibitor in preclinical development (Thomson Reuters Pharma, update of May 9, 2011).

**Epothilone** improved microtubule density, axonal integrity and cognition in a transgenic mouse model of tauopathy [1523].

**Fulvic acid** inhibited aggregation and promoted the disassembly of tau fibrils associated with AD [639].

**Insulin intranasal** ameliorated tau hyperphosphorylation in a rat model of type 2 diabetes [1524].

**L-3-n-butylphthalide** reduced tau phosphorylation and improved cognitive deficits in AβPP/PS1-Alzheimer’s transgenic mice [1746].

**NBB BSc584** (TU Darmstadt and Max-Planck-Unit for Structural Molecular Biology Hamburg) (Fig. 15) is a N′-benzylidene-benzohydrazide showing remarkable tau aggregation inhibition (IC50 > 0.97 μM) and paired helical filament depolymerization (DC50 > 1.14 μM), but poor affinity towards Aβ1-42 fibrils (IC50 > 33 μM) [1525].

**NC-11813** (Eli Lilly and Nymirum, Ann Arbor, MI) is an inhibitor of tau exon 10 splicing, which stabilized the tau splice regulatory element (Thomson Reuters Pharma, update of August 10, 2012). The structure was not communicated.

**NP-11001 derivatives** (Noscira, Madrid) act as tau phosphorylation inhibitors (Thomson Reuters Pharma, update of January 12, 2012). The structures were not communicated.

**NPT-002** (NeuroPhage Pharmaceuticals, Cambridge, MA) targets Aβ and tau aggregates for the potential treatment of AD (Thomson Reuters Pharma,
Fig. 15. Molecules preventing tau aggregation.
update of July 16, 2012). The structure was not communicated.

Protein phosphatase methylesterase 1 (PME1) inhibitors (Signum Biosciences and GSK) are small molecules blocking the enzyme which demethylates PP2A. Normally PP2A is almost all methylated, but in Alzheimer’s disease PP2A methylation is reduced in half. The structural mechanism of demethylation and inactivation of protein phosphatase 2a was described [1747–1749] (Thomson Reuters Pharma, update of November 15, 2012). The structures were not communicated.

Protein phosphatase 2A stimulators (Cognosci, Research Triangle Park, NC) inhibit the formation of apoE/inhibitor 2 of PP2A (2PP2A) complex. The topic protein phosphatases and AD was reviewed [1526, 1527] (Thomson Reuters Pharma, update of February 24, 2012). The structures were not communicated.

ReS3-T, ReS8-T, ReS10-T and ReS19-T (remYND, a spin-off from the University of Leuven, Belgium and licensee Roche) are four series of tau detoxifying compounds targeting tau-mediated cytotoxicity (Thomson Reuters Pharma, update of September 14, 2012). The structures were not communicated.

The ReS9-S7 and ReS12-S programs (remYND, a spin-off from the University of Leuven, Belgium and licensee Roche) investigate the attenuation of the cytotoxic effects of α-synuclein aggregation in dopaminergic neurons for the potential treatment of PD (Thomson Reuters Pharma, update of September 14, 2012). The structures were not communicated.

SIG-1012 (Cognosci) and SIG-1106 (Signum Biosciences, Monmouth Junction NJ in collaboration with Princeton Univ.) are phosphoprotein 2A modulators and presumed to also include the PP2A methylesterase 1 inhibitor eicosanoyl-5-hydroxytryptamide (EHT), all extracted from coffee and acting as tau aggregation inhibitors (Thomson Reuters Pharma update of October 11, 2012).

Thiamet-G (Simon Fraser University) is a potent inhibitor of human O-GlcNAcase (Kᵢ = 21 nM) (Fig. 15) and efficiently reduced phosphorylation of tau at Thr231, Ser396, and Ser242 in both rat cortex and hippocampus [1529–1533]. For commentaries, see [1534, 1535]. See also Part 2, Chapter 2.27. Drugs interacting with O-GlcNAcase.

ThQ-4S and ThQ-5S (Fig. 15) interact specifically with oligomeric forms of tau inhibiting their assembly into AD filaments [1536, 1537].

TRx-0237 (TauRx Therapeutics, Singapore) is the lead compound of second-generation tau aggregation inhibitors. Safety and efficacy studies in AD and frontotemporal dementia patients are planned for 2012 (Thomson Reuters Pharma, update of September 25, 2012). The structure was not communicated.

Small molecule Tau protein modulators (Asceneuron, a spun-out of Merck Serono, Geneva, Switzerland) are drugs for the potential treatment of AD (Thomson Reuters Pharma, update of October 3, 2012). Structures were not disclosed.

Small molecule tau modulators (Yuma Therapeutics, Brookline, MA) target neurofibrillary tangles resulting from abnormal forms of the protein tau (Thomson Reuters Pharma, update of March 29, 2011).

Sodium selenate mitigated tau pathology and functional deficits in AD models [1528].

Tau aggregation inhibitors (Catholic University of Leuven, Belgium) are currently in the preclinical Phase (Thomson Reuters Pharma, update of July 30, 2012). Structures were not communicated.

Tau aggregation inhibitors (ProtoTech, Kirkland, WA) have a potential for the treatment of AD (Thomson Reuters Pharma, update of July 30, 2012). Structures were not communicated.

Tau oligomer inhibitors (Oligomix, New York, NY) are presumably curcumin derivatives (Thomson Reuters Pharma, update of April 24, 2012).

Tau phosphorylation inhibitors (ProQinase, Freiburg im Breisgau, Germany) (Fig. 15) reduced in vivo GSK-3β selective phosphorylation of Ser396/Ser404 and Ser262 in the brains of triple transgenic mice after i.p. administration. It appears that the development was terminated (Thomson Reuters Pharma update of October 11, 2012).

Therapeutic program (B & C Biopharm and EquiPharm, both South Korea) is targeting tau kinase (Thomson Reuters Pharma update of May 18, 2012).

Excellent reviews on tau-focused drug discovery and lead compounds (in chronological order) 2004: [1539], 2005: [1540] (benzothiazoles such as N-744, Fig. 15), 2006: [1543]; 2007: [1544–1550], 2009: [1551–1555], 2010: [1556, 1557], 2011: [1558, 1559], 2012: [1560, 1561].

Excellent papers on small molecule inhibitors of tau aggregation were published by researchers at universities (in chronological order) 2004: [1539], 2005: [1540] (benzothiazoles such as N-744, Fig. 15), [1541, 1542] 2006: [1543]; 2007: [1544–1550], 2009: [1551–1555], 2010: [1556, 1557], 2011: [1558, 1559], 2012: [1560, 1561].

Excellent reviews on tau-focused drug discovery for AD were presented (in chronological order) 2000: [1562]; 2002: [1563], 2006: [1564], 2007:
Interestingly, synergistic interactions between repeats in tau protein and Aβ were described [1582]. The development of the tau aggregation inhibitors aminothienopyridazines (University of Pennsylvania), AZD-1080 (AstraZeneca), BPU-410 and BPU-430 (Champions Biotechnology under license from Johns Hopkins University), LDN-33960 (a striatal-enriched protein tyrosine phosphatase (STIP) inhibitor, Yale University), SHT-0112 (Neuro-Hitech), protein phosphatase methylesterase 1 (PME1) inhibitors (Scripps Research Institute and Massachusetts Institute of Technology), SDGI-T200801 and SDGII-T200801 (both Bioalvo), SRN-003-556 (SIRENADE Pharmaceuticals) and of TRx-0037 (TauRx) were terminated.

Ligands interacting with tau

T-777, T-807, and T-808 (Siemens Medical Solution Molecular Imaging) (Fig. 15) are tau-binding molecules as PET tracers for the diagnosis of AD. They are benz[4,5]imidazo[1,2-a]pyrimidines. 18F-T808 displayed a high level of binding affinity (Kd = 22 nM) and good selectivity for tau aggregates over Aβ plaques [1583] (Thomson Reuters Pharma, update of September 19, 2011).

Novel in vivo tau imaging agents 18F-THK-523 (University of Melbourne) [1584] and 13C-THK-951 (Tohoku University) (both Fig. 15) were published [1585] after preliminary results of 2005 [1752] (Thomson Reuters Pharma, update of September 19, 2011). The University of Melbourne is investigating 18F labeled arylquinoline derivatives, such as 18F-THK-5105, 18F-THK-5116, 18F-THK-5117, and 18F-THK-5125 for the potential use in imaging tau deposition in neurofibrillary tangles for AD (Thomson Reuters Pharma, update of June 13, 2012). The structures were not communicated.

Researchers of Amersham (GE Healthcare) published a patent describing ligands with an exceptional selectivity to tau: compound 18 (Fig. 15): Kd = 0.9 nM for tau and Kd = 30 μM for Aβ1-40 [1586].

A 125I-3-oxindole derivative stained neurofibrillary tangles in AD brain sections [1587]. Also bis(arylvinyl)prazinelines, -pyrimidines, and -pyridazines were described as imaging agents for tau fibrils and Aβ plaques [1588] as were 2-styrylidolindol based fluorescent probes [1753].

Research toward tau imaging was reviewed [1553, 1589, 1590] stating that ligand polarizability contributes to tau fibril binding affinity.

Vaccines against tau

Recombinant misfolded truncated tau protein vaccine (Axon Neurosciences, Vienna, Austria) attenuated pathology in vivo in a transgenic rat model of tauopathy (Thomson Reuters Pharma, update of February 17, 2011).

RV-03 (Intelect Neurosciences, New York, NY) is a peptide vaccine developed using the RECALL-VAX technology targeting both the Aβ and a truncated delta tau protein (Thomson Reuters Pharma, update of August 21, 2012). Phosphorylated tau peptides were used to immunize transgenic mice to produce robust anti-neurofibrillary tangle effects [1591].

The development of the chimeric peptide vaccine RV-02 (Intelect Neurosciences) was terminated.

Antibodies against tau and α-synuclein

Humanized tau monoclonal antibodies (AC Immune, Lausanne, Switzerland) had high specific affinity binding to pTau. The compound was out-licensed to Genentech (Thomson Reuters Pharma, update of June 19, 2012).

Lilly presented data on passive immunization with anti-tau antibodies in two transgenic mouse models [1754].

NI-105 (Biogen Idec, Weston, MA through the acquisition of Panima, previously a subsidiary of Neurimmune Therapeutics, Zurich Switzerland) is a human recombinant monoclonal antibody targeted to tau protein created using Neurimmune’s reverse translational medicine platform (Thomson Reuters Pharma, update of May 4, 2012).

PD-0805 (Bioarctic Neuroscience, Stockholm, Sweden) is a monoclonal antibody targeting α-synuclein for the potential treatment of PD and DLB (Thomson Reuters Pharma, update of September 2, 2011).

Pfizer presented the first X-ray structure of an avian antibody to its cognate phosphopeptide pT231/pS235 at 1.9 Å resolution [1755].

T01-OX2 (Intelect Neurosciences, New York, NY) is an antibody drug conjugate that consists of a mAb targeting oligomeric forms of tau protein conjugated to melatonin (Thomson Reuters Pharma, update of August 17, 2012).
TaurC3 monoclonal antibody (Intellect Neurosciences, New York, NY under license from Northwestern University) is targeting the neoeptope tauC3 (Thomson Reuters Pharma, update of September 20, 2012).

Tau protein modulator (iPierian, South San Francisco, CA) is a monoclonal antibody for the potential treatment of AD, frontotemporal dementia and progressive supranuclear palsy (Thomson Reuters Pharma, update of May 22, 2012).

Tau-targeted antibody therapy (Neotope Biosciences, South San Francisco, CA and Elan) is a monoclonal antibody targeted to tau (Thomson Reuters Pharma, update of August 13, 2012).

TOC-1 (Intellect Neurosciences, New York under license from Northwestern University) is a tau-oligomer-targeting monoclonal antibody [1592, 1593] (Thomson Reuters Pharma, update of September 20, 2012).

The detection of naturally occurring anti-tau antibodies was described [1594].

Already in 1985 monoclonal antibodies to AD neuropil tangles were described [1595]. Excellent papers on passive immunization targeting pathological phospho-tau protein were published (in chronological order) 2005: [1596], 2007: [1597], 2008: [1598, 1599], 2009: [1600, 1601], 2010: [1602, 1603], 2011: [1604–1607], 2012: [1756].

The development of TTR3/78F (University of Porto), an anti-transthyretin monoclonal antibody, was terminated.

STEM CELLS

Substantial progress has been achieved in research for stem cells for the potential treatment of AD communicated in chronological order: 2000: [1608], 2001: [1609–1611], 2006: [1612–1614], 2007: [1615, 1616], 2008: [1617, 1618], 2009: [1619–1622], 2010: [1623–1630], 2011: [1631–1635], 2012: [1636–1642, 1757].

Human neural stem cells overexpressing choline acetyltransferase restored cognitive function in kainic acid-induced learning and memory deficits in rats [1643, 1644]. Neural stem cells reduced hippocampal tau and reelin accumulation [1645]. Intracerebral transplantation of bone marrow-derived mesenchymal stem cells reduced Aβ deposition and rescued memory deficits in AD mice by modulation of immune responses [1626]. Neural stem cells improved cognition via BDNF in a transgenic model of AD [1646–1648]. Human neural stem cells genetically modified to express human NGF gene restored cognition in mice [1649]. Human neural stem cells genetically modified to overexpress BDNF promote functional recovery and neuroprotection in a mouse stroke model [1650]. Neural stem cells improved learning and memory in rats with AD [1651] and improved neuronal survival in cultured postmortem brain tissue from aged and AD patients [1652].

Induced pluripotent stem cells may be used to model patient-specific AD in vitro [1653, 1654]. For a commentary, see [1655]; to model pathology in Down syndrome [1656] and in HD [1657]. They may create new opportunities for disease modeling and drug discovery [1758].

GDNF/BDNF-producing glial and brain-derived stem cells (NurOwn, BrainStorm Cell Therapeutics, New York, NY) is investigated as a potential treatment of PD, sciatica, and multiple sclerosis [1658, 1659]. A Phase III clinical trial in ALS patients started in June 2011 in Israel. In January 2012 positive data were reported (Thomson Reuters Pharma, update of July 24, 2012).

Human neuro stem cell therapy (HuCNS-SC; StemCells, Newark, CA, formerly CytoTherapeutics under license from NeuroSperes) is a proprietary transplanted 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 [1759] and in the human brain [1760]. A Phase II trial for spinal cord injury was initiated in Switzerland in March 2011. The neuroprotective effects in retinal degeneration were described [1660] (Thomson Reuters Pharma, update of September 28, 2012).

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 expected to be completed in February 2013 (Thomson Reuters Pharma, update of April 11, 2012).

NSI-189 (Neuralstem, Rockville, MD, in collaboration with Japanese licensee Summit Pharmaceuticals) (Fig. 16) is an orally bioavailable small-molecule neuroregeneration stimulator in Phase I, which was completed in October 2011. The FDA approved the Phase Ib trial in December 2011 (three cohorts of eight patients each). In June 2012, the first patients were dosed (Thomson Reuters Pharma, update of September 28, 2012).

NSI-566RSC (Neuralstem, Rockville, MD) are human neural stem cells including spinal cord stem
Fig. 16. A neurogenesis stimulator and two SV2A ligands.

cells for the potential injectable treatment of ALS, stroke, HD, and AD. Long-distance growth and connectivity of neural stem cells after severe spinal cord injury were investigated [1661]. A Phase I clinical trial for ALS started in January 2010 in the US. The results of a Phase I trial in 12 ALS patients receiving lumbar intraspinal injection of neural stem cells were described [1662] (Thomson Reuters Pharma, update of September 28, 2012).

**Neurostem-AD** (Medipost, South Korea) 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 AD-type (Thomson Reuters Pharma, update of September 25, 2012).

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

**Adult mesenchymal precursor stem cell therapy** (Mesoblast, Melbourne, Australia and Cephalon, a wholly-owned subsidiary of Teva) is evaluated for the potential treatment of AD and PD and stroke (Thomson Reuters Pharma, update of September 6, 2012).

**Allogenic umbilical cord stem cell therapy** (U-CORD; CellPraxis Biogenentharia, Bela Vista, Brazil) is investigated for the potential treatment of Alzheimer’s disease. (Thomson Reuters Pharma, update of November 07, 2012).

**Brain-derived stem cell therapy** (Celprogen, San Pedro, CA, in collaboration with the Indiana University School of Medicine) can be differentiated into neurons. *In vivo* preclinical studies demonstrated improvement in short and long term memory in AD experimental models (Thomson Reuters Pharma, update of July 14, 2011).

**CPG23NEUR** (Celprogen, San Pedro, CA) derives from cord blood stem cells, which are trans-differentiating into neuronal cells (Thomson Reuters Pharma, update of January 30, 2012).

**Glia progenitor cell therapy** (Q Therapeutics, Salt Lake City, UT) has the potential to replace myelin on damaged neurons for the treatment of transverse myelinitis, spinal cord injury, multiple sclerous, PD, and AD (Thomson Reuters Pharma, update of January 20, 2012).

**Human neural progenitor cells** (Cedars-Sinai Medical Center, Los Angeles, CA), which secrete growth factors including glial cell-derived neurotrophic factor, may be useful for the treatment of ALS (Thomson Reuters Pharma, update of July 31, 2012).

**Human umbilical cord blood cells** (Saneron CCEL Therapeutics, Tampa FL) are cerebroprotective agents which showed cognition enhancing and amyloid-β reducing activities for the potential treatment of stroke and Alzheimer’s disease (Thomson Reuters Pharma, update of October 26, 2012).

**NBI-18** (NeoCytex Biopharma, Covington, KY), a heterocyclic pyrimidine derivative, is a stem cell stimulator for the potential treatment of neurodegenerative diseases including ALS, AD, and PD (Thomson Reuters Pharma, update of January 19, 2012). The structure was not communicated.

**Neural stem cell therapy** (Stemedica Cell Technologies, San Diego, CA) is an allogenic therapy for the potential treatment of AD (Thomson Reuters Pharma, update of February 22, 2012). Another stem cell therapy is evaluated for spinal cord injury (Thomson Reuters Pharma, update of February 28, 2012).

**NeurotrophinCell** (Living Cell Technologies, Auckland, NZ) is an alginate-microencapsulated porcine choroid plexus cell product for the potential treatment of neurodegenerative diseases including HD, PD, and dementia [1663, 1664] (Thomson Reuters Pharma, update of May 16, 2012).

**NGN-9079** (neural stem cell therapy; NeuroGeneration, Los Angeles, CA) is evaluated 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 March 2, 2012).

**ReN-004** (ReNeuron, Guildford, UK) is a neural stem cell therapy for PD and AD (Thomson Reuters Pharma, update of September 5, 2012).

**ReN-005** (ReNeuron, Guildford, UK) is a neural stem cell therapy for HD (Thomson Reuters Pharma, update of December 24, 2010).

**Stem cell therapeutics** (Samaritan Pharmaceuticals, Las Vegas, NV) are non-embryonic neuronal stem cell differentiation therapeutics including the naturally occurring compounds SP-sc4 and SP-sc7 to induce stem cell differentiation for the potential treatment of AD (Thomson Reuters Pharma, update of March 16, 2011).

**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 [1665–1667].

**Granulocyte colony-stimulating factor** is known to mobilize hematopoietic stem cells from the bone marrow into the peripheral blood. Subcutaneous administration of granulocyte colony-stimulating factor into two different Aβ-induced AD mouse models substantially rescued their cognitive/memory functions [1668].

**Valproic acid** can induce neurogenesis of neural progenitor/stem cells both in vitro and in vivo via multiple signaling pathways [1669].

The development of GRN0PC-1 (Geront, oligodendrocyte precursor cells differentiated from a human embryonic stem cell line that produce neurotrophic factors and remyelinate axons for the potential injectable treatment of PD, stroke, AD, multiple sclerosis, and spinal cord injury in Phase 1 since October 2010 was terminated. Also the development of the human embryonic stem cell therapy (GRNC-1, Geront), the cell-based therapy MDA-200C (Medea Therapeutics), NEBO-176 (Neuro Bioscience and RLI), propentofylline (Endogenous Stem Cells Activators (ESAI) under license from sanoite) and of stem cell therapies for glaucoma, macular degeneration, PD, traumatic brain injury, and vascular dementia (Stemedica) was terminated.

**MISCELLANEOUS**

**Autophagy inducer JRP-900** (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 July 23, 2012). The structure was not communicated. For reviews on autophagy in Alzheimer’s disease and tauopathies see [1761–1764].

**Cellular homeostasis modulator CNS-102** (Coyote Pharmaceuticals) acts on protein misfolding for the potential treatment of AD, multiple sclerosis, and ALS (Thomson Reuters Pharma, update of October 2, 2012). The structure was not communicated.

**Glycan inhibitors** (Stelic Institute, Tokyo) are investigated for the potential treatment of Parkinson’s and Alzheimer’s disease. An exhaustive review was provided [1765]. (Thomson Reuters Pharma, update of October 16, 2012). Structures were not communicated.

**Macrophage migration inhibitory factor (MIF) inhibitor INV-88** (Innovoimmune Biotherapeutics, New York) is investigated for the potential oral treatment of inflammatory diseases, central nervous system diseases including Alzheimer’s disease and multiple sclerosis and age-related macular degeneration (Thomson Reuters Pharma, update of October 18, 2012). The structure was not communicated.

**MicroRNA (miRNA) mimetics** (University of Göttingen, MBM Science) are evaluated for the potential diagnosis and treatment of memory impairment. By June 2012, proof of concept was achieved in an AD mouse model and in human AD patient samples. The relationship of miRNAs in the brain and Aβ generation was discussed [1670] (Thomson Reuters Pharma, update of August 7, 2012).

**Proteosome-gating modulators** are investigated by Proteostasis Therapeutics, Cambridge, MA under license from Harvard University for the potential treatment of neurodegenerative diseases including AD and PD (Thomson Reuters Pharma, update of August 15, 2012).

**Synaptic vesicle glycoprotein 2A (SV2A) ligand leviteracetam** (L-059, Keppra; UCB Pharma, Brussels, Belgium and Japanese licensee Otsuka) (Fig. 16) is an antiepileptic drug launched in the US and EU in 2000 and in Japan in 2010 [1671–1676]. It binds to the same binding site as botulinum neurotoxin A and tetanus neurotoxin [1677, 1678]. It is still unclear how leviteracetam modulates SV2A’s function(s). It inhibited presynaptic Ca2+ channels through an intracellular pathway [1679, 1680]. It may promote glutamate uptake by increasing glutamate transporter expression [1681]. There are hints that leviteracetam may interact with GABAA receptors [1682–1684].

Leviteracetam had a positive impact on emotional learning and memory in naïve mice [1685] and
reversed cognitive deficits in hAβPP transgenic mice [1686]. Levetiracetam improved cognitive function in drug-naïve epilepsy patients [1687] and in children aged 4 to 16 years [1688]. The sales of levetiracetam reported by UCB for 2011 were EUR 1.345 million and by Osuka, USD 60.5. An injectable formulation was launched in the US in August 2006, an extended release formulation in September 2008 (Thomson Reuters Pharma, update of October 1, 2012).

Low-dose therapy Levetiracetam (AgenBio, Carmel, IN under license from John Hopkins University) is investigated for the potential treatment of amnestic MCI (aMCI) in Phase II clinical trials since December 2009 in 144 aMCI patients in the US. Reduction of hippocampal hyperactivity in aMCI patients by using a low dose of levetiracetam improved cognition [1766]. It appears that the development was terminated (Thomson Reuters Pharma, update of September 7, 2011).

Brivaracetam (UCB-34714; Rikelta; UCB Pharma, Brussels, Belgium) (Fig. 16), the n-propyl analogue of levetiracetam, is an orally active ligand of synaptic vesicle protein 2A (SV2A) currently in Phase III clinical trials for the treatment of epilepsy since November 2008 (n = 600). The study is expected to complete in June 2015 [1689, 1690]. Its binding characteristics as a high affinity SV2A ligand in rat, mouse and human brain were reported [1691] as was its effect on the inhibition of Na+ currents [1692]. Its neurocognitive effects were similar to the ones of levetiracetam [1693, 1694] (Thomson Reuters Pharma, update of August 8, 2012).

CONCLUSION

Two products were launched in 2012: tafamidis (Vyndaquil, Pfizer) for the treatment of transthyretin familial amyloid polyneuropathy in Europe in March and 18F-flurbeta 1 (Amyvid; Avid Radiopharmaceuticals, Lilly) as a PET imaging agent to estimate Aβ neuritic plaque density in patients with cognitive impairment in the US in June.

Phase III Alzheimer’s disease trials of a disease modifying drug, the monoclonal antibody against Aβ solanezumab (Lilly), are completed. Two Phase III monoclonal antibody agents, 18F-flurbeta 1 and 18F-flutemetamol (GE Healthcare), may be successfully completed by next year. The completion of Phase III clinical trials of the VMAT2 PET ligand 18F-florbetaben (Avid Radiopharmaceuticals, Lilly) is planned for September 2014.

Two Phase III clinical trials of other disease modifying drugs, of monoclonal antibodies against Aβ gantenerumab, crenezumab, GSK-93377A, intravenous immune globulin, and octagam, of vaccines against Aβ AD-02, CAD-106, and vanutide crizilfcar and the PET ligand 18F-AZD-4694 (Navidea) will require several years. This applies also for the Phase II clinical trials of small molecules preventing Aβ aggregation or inhibiting formation of transthyretin amyloid fibrils, such as doxycycline hyclate, ELND-005, and SOM-0226 or preventing tau aggregation, such as PBT-2, tidegulib, and TRX-0014.

Concerning drugs for palliative treatment of AD, two Phase III compounds are currently frontrunners, DP-b99 (a calcium and zinc chelator) and SK-PC-B70M (a natural product) followed by 22 Phase II compounds, RV-208 (a gene expression stimulator), ARC-029 and ZSET-1446/ST-101 (calcium channel blockers), CERE-110, GM-607, PYM-50058, and T-817MA (trophic factor stimulators), circadin, KD-501, PFL, PEX-200, resveratrol, RPh-201 (natural products), LSL-001, N-251, PF-03049423, TRM-189, VI-1121 (nootropics), davunetide, AM-111, etanercept, and FGL (peptides).

DISCLOSURE STATEMENT

Authors’ disclosures available online (http://www.j-alz.com/disclosures/view.php?id=1543).

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