Drugs of the Future 2011, 36(9): 719-722
Copyright © 2011 Prous Science, S.A.U. or its licensors. All rights reserved.
CCC: 0377-8282/2011
DOI: 10.1358/dof.2011.36.9.1688492

MEETING REPORT

ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE

JULY 16-21, 2011, PARIS, FRANCE

J. Burt and C. Dulsat

Thomson Reuters, London, UK/Barcelona

CONTENTS

SUMMARY

The Alzheimer's Association is the world's largest private, nonprofit funder of Alzheimer's disease (AD) research. The Alzheimer's Association International Conference (AAIC), previously known as the International Conference on Alzheimer's Disease (ICAD), brings together thousands of experts to share information and findings, and contributes to the Alzheimer's Association's commitment to stimulate and expedite the development of new treatments, and ultimately a cure. This report covers some highlights from Monday's poster presentations.

Correspondence: Jessica Burt, Thomson Reuters, 77 Hatton Garden, EC1N 8JS London, UK. E-mail: jessica.burt@thomsonreuters.com.

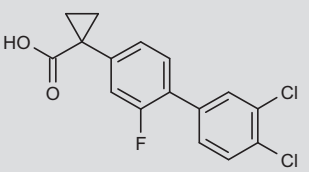
γ-SECRETASE MODULATORS FROM ROCHE

One of the physiological characteristics of Alzheimer's disease (AD) is the formation of extracellular β-amyloid (Aβ) plaques in the brain. Aβ is produced by the cleavage of amyloid precursor protein (APP) by β- and γ-secretase. γ-Secretase is therefore an attractive therapeutic target for AD. A poster presented by Anja Limberg (F. Hoffmann-La Roche) described an HTS campaign to identify modulators of γ-secretase rather than inhibitors, as inhibition of γ-secretase produces toxicity in the gut, spleen and thymus. By modulating γ-secretase activity, shorter nontoxic Aβ fragments are produced rather than toxic $Aβ_{42}$.

An initial HTS hit had an $Aβ_{42}$ IC_{50} value of 800 nM. Potency was improved by replacing the oxadiazole head group with an imidazole (IC_{50} = 100 nM) and replacing the aminothiazole core with an aminopyrimidine (IC_{50} = 180 nM). In transgenic mouse models of AD these compounds demonstrated brain activity, as well as significant activity on $Aβ_{42}$ in the cerebrospinal fluid (CSF) of nontransgenic rats. The most active compound described had an $Aβ_{42}$ EC_{50} value of 0.10 μM and demonstrated dose-dependent efficacy in transgenic APPswe mice, lowering levels of $Aβ_{42}$ and increasing $Aβ_{38}$ in the brain. CSF $Aβ_{42}$ levels were reduced in nontransgenic rats for longer than 8 hours. The pharmacokinetic profile of this compound in mice included a half-life of 4.1 hours (p.o.), a steady-state volume of distribution of 1.6 L/kg, 58% oral bioavailability, a clearance of 8.5 mL/min/kg and a C_{max} of 190 ng/mL.

CHF-5074 WELL TOLERATED IN PHASE I TRIAL

Clinical data on another γ-secretase modulator, **CHF-5074**, previously shown to reverse memory deficits and inhibit brain plaque deposition in transgenic mouse models of AD, were presented by



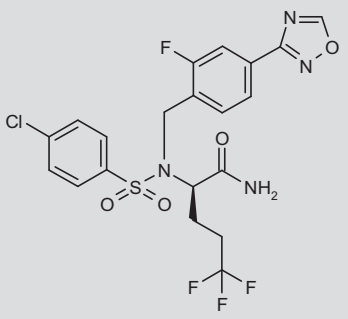
CHF-5074

Bruno Pietro Imbimbo (Chiesi Farmaceutici). A double-blind, placebo-controlled phase I ascending-oral-dose study of CHF-5074 was undertaken in 48 healthy males. Three doses were evaluated (200, 400 and 600 mg/day for 14 days), with 12 patients administered CHF-5074 at each dose level and 12 patients in total receiving placebo. The study has been completed and the maximum tolerated dose (MTD) was not reached. There were no serious adverse events; the most common mild to moderate adverse event was diarrhea. C_{max} values were 56.3, 88.7 and 151 μM and AUC values were 621, 948 and 1530 μM.h for doses of 200, 400 and 600 mg, respectively. Peak plasma levels of CHF-5074 were reached 2-3 hours after administration, with the terminal half-life being approximately 30 hours. Metabolite levels, which accounted for approximately 25% of parent compound, peaked 4-5 hours after administration. Systemic exposure was proportional to dose.

QT_C STUDY OF BMS-708163 SHOWS IT TO BE SAFE AND WELL TOLERATED

Gary Tong (Bristol-Myers Squibb) presented clinical data on **avagacestat** (BMS-708163), a γ-secretase inhibitor in phase II development for the treatment of AD. In a randomized, double-blind, 4-period, 4-treatment, crossover study, healthy subjects (N = 62) received 4 single doses of either 200 or 800 mg avagacestat as an oral solution, moxifloxacin (400 mg, open-label) or placebo, each separated by a 14-day washout period. The 200- and 800-mg avagacestat doses showed C_{max} values of 670 and 3072 ng/mL, t_{max} values of 1.18 and 1.67 hours and $AUC_{(0\text{-}72\ h)}$ values of 6562 and 32,852 ng.h/mL, respectively.

Serial triplicate and single 12-lead safety ECG measurements were collected during the study, with primary outcome measures being the change from baseline in QT_c and the time-matched difference between this mean change after administration of avagacestat or moxifloxacin and placebo. Of the enrolled subjects, 55 completed the study. Moxifloxacin confirmed assay sensitivity. The higher dose of avagacestat did affect heart rate (< 10 bpm) during on-treatment, but both doses of avagacestat were safe and well tolerated, with no clinically relevant effect on QT_c interval.



Avagacestat

AD IMMUNOTHERAPY: VANUTIDE CRIDIFICAR PRODUCES IMMUNE RESPONSE

Anti-Aβ active immunization is a potential therapeutic approach to AD. Immunization of patients with AN-1792, full length $Aβ_{1\text{-}42}$, led to reductions in brain Aβ levels in patients with an immune response. However, 6% of patients developed signs of meningoencephalitis, possibly caused by an Aβ-directed cytotoxic T-cell response, leading to the discontinuation of development. Michael Hagen (Pfizer Vaccines Research) described efforts to circumvent T-cell activation by using a shorter Aβ fragment (the first 7 amino acids from the *N*-terminal [DAEFRHD]) conjugated to a mutant diphtheria toxin carrier (CRM197) to produce the active vaccine construct vanutide cridificar (ACC-001, PF-5236806; Janssen Alzheimer Immunotherapy/Pfizer).

In a PDAPP mouse model, animals administered vanutide cridificar produced an immune response; administration of the QS-21 adjuvant further enhanced relevant titers. Plaque levels were decreased and cognitive impairment reversed following vanutide cridificar immunization. Vanutide cridificar, alone and with QS-21, was also tested in nonhuman primates. Vanutide cridificar + QS-21 produced measurable anti-Aβ titers without an anti-Aβ-directed T-cell response.

OGA INHIBITORS FROM SUMMIT OFFER A NEW APPROACH TO AD TREATMENT

In the brains of people with pathologically confirmed AD, phosphorylation levels of soluble tau are higher than in healthy brains and there is significantly less *O*-linked *N*-acetylglucosamine (*O*-GlcNAc) on the protein. Inhibiting tau hyperphosphorylation therefore offers a potential therapeutic approach to the treatment of AD and significant research is under way in this area. A poster presented by Jon Tinsley (Summit Pharmaceuticals) detailed a different approach in which the *O*-GlcNAcase (OGA) enzyme is inhibited in order to modulate the dynamic balance between phosphorylation and *O*-GlcNAcylation of tau.

Summit used its Seglin (second-generation leads from iminosugars) technology platform to identify several series of OGA inhibitors with moderate potency (IC_{50} = 16-230 μM). Optimization efforts led to four compounds with improved potency and selectivity; for example, SEG-4 had an OGA IC_{50} value of 0.01 μM, an OGA K_i value of 0.072 μM and selectivity in excess of 28,500 for OGA over β-hexosaminidase subunit alpha/beta (HEXA/B), an *N*-acetylhexosaminidase with a similar catalytic mechanism. Treatment of SH-SY5Y cells with the optimized compounds (10 μM for 4 hours) resulted in 1.6- to 2.2-fold increases in levels of cellular *O*-GlcNAc and no cytotoxicity was observed. Compounds significantly reduced tau phosphorylation (measured at Thr231) in an SH-SY5Y human (h) Tau441 Val337Met/Arg406Trp cell line which overexpresses the longest hTau isoform in a hyperphosphorylated state. To verify that this reduction was not due to tau kinase inhibition, SEG-4 was screened against a panel of kinases. Minimal inhibition was observed, indicating that the compounds work via OGA inhibition. Optimization of the compounds is ongoing.

$GABA_A$ RECEPTOR INVERSE AGONIST DEMONSTRATES IN VIVO PROCOGNITIVE EFFECT

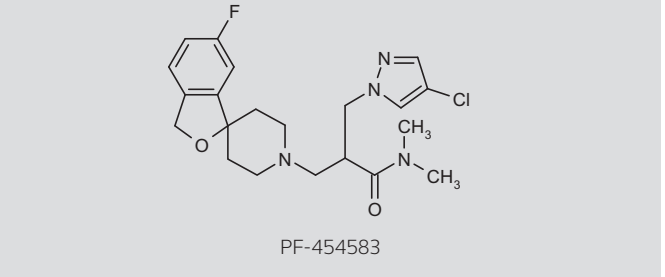
Cholinergic dysfunction contributes to memory impairment, one of the major characteristics of AD. Inverse agonism of central benzodiazepine receptors (allosteric modulatory sites on $GABA_A$ receptors) to produce a positive effect on cholinergic transmission could provide a potential therapeutic approach. Yuki Hatayama (Dainippon Sumitomo Pharma) detailed the identification of AC-4402 as a selective central benzodiazepine receptor ligand which acts as a partial inverse agonist of the $GABA_A$ receptor. AC-4402 (3 and 10 μM) augmented long-term potentiation in the CA1 region of the hippocampus. In the mouse Y-maze test, oral administration of AC-4402 (0.03, 0.1, 0.3 and 1.3 mg/kg) reversed scopolamine-induced memory impairment; flumazenil, a specific central benzodiazepine receptor antagonist, reversed this activity. The same dose levels demonstrated procognitive effects on MK-801-induced memory impairment. Oral doses of AC-4402 (10 and 30 mg/kg) dose-dependently enhanced acetylcholine release in the hippocampus in freely moving rats.

POTENT 5-HT_4 RECEPTOR AGONIST FROM SUVEN

Procognitive activity has been demonstrated for 5-HT_4 receptor agonists in various animal models; these agonists activate a secretase enzyme, thereby shifting APP from an amyloidogenic to a nonamyloidogenic pathway. Ishtiyaque Ahmad (Suven Life Sciences) presented preclinical data on SUVN-1004028, a potent and selective 5-HT_4 receptor agonist. This compound had a good pharmacokinetic profile, with a 5 mg/kg i.v. dose having a half-life of 1.09 hours, an $AUC_{(0\text{-}24)}$ of 537 ng.h/mL, a clearance of 155 mL/kg/min and a V_{ss} of 12 L/kg. The profile of a 10 mg/kg oral dose included 60% bioavailability, a C_{max} value of 526 ng/mL, a t_{max} value of 0.3 hours and an $AUC_{(0\text{-}24)}$ of 644 ng.h/mL. SUVN-1004028 demonstrated effective brain penetration, with levels of 230 and 270 ng/mL in the plasma and brain, respectively, 1 hour after administration. Working memory deficit induced by scopolamine was reversed by SUVN-1004028 at doses of 1, 3 and 10 mg/kg in the radial arm maze task. Episodic memory deficit induced by time was also reversed in the novel object recognition task. Acetylcholine levels were augmented by the compound and there was dose-dependent augmentation of soluble APP levels in the brain. No adverse effects on QT_c and blood pressure were observed at tested doses (3 mg/kg i.v. in guinea pigs).

NOP RECEPTOR ANTAGONIST FROM PFIZER

A novel therapeutic approach to treating the cognitive symptoms of AD could be to antagonize the opioid receptor NOP (ORL1). Allen Duplantier (Pfizer) explained that the challenges of such an approach are securing sufficient selectivity for NOP over μ and δ opioid receptors, without compromising potency, at the same time as obtaining a desirable physicochemical profile that enables oral dosing and brain penetration. In the rat Morris water maze, the NOP antagonist **PF-454583** (0.1 and 0.32 mg/kg), with a K_i value of 8 nM, showed some activity in reversing scopolamine-induced deficits; the effect was of similar magnitude to donepezil (3.2 mg/kg). Administration of a dose of 1 mg/kg s.c. of this compound to rats produced a brain:plasma ratio of 2.6 and 85% receptor occupancy. It was concluded that NOP receptor antagonism has potential as a safe therapeutic approach for AD.



PF-454583

PHYTOESTROGEN FORMULATION TACKLES SYMPTOMS OF MENOPAUSE AND AD

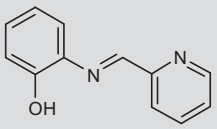
Decreasing hormone levels following menopause has been identified as a risk factor for the development of AD, an observation supported by the fact that two-thirds of AD patients are female. Liqin Zhao (University of Southern California School of Pharmacy) detailed the discovery of an estrogen receptor-β (ERβ)-selective phytoestrogenic formulation, referred to as phyto-β-SERM, with therapeutic potential for the prevention and/or alleviation of symptoms of both menopause and AD. A 9-month study in female normal menopausal mice (ovariectomized) fed with phyto-β-SERM showed that the formulation improved general and neurological health: spatial learning and memory in a Y-maze two-trial recognition memory test were improved; body weight was unaffected; there was increased expression of proteins involved in neural plasticity and amyloid degradation (brain-derived neurotrophic factor, neprilysin, insulin-degrading enzyme, synaptophysin); and phosphatidylinositol 3-kinase (PI3K)/serine/threonine-protein kinase (Akt)/glycogen synthase kinase-3 β (GSK-3 β)-mediated insulin signaling and glucose uptake in the cortex was promoted.

In a second study, female 3xTG mice (a novel triple-transgenic model of AD) were fed phyto-β-SERM again for a period of 9 months. The formulation improved general health and reduced neurological changes in the animals, preventing weight loss associated with disease progression, promoting survival (15% mortality in control arm compared with 0% in treatment arm at 3 months) and improving spatial learning and memory in a Y-maze two-trial recognition memory test. Amyloid deposition and plaque formation in the hippocampus were attenuated, and the expression of pro-AD genes was downregulated and the expression of anti-AD genes was upregulated in the cortex of treated animals.

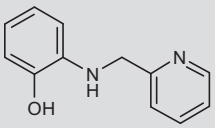
The phyto-β-SERM formulation, which is comprised of three phytoestrogens, is currently undergoing phase I/II clinical testing in menopausal and postmenopausal women. A phase I study is examining its safety and pharmacokinetic profile and will determine dosage. The phase II portion is a proof-of-concept study evaluating the effect of the agent on hot flashes and cognition.

INHIBITING Aβ AGGREGATION

Martin Sadowski (New York University School of Medicine) presented research carried out in collaboration with Aria Neurosciences to develop a blood–brain barrier-permeable, small-molecule inhibitor of Aβ aggregation for the potential treatment of AD. Compound



ARN-4261



ARN-2966

libraries containing multi-aryl and heteroaryl groups were screened for Aβ aggregation-inhibitory activity and for toxicity in human neuroblastoma SK-N-SH cells. **ARN-4261**, identified as a lead compound, demonstrated neuroprotective effects on excitatory synapses in an 18-day in vitro study in primary hippocampal neuronal cultures exposed to Aβ. This compound was further modified to produce **ARN-2966**, which showed comparable Aβ anti-aggregation potency but improved physicochemical properties. A dose of 5 mg/kg i.v. of ARN-2966 in mice had a half-life of 6.13 hours, a t_{max} of 0.25 hours, a C_{max} (plasma) of 1031 μg/L, an AUC of 1229.78 μg/L.h and a clearance of 4.07 L/h/kg. An oral dose of 25 mg/kg in mice had a half-life of 3.59 hours, a t_{max} of 0.50 hours, a C_{max} (plasma) of 2658 μg/L and an AUC of 3947.65 μg/L.h. Brain C_{max} values were 21.4 and 12.5 μg/kg for the i.v. and p.o. doses, respectively, suggesting that the compound can cross the blood–brain barrier. Studies in AD transgenic mice were ongoing at the time.

M_1 RECEPTOR AGONIST FROM GSK IMPROVES EPISODIC MEMORY

Muscarinic acetylcholine M_1 receptors, which are highly expressed in the hippocampus, play an important role in modulating learning and memory, and are altered in neurodegenerative diseases such as AD. GSK-1034702 (GlaxoSmithKline) is a potent M_1 receptor allosteric agonist with a pEC_{50} value of 8.1 at the human M_1 receptor and > 100-fold selectivity over M_2, M_3, M_4 and M_5 receptors. Pradeep Nathan (GlaxoSmithKline/University of Cambridge) presented the first clinical data on this compound from a study in healthy smokers (N = 20; smoking at least 10 cigarettes/day for at least 1 year) using the nicotine abstinence model of cognitive dysfunction. In this double-blind, randomized, placebo-controlled study, subjects received GSK-1034702 (4 or 8 mg) or placebo and were assessed using the Cogstate neuropsychological tests of episodic memory, attention, working memory and executive function. In this model, nicotine absence for 12 hours significantly reduced both immediate and delayed recall compared with baseline (nicotine on-state). Immediate recall was significantly improved by 8 mg of GSK-1034702, but delayed recall was not improved. Other cognitive tasks were not modulated by either nicotine abstinence or GSK-1034702. GSK-1034702 was well tolerated, the most common adverse events being headache, fatigue, salivary hypersecretion and hyperhidrosis. It was concluded that the study provided some evidence that M_1 receptor agonism may constitute a therapeutic approach to AD.

H_3 RECEPTOR ANTAGONIST FROM GSK SHOWS ONLY MODERATE CLINICAL ACTIVITY

Richard Allan Grove (GlaxoSmithKline) presented clinical data on the histamine H_3 receptor antagonist GSK-239512 from a 16-week, double-blind, randomized, parallel-group study. Subjects with mild to moderate AD (N = 196) were administered once-daily oral GSK-239512 (n = 97) or placebo (n = 99). A 4-week flexible titration period (10, 20, 40 or 80 μg GSK-239512) was followed by a 12-week maintenance phase. Primary endpoints were change from baseline in executive function/working memory and episodic memory composite scores from the Cogstate battery at week 16. Study completion rates for GSK-239512- and placebo-treated subjects were 85% and 88%, respectively. The incidence of adverse events, while generally low, was higher for GSK-239512 compared with placebo in the first 2 weeks, particularly those in the psychiatric system organ class. During the maintenance phase rates of adverse events were similar between treatment arms. Mild to moderate effects on some measures of the computerized Cogstate battery were observed in the GSK-239512-treated arm, but other noncomputerized measures showed no separation at week 16.

DISCLOSURES

The authors state no conflicts of interest.

The website for this meeting can be found at http://www.alz.org/aaic/overview.asp.