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THE 9TH INTERNATIONAL CONFERENCE ON ALZHEIMER'S AND PARKINSON'S DISEASES (AD/PD) 2009

THE LATEST NEWS FROM TWO DISEASE FRONTS

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CONTENTS

ABSTRACT

The 9th International Conference on Alzheimer's and Parkinson's Diseases (AD/PD), held in Prague on March 11-15, 2009, offered scientists and clinicians the opportunity to explore the common ground between Alzheimer's disease and Parkinson's disease in terms of conceptualizing the diseases, their symptoms and pathophysiology. Everything from the history of dementia research in Bohemia to the latest compounds under preclinical and clinical investigation as treatments was covered in oral and poster sessions. In addition to a sampling of some of the most interesting of these sessions, this report provides an overview of EU-funded projects in Alzheimer's disease research.

INTRODUCTION

Projected onto the walls of the main conference hall, the symbol of this year's international AD/PD conference was a design in which the distinctive church steeples of Prague, the host city, were in silhouette and contained within the outline of a brain. Indeed, with the view of the city's Castle District from the large picture windows of the congress center, and the castle's fairy tale-like appearance, it would be tempting to conclude that the city exists only in the mind. But a step outside into the brisk March air and a quick walk through the center of town and one is excited to find it is all wonderfully real.

The Alzheimer's disease (AD)/Parkinson's disease (PD) conference provides a special opportunity to examine two different disease entities at the same meeting, allowing specialists in each area to learn from each other and find similarities in conception, investigation and treatment. This year's conference was titled Alzheimer's and Parkinson's Diseases: Advances, Concepts and New Challenges. Apart from covering these areas in oral and poster sessions, this year's conference also included sessions where younger investigators could meet with well-known professors. Here we provide an overview of select oral sessions and data on treatment candidates in preclinical and clinical investigation for AD, PD or related diseases. A review of EU-funded AD research projects closes the report.

ORAL SESSIONS I

The first lecture of the congress was given by Pavel Kalvach of Charles University in Prague, who provided an overview of the history of research into dementia in Bohemia and nearby regions (1). Later presentations would make clear that a fundamental problem in dealing with dementia in past centuries –how to accurately conceptualize the disease– is still a problem in AD and PD research. Investigation into neurological disorders can be said to have begun in the 18th century in Prague, but through the better part of the following century it was framed more in terms of psychiatry. These periods were characterized by various misinterpretations and holes in understanding: inborn and acquired illnesses were not differentiated, and "idiocy" and epilepsy were thought to be the same. Research was hampered by the fact that few people lived long enough to manifest the symptoms of acquired dementia, and the fact that the formal testing of intelligence did not begin until the end of the 19th century. The term dementia was nevertheless first used in 1798, although it was not related to age, and the term "dementia praecox" was coined in 1851.

Neurology in this part of the world would start to come into being in the late 19th century, the first major work in Czech being published in 1897, and the figure of Arnold Pick standing out as a leading scientist in the field. Dr. Kalvach also described a curious historical discovery: that of the advanced work of Oskar Fischer, who, among other things, provided detailed descriptions of plaques. Fischer died tragically in a concentration camp during the Second World War, and his contributions were forgotten until very recently.

John Hardy stood in for Dennis Selkoe as the next plenary speaker, giving a presentation on Lewy body PD disease as a disorder of ceramide metabolism (2). Dr. Hardy contended that PD is defined clinically, by symptoms and by the response to levodopa, when it should be defined pathologically. An overview of genetic mutations linked to PD was provided, starting with the first such link described in 1997, through the more recent description of glucocerebrosidase mutations. Dr. Hardy then pointed out how nearly all of the gene links to Lewy body disease are connected to ceramide metabolism. Whole-genome studies have been and continue to be conducted to further flesh out these connections. At the moment, genetic studies indicate that ceramide metabolism is a potential common pathway, although the leucine-rich repeat serine/threonine-protein kinase 1 *LRRK1* gene does not appear to fit the pattern.

The last of the plenary speakers was Werner Poewe of the Medical University of Innsbruck, who discussed possible future directions for PD investigation (3). Parkinson's disease was described (much more clearly than dementia) in the 19th century, and some effective treatments were available in that century. However, the biggest breakthrough came in the 1960s with the experimental use of levodopa. Although the effects were often dramatic, it still took years for the treatment to be accepted. The incidence of motor complications has been an important drawback to levodopa use. This led in turn to the search for more effective levodopa administration strategies. Failing these, a patient can undergo surgery in the form of deep brain stimulation, but this also carries risks.

The view of the therapeutic needs in PD thus changed over time, going from control of motor symptoms as the goal, to control of motor complications, and more recently to prevention of motor complications, prevention of underlying progression and restoration of striatal dopaminergic innervation. PD therapies aimed at restoring nigrostriatal innervation have been investigated, including the use of human retinal epithelial cells, gene therapy, intraputaminal trophic factor delivery and stem cells. Success has been limited. These approaches would not affect the long-term prognosis of PD, a fact emphasizing the central role of neuroprotection in treatment. Several therapies aimed at neuroprotection have failed, however. One of the reasons these studies have failed may be the difficulty in choosing an appropriate target population for study.

When looking toward the future, Dr. Poewe emphasized innovations in disease biomarkers, which may aid in the development of neuroprotective therapies for PD. In the future, it will be possible to define at-risk subjects and to define conversion rates, and the use of risk markers will allow investigators to conduct disease prevention trials.

The "Mechanism and Treatment Strategies in PD" symposium on Friday covered the status quo in current practice for managing PD and highlighted the desires of clinicians and investigators for improving the way the disease is understood, studied and treated. Leading off the session was C. Warren Olanow of Mount Sinai School of Medicine, who discussed unmet medical needs in PD (4). Current therapy, he noted, has its good points: it can improve the classic motor features of the disease and almost all patients respond. But it is limited by drug-related side effects, there is some measure of nonresponsiveness and it does not alter disease progression. There are also nondopaminergic features of PD which are not affected by current therapy, including falling, freezing and dementia. Therapies are needed with the benefits of levodopa but without the side effects, therapies that improve nondopaminergic features and therapies that are neuroprotective.

Motor complications affect many PD patients –as many as 80-90% on chronic levodopa therapy. Treatments have been devised to address this, such as dopamine agonists, which delay the onset of motor complications, and deep brain stimulation (DBS), which improves "on" time and reduces dyskinesias but is not without drawbacks. Possibilities for the future include gene and cell-based therapies, although studies using these approaches have failed so far. Also under investigation are transdermal levodopa patches to provide continuous drug delivery, which has proved to be a difficult proposition, and long-acting levodopa formulations and levodopa prodrugs.

Motor features may only be a small part of PD. The nondopaminergic features of the disease require better treatments, as they can manifest early, are very common and are sometimes the major source of disability. Perhaps the most important unmet need is that of a neuroprotective therapy, for which there have been many candidates, none of which have been confirmed as neuroprotective. The obstacles to developing these treatments are several, such as the lack of a precise understanding of PD etiology and of an animal model accurately reflecting that understanding. It is also not known how to determine the correct doses for clinical trials, and there is a lack of validated endpoints to measure underlying disease.

There have been advances, however. Genetic mutations linked to PD have been described, and these could form the basis for the creation of transgenic animal models for study. Bioengineering shows promise as a means to solve the dosing problem, and there has been a move toward new trial designs that focus on cumulative disability.

One question at the center of the debate in PD treatment centers on when treatment should begin. This was taken up in the session by Anthony Schapira of the Royal Free Hospital in London (5). Although the diagnosis of this disease is essentially a clinical diagnosis focused on motor function, nonmotor function characteristics, including olfactory dysfunction, depression, sleep disorders and constipation, may be evident years earlier. How early before the manifestation of motor complications can presymptomatic PD exist? The answer depends on the criteria, ranging up to 8 years for clinical, pathological and imaging clues, to decades for genetic causes. It is also known that dopamine levels decline before motor symptoms are seen. The explanation for continued functioning in this situation is unclear, but may be due to either a large number of redundant dopamine neurons or compensatory mechanisms maintaining motor function in the absence of dopamine. The diagnosis of PD is also difficult, and accuracy rates depend on who is evaluating a patient. In any case, motor dysfunction increases rapidly in early PD.

At present, treatment is usually delayed until symptoms are sufficiently bad to avoid side effects and the wearing off of effects. But early treatment has the benefit of providing early symptom control, improved quality of life and possibly better outcomes. The disadvantages are of course the requirement to take tablets and the side effects of treatment.

Further details on PD treatment, with a focus on continuous dopaminergic stimulation, were provided by Fabrizio Stocchi of the

Institute of Research and Medical Care IRCCS in San Raffaele, Italy (6). Fundamental to treatment decision-making is consideration of patient characteristics, the use of physiological stimulation, the avoidance of motor and nonmotor fluctuation and side effects. Dr. Stocchi showed brief films of three patients with the same level of impairment but who experienced different levels of impact on their lives, depending, for instance, on the side of the body affected.

Dr. Stocchi pointed to the modification of disease progression, the improvement of symptoms and quality of life, and the avoidance of side effects as the objectives of treatment. Dopaminergic therapy is the mainstay of PD treatment, but the resulting variation in dopamine levels leads to fluctuations in motor performance. Thus, a more physiological approach, with continuous treatment, could be better. Dopamine agonists have shown promise in this regard. The goal for these agents would be once-daily oral dosing, for which ropinirole PR has been developed. Transdermal administration is also a possibility, and the first product in this area was the rotigotine patch. Dopamine agonists are, however, generally less effective than levodopa. They can nevertheless act on other symptoms, such as fatigue, depression and sexual dysfunction. Safety is an issue, with impulse control disorder one of the issues identified with these agents.

Levodopa therapy, while more effective, is limited by several unanswered questions: How much should be given daily? At what dose? What formulation is optimal? At present, the best way to use the drug is still not known.

Olivier Rascol of Toulouse University provided the flipside to Dr. Schapira's talk, discussing the management of motor complications in patients with more advanced disease (7). In these patients, fluctuations are less predictable and are described as such or as sudden or random. Still, motor fluctuations may not be the only problem for these patients. Among other symptoms, they may also suffer from anxiety, pain, fatigue, cognitive impairment, psychosis and sleep problems.

It is not entirely clear what causes motor fluctuations. They may be due to disease progression and/or the pharmacokinetics and/or pharmacodynamics of levodopa treatment. The first-line approaches used to manage fluctuations involve adjustment of the levodopa dose or formulation, the use of dopamine agonists, MAO-B blockade and catechol *O*-methyltransferase (COMT) inhibitors. In difficult cases, surgery (primarily deep brain stimulation) is an option, as is subcutaneous apomorphine and intraduodenal administration of the Duodopa levodopa formulation. Dr. Rascal proposed an algorithm for choosing a treatment in which listening to the patient was essential in order to discern the role, if any, of environmental factors in fluctuations. Comparison of the pros and cons of first-line treatments follows, and combination therapy can be tried afterwards if needed. The second-line treatments are the final option. Options which may become available in the future include new agents and the earlier employment of surgery.

Surgery was the topic of the last presentation in the symposium, which was given by Anthony Lang of the University of Toronto, who spoke primarily about deep brain stimulation (8). Deep brain stimulation, he pointed out, can modulate the disease and does not create permanent lesions. It is costly, however, and requires the involvement of a team of clinicians. There is debate about the ideal focus for deep brain stimulation: the subthalamic nucleus (STN) or the globus pallidus (GBi). Although the former appears to be associated with more side effects, it can also improve nonmotor fluctuations.

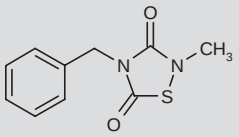
An interesting facet of the outcomes of STN deep brain stimulation is that while it may improve symptoms, it does not necessarily improve social adjustment. There is some evidence for a risk of social difficulties, including work and marital problems, in patients who undergo the procedure. These are due in part to the fact that patients usually have PD for years before undergoing surgery and have changed their lives to accommodate the disease. This accommodation can be disrupted by treatment, however successful it may be. As mentioned in the previous talk, STN deep brain stimulation may be made available earlier, which may lessen the patient's psychosocial burden. Presently, it is primarily used in patients with advanced disease who are frequently dependent and retired.

Dr. Lang closed by pointing to long-term follow-up of STN deep brain stimulation, showing that, gradually, some motor features become resistant to the treatment. He also pointed out that deep brain stimulation in the pedunculopontine nucleus is in the very early stages of investigation.

Saturday's symposia included one sponsored by Noscira, which is investigating the glycogen synthase kinase-3 (GSK-3) pathway in neurodegeneration. Fred Van Leuven from KULeuven in Belgium discussed this potential drug target and how research in various mouse models appears to confirm its validity (9). Among these studies were those showing that amyloid activates GSK-3beta and GSK-3alpha. In other experiments, mutant APP mice displayed an early phenotype of AD, and this was found to correlate with GSK-3 activation. The overall picture provided by these studies and others is that amyloid causes tauopathy by activating GSK-3alpha and beta isozymes. Neither amyloid nor tangles cause neurodegeneration, which is caused by phosphorylated tau. The working hypothesis of Dr. Van Leuven's group is that amyloid is the trigger, phospho-Tau is the executor and GSK-3 is the mediator.

Further detail on the role of GSK-3 in the process of neurodegeneration was provided by Simon Lovestone of King's College London (10). It was noted some time ago that GSK-3 alters tau phosphorylation, and the ability of GSK-3 to induce neurodegeneration was observed later. Investigations into how GSK-3 induces neurodegeneration in a *Drosophila* model revealed a GSK-3-dependent tau phenotype in the absence of tau aggregation. Addressing the question of how GSK-3 induces cognitive dysfunction, Dr. Lovestone described data from experiments in animals overexpressing GSK-3beta (Tet/GSK-3Beta mice), in which cognitive dysfunction was seen prior to neuronal loss. GSK-3 inhibition appeared to be necessary for plasticity. Still, although a good deal of evidence indicates that GSK-3 signaling is altered in AD, the question requires further investigation.

Dr. Lovestone then asked a key question: Can this pathway be targeted by drugs? Investigations with the GSK-3 inhibitor lithium show that it can restore tau function. In an open-label safety trial in AD patients treated for up to 1 year, there were 2 deaths, neither related to the treatment. There were three side effects: tremor and confusion, which were related to lithium, and falls, which were possibly related to the drug. Of 22 patients who started the treatment, 8



NP-12

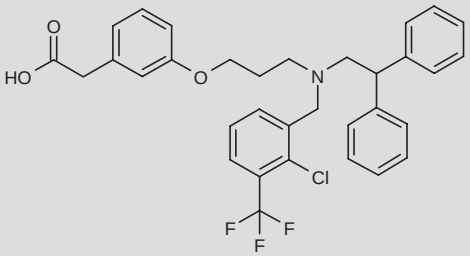
completed 1 year of treatment. The numerous withdrawals were due in part to a strict compliance requirement. Although the study was not designed to evaluate these outcomes, there was no correlation between lithium levels and cognition, function or behavior. No effect on Mini-Mental State Examination (MMSE) scores was seen. The question of whether this target can be approached with drugs therefore remains open, warranting further investigation. Dr. Lovestone closed his discussion by moving further afield, mentioning the link between GSK-3 and another cognitive disorder, schizophrenia.

In the final talk, Miguel Medina of Noscira detailed the development of the company's GSK-3 inhibitor **NP-12** (11). This candidate is an orally bioavailable, moderately potent inhibitor of GSK-3 that has shown efficacy in various AD models. In transgenic mice with amyloid pathology, tau pathology, neuronal loss and memory deficits (APP_{SW}-Tau_{VLW}), NP-12 improved the spatial memory deficit, reduced the amyloid plaque load, reduced phosphorylation of tau protein and reduced astrogliosis and microglial activation in the hippocampus and entorhinal cortex.

The compound was well tolerated in phase I studies, including the first-in-man study in 34 healthy young volunteers, a multiple ascending dose study in 48 healthy elderly volunteers treated for 5 days and a multiple ascending dose study in 72 healthy elderly subjects treated for 14 days. Doses for use in elderly patients were established and a phase IIa study, with a planned enrollment of 30 patients with mild to moderate AD, has been initiated. The double-blind, placebo-controlled, escalating-dose trial will last 14 weeks and is being conducted at 3 German centers. A phase II study of NP-12 in progressive supranuclear palsy is also planned for the first half of this year.

NEW TREATMENT CANDIDATES: PRECLINICAL INVESTIGATIONS

Among therapeutic candidates for neurodegenerative diseases presented at the conference was the 5-HT_6 antagonist **AVN-322**. Avineuro Pharmaceuticals developed a series of potent, safe, blood–brain barrier-penetrating 5-HT_6 receptor antagonists, with testing leading to selection of AVN-322 for further investigation. With a binding IC_{50} of 0.84 nM and a functional IC_{50} of 38 nM, AVN-322 displayed a high level of selectivity for the 5-HT_6 receptor. The compound did not affect the activity of the cytochrome P450 CYP1A2, CYP2C19, CYP2D6 or CYP3A4 enzymes. In vivo AVN-322 restored scopolamine- and MK-801-induced cognitive dysfunction and had a similar or better anxiolytic effect than lorazepam and buspirone in the elevated plus-maze model, elevated platform and open field tests. AVN-322 was associated with a pharmacokinetic profile, metabolic stability and safety encouraging further development (12).

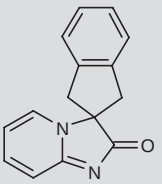


GW-3965

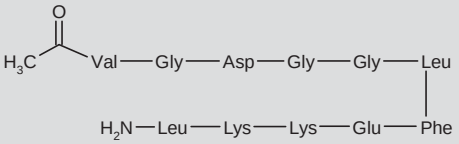
University of British Columbia studies of the liver X receptor (LXR) agonist **GW-3965**, from GlaxoSmithKline, showed its potential as a treatment for AD and have shed light on the ATP-binding cassette transporter 1 (ABCA1) as a therapeutic target in the disease. GW-3965 was found to dose-dependently induce ABCA1 and apolipoprotein E (apoE) in primary wild-type glia. In mice, the agent increased the size and abundance of apoE lipoproteins in cerebrospinal fluid and cortical concentrations of ABCA1 and apoE after 3 months of treatment, effects requiring ABCA1, as shown in *ABCA1*$^{-/-}$ mice. In cognitively impaired APP/PS1 mice, treatment significantly improved Morris water maze latency to platform, an effect not seen in *ABCA1*$^{-/-}$ mice. ABCA1 was also required for the restoration of novel object recognition in APP/PS1 mice, and prophylactic as well as therapeutic treatment was effective on this measure (13). GW-3965 had previously been investigated as an antiatherosclerotic and hepatoprotective agent.

A potent and selective $GABA_A$ α5 receptor inverse agonist (K_i = 37.3 nM, efficacy = –75% in rats) synthesized by Kyowa Hakko Kirin was recently evaluated in rodent models of cognitive function. The studies found that the compound (1 mg/kg p.o.) significantly improved scopolamine-induced cognitive impairments in mice, as revealed in the Y-maze test, and significantly ameliorated AF65A-induced cognitive deficits, as evaluated in the radial-arm water maze test. The contextual fear conditioning test in rats revealed that the compound (10 mg/kg p.o.) significantly improved the contextual memory impairment (reduced freezing response) induced by ethanol administration (0.75 g/kg i.p.). The compound (3 mg/kg p.o.) also significantly decreased the choice reaction time on delayed nonmatching to sample performance in rats, without affecting the percentage of correct responses. The study concluded that the selective $GABA_A$ α5 receptor inverse agonist activity of the compound, in conjunction with a lack of anxiogenic and proconvulsant liabilities, render it a strong candidate for the development of a novel treatment for AD (14).

The azaindolizinone derivative **ZSET-1446** (ST-101) was previously found to improve scopolamine-induced cognitive impairment, and this model has now been used by Zenyaku Kogyo researchers to evaluate the combination of ZSET-1446 and donepezil. In mice undergoing a passive avoidance task, neither oral ZSET-1446 0.0001 mg/kg or donepezil 0.01 mg/kg significantly prolonged step-through latency compared to controls, but coadministration of the agents did so compared to controls and animals treated with donepezil 0.01 mg/kg. While ZSET-1446 0.001 mg/kg and donepezil 1 mg/kg did not significantly increase extracellular levels of acetylcholine (ACh) in the hippocampus compared with controls,



ZSET-1446



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concomitant administration at these doses did so. This may have been a result of enhanced ACh release by ZSET-1446 and inhibition of ACh degradation by donepezil (15).

A study of the mechanisms by which ZSET-1446 improves learning deficits in animal models and restores β-amyloid (Aβ)-induced reductions in nicotine-induced ACh release in the hippocampus has also been reported. Here, the effects of ZSET-1446 on the synaptic effects of nicotinic ACh receptor (nAChR) activation in rat hippocampus slices were assessed. It was found that ZSET-1446 potentiated the facilitatory effect of ACh on excitatory and inhibitory spontaneous postsynaptic currents in CA1 pyramidal neurons, without affecting nAChRs themselves. The effects of ZSET-1446 on cognition may therefore involve a novel mechanism of action (16).

Sonexa Therapeutics is sponsoring an ongoing randomized, double-blind, placebo-controlled, parallel-assignment phase II study to evaluate the ability of ST-101 to improve cognition in patients with AD, as well as the safety/tolerability of the drug.

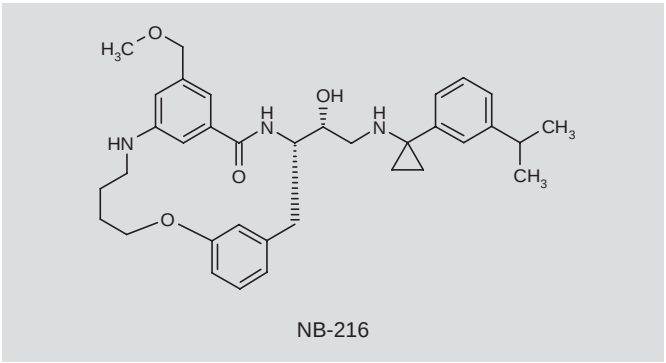
The possibility of improving cognition in AD with active peptides of neurotrophic factors has led to the creation of small ciliary neurotrophic factor (CNTF) peptides, which showed promise in mouse models of the disease. Previously, it was shown that neuronal maturation is reduced in the AD brain, in which there is also an imbalance of trophic factors. The peptide [**1**] was developed and found to induce proliferation of BrdU-IR cells in the dentate gyrus, to increase the percentage of BrdU-IR neurons expressing a mature neuronal marker and to be neurotrophic in mice. The peptide also improved spatial learning and retention in normal mice tested in the Morris water maze. It was found to be relatively stable in mouse plasma, to have an in vitro plasma half-life of over 6 h and to be able to cross the blood–brain barrier in vivo. While plasma levels declined 10-60 min after i.p. injection in mice with a half-life of < 27 min, brain levels increased approximately 2.5-fold during the same period (17). This peptide has been described in a recent Ebewe patent (WO 2008113536).

Scientists at Merck Research Laboratories presented a series of drug-like compounds that act as potent and selective allosteric modulators of the muscarinic acetylcholine M_1 receptor. Restoration of cholinergic signaling via postsynaptic muscarinic acetylcholine receptors is believed to represent a promising therapeutic strategy to ameliorate cognitive decline associated with AD. Benzylpyrazole-quinolone carboxylic acid (**BPQCA**), a representatiive compound from this series, was able to potentiate the response of recombinant human M_1 receptors expressed in cells to ACh (IP = 171 nM), without any intrinsic effects on M_2, M_3 and M_4 receptors (up to 100 μM). The compound (1, 3 and 10 mg/kg i.p.) was found to significantly attenuate the effects of cholinergic basal forebrain lesion induced by IgG192-saporin in the novel object recognition test of short-term episodic memory in rats, indicating a procognitive effect. In the contextual fear conditioning test of long-term episodic memory in mice, BPQCA (3 mg/kg i.p.) was shown to significantly alleviate the scopolamine-induced performance deficit. The study underlines the potential of BPQCA to induce cognitive enhancement in AD patients (18).

The neuroprotective effects of **NST-0021**, a biomolecule selected by NEURON BPh in a drug reprofiling program, have been assessed in transgenic AD mouse models developed by the same company. NST-0021 was able to prevent cognitive decline in the early stages of neuronal damage and was shown to confer significant protection against temporal memory loss induced by neuronal damage ($P < 0.05$). NST-0021 demonstrated the ability to protect against neurodegeneration, apoptosis and astrogliosis in an AD-sporadic model. The compound efficiently supported cellular structure and displayed an antioxidant effect in the hippocampus of the AD-sporadic model. Subchronic administration (3 months) of NST-0021 reduced Aβ plaque load in the hippocampus and cortex of a classic AD-familial mouse model. The study concluded that, although the significant neuroprotective effects of NST-0021 in mice require further validation in clinical trials, the compound represents a good candidate for the treatment and/or prevention of neurodegeneration occurring in AD and similar diseases (19).

A characteristic feature of AD is the deposition of amyloid plaques. These plaques typically consist of $A\beta_{40-42}$ peptides derived from amyloid precursor protein (APP) following cleavage by the β-site APP-cleaving enzyme β-secretase (BACE). Inhibition of BACE is expected to provide a therapeutic option for AD since BACE knockout mice have shown an inability to produce Aβ peptides. At the conference, scientists from Novartis reported the identification of a series of potent macrocyclic BACE inhibitors. Compounds **NB-216, NB-851** and **NB-972** from this series displayed increased brain permeability following a single oral dose (60 μmol/kg) to preplaque APP51/16 transgenic mice and significantly reduced the levels of $A\beta_{40}$ in the forebrain (up to 70%) (20). Treatment of preplaque APP51/16 mice with a single dose of NB-216 (0-300 μmol/kg p.o.) revealed a dose-dependent reduction in $A\beta_{40}$ in the forebrain and cerebrospinal fluid (CSF) at doses between 60 and 300 μmol/kg. The compound showed no selectivity over the related proteases β-secretase 2, cathepsin D and E. It was able to reduce amyloidogenic pathway products of APP in vivo and it increased APP products from the nonamyloidogenic pathway in a dose- and time-dependent manner (21).

NB-216 was subsequently assessed in transgenic and nontransgenic rodent models in order to evaluate model-specific differences. It was found to produce a dose-dependent reduction (at 60 and 120



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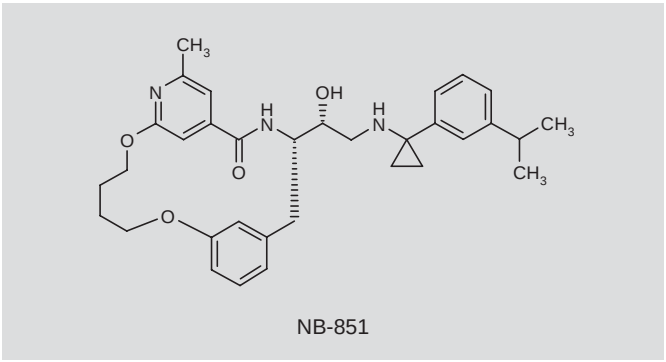

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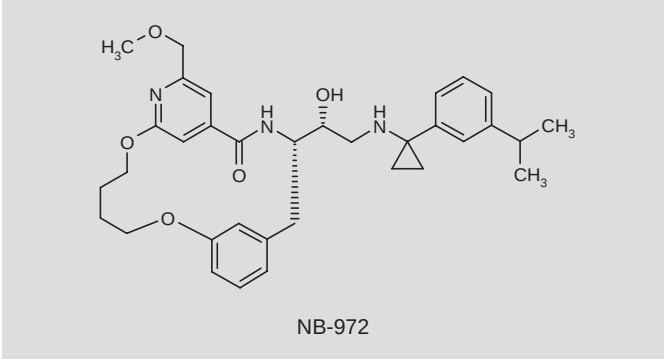

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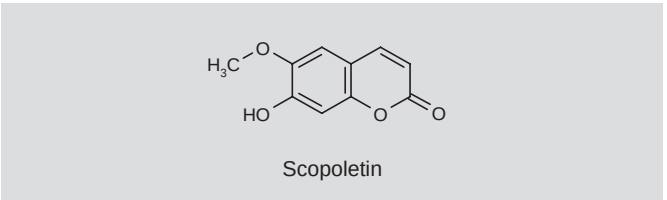
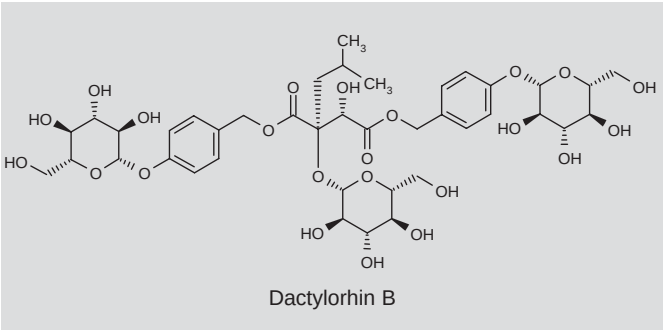


Scopoletin



Dactylorhin B

μmol/kg; $P < 0.001$) in forebrain $A\beta_{40}$ in nontransgenic mice (C57BL/6) and to influence APP processing in APP23 mice in a dose-dependent manner. Optimal efficacy of NB-216 against $A\beta_{40}$ was seen in the APP51/16 mouse model in which human wild-type APP is overexpressed in the brain. In rats, NB-216 (60 μmol/kg) displayed significant but reduced efficacy against forebrain $A\beta_{40}$ at 2 h compared to APP51/16 mice (22). These compounds have been described previously in patent literature (WO 2006074950, WO 2007077004).

Cognition-enhancing properties based on increased brain ACh were observed with the coumarin **scopoletin** in a series of experiments conducted by investigators from Leopold-Franzens University of Innsbruck. The compound dose-dependently increased extracellular brain ACh with a potency similar to galantamine in rats and enhanced the K^+-induced release of ACh from synaptosomes, an effect blocked by the nicotinic acetylcholine receptor antagonist mecamylamine. In an assessment of hippocampal long-term potentiation (LTP) using superfused slices from rat hippocampus, scopoletin did not affect basal field excitatory postsynaptic potentials (EPSPs) but amplified the LTP-induced increase in field EPSPs, an effect on neuronal plasticity that was abolished by mecamylamine. In C57BL/6N mice, scopoletin abolished the scopolamine-induced impairment in object recognition, improved alternation rates of normal mice in the T-maze test and abolished the suppressive effect of scopolamine on alternation. These studies characterize scopoletin as an agonist at nicotinic acetylcholine receptors (23).

Dactylorhin B (DHB), an extract of *Coeloglossum viride* (L.) Hartm. var. *bracteatum* (Willd.), was found to improve learning and memory, while also reducing motor disability and neuronal cell loss, in the four-vessel occlusion model of transient global forebrain ischemia and the transient middle cerebral artery occlusion (tMCAO) model of focal cerebral ischemia. The experiments evaluated treatment with oral DHB at 5 mg/kg b.i.d. The treatment improved performance on the Morris water maze test in mice with four-vessel occlusion-induced deficits and on passive avoidance and rotarod tests in mice with behavioral deficits induced by tMCAO. Neuronal loss in the hippocampus was significantly reduced in DHB-treated mice that underwent four-vessel occlusion, and lesion volume in tMCAO mice was also significantly reduced with DHB treatment. The results suggest the potential of DHB in treating vascular dementia. The compound is being evaluated at the Chinese Academy of Medical Sciences (24).

reMYND investigators presented first-in-class drug candidates for AD and PD at the congress. They used a yeast-based high-throughput screening platform modeling tau and α-synuclein protein misfolding and cytotoxicity to identify drug candidates. One result of these efforts was the ReS19-T family of tau toxicity inhibitors. **ReS19-T38**, the lead compound, rescued learning and spatial memory in the APP-London mouse model of AD, without affecting parenchymal amyloid accumulation and related inflammatory and neuritic pathology (25). The ReS9-S family of small molecules was also developed, displaying potent cytoprotective properties in a human neuronal cell model of α-synucleopathy. The lead compound, **ReS9-**

S7, completely inhibited paraquat-induced dopaminergic neurodegeneration in the substantia nigra in mice. The compound also normalized dopamine-controlled anxiety and reduced motor deficits in a transgenic α-synuclein mouse model of PD. ADMEtox studies revealed no toxicity and indicated that once-daily oral dosing provided sufficient brain exposure. Genes involved in vesicular-driven transport to the lyosome appeared to be involved in the mechanism of action of ReS9-S7, suggesting that ReS9-S7 facilitated lysosomal-dependent clearance of pathological α-synuclein (26). ReS9-S7 may begin clinical investigation this year (27).

Details on the development of Synuclere™ (**PD-61-W3**), a small molecule targeting α-synuclein aggregation for PD, were reported by ProteoTech researchers. After lead compounds were identified that markedly reduced α-synuclein aggregation in vivo, seven compounds were chosen for assessment in transgenic mice and in drugability screening. One of these compounds, Synuclere™, was found to markedly reduce (by 81%) α-synuclein accumulation in the cortex of 18-month-old α-synuclein transgenic mice treated for 6 months, as shown by immunohistochemistry and image analysis quantitation. The compound also reduced α-synuclein accumulation in the particulate and cytosolic fractions of the anterior brain in these mice, as shown by Western blotting and quantitation. Beam traversal and pole tests showed improved motor dysfunction in 18-month-old α-synuclein transgenic mice treated with Synuclere™ and in younger (4- to 5-month-old) α-synuclein transgenic mice. Synuclere™ was nontoxic in vivo and displayed good drugability characteristics (nonbinding to brain receptors, transporters and/or channels, no significant CYP450 inhibition, good levels of free drug in plasma, moderate to high stability in human and mouse microsomes). Studies in preparation for an IND are planned (28).

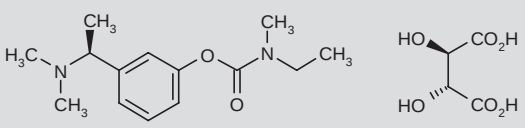
ORAL SESSIONS II

On Thursday, investigators from AFFiRis presented data from their work on developing vaccines for AD, research that may also have applications for PD and atherosclerosis. The first speaker at this sponsored symposium was Markus Mandler (AFFiRiS GmbH), who introduced the AFFITOPE® peptides (29). Vaccines are constructed according to a modular approach using a peptide, a carrier and a linker and are administered with an adjuvant. The peptides are designated AFFITOPES® and the technology used to identify them as AFFITOME® technology. The short peptides target the Aβ neoepitope and bind to amyloid plaques while sparing full-length APP. Preclinical experiments in mice have shown reductions in plaque area of 50-80% and the candidate vaccine **AD-01** was found to improve spatial learning in APP transgenic mice. Neuropathological studies have revealed reduced astrocytic foci, microgliosis and neuritic alterations with the peptides. Furthermore, no detrimental T-cell response has been observed and single- and repeat-dose studies have revealed a favorable safety profile.

Dr. Mandler was followed by AFFiRis' Achim Schneeberger, who reported preliminary results of the first-in-man studies of the AFFITOPE® products AD-01 and **AD-02** in patients with mild to moderate AD (30). AD-01 is being given in 4 vaccinations at 4-week intervals to 24 patients aged at least 50, with some patients also receiving adjuvant. The study includes a 6-month assessment followed by 1 year of follow-up in patients choosing to enroll. With 96 total vaccinations given, most adverse events were local reactions, and these were more common in the adjuvant group. There were three serious adverse events, but none were related to the treatment. AD-01 was deemed safe to continue in clinical development by the safety monitoring board. Further analysis of the activity of the vaccine is ongoing. AD-02 has likewise been evaluated in 24 patients, with some also receiving adjuvant. Again, most adverse events were local reactions that were mild to moderate in severity. Two serious adverse events were not treatment-related. The primary endpoint of overall safety was expected to be met, and most patients were expected to enter the follow-up phase. The future development plan for these vaccines includes a phase Ib study to evaluate dose titration and optimize the administration schedule and a phase II study to assess disease modification. Dr. Schneeberger pointed out that AFFiRiS has partnered with GlaxoSmithKline Biologicals for further development of AD vaccines.

Rounding out the session was a talk by Eliezer Masliah from the University of California at San Diego, who discussed immunotherapies for AD and PD more generally (31). Dr. Masliah drew attention to the common pathogenic pathway for AD and Lewy body disease, Aβ protein. Studies indicate that the mechanism of neurodegeneration is mediated by interactions between $A\beta_{42}$ and α-synuclein aggregation. This provides an opportunity for therapeutic intervention. Immunotherapies may reduce pathogenesis by different means, including increasing Aβ degradation and $A\beta_{42}$ clearance. $A\beta_{1\text{-}42}$ immunization was found to reduce α-synuclein accumulation and neurodegeneration in a mouse model. Also, anti-α-synuclein antibodies can promote clearance of α-synuclein aggregates. Dr. Masliah closed by emphasizing the promise of inducing the autophagy pathway via immunization, gene therapy or pharmacologically to promote clearance of $A\beta_{42}$ and α-synuclein.

In one of the final oral sessions of this year's congress, a selection of clinical studies were discussed by five different investigators. The first, P.S. Miettinen from the University of Kuopio, detailed an fMRI evaluation of the effects of cholinesterase inhibition in patients with mild AD (32). Twenty patients with a mean age of 76.1 years were scanned 3 times: after a single dose of **rivastigmine** treatment, after a single placebo treatment and after 4 weeks of rivastigmine treatment. fMRI was conducted as participants completed a face recognition task. Increased brain activation was seen during acute and chronic rivastigmine treatment compared to placebo administration. During cholinergic stimulation, however, differences in prefrontal activity were seen: those with relatively spared cognition with high prefrontal and low hippocampal activity at baseline had decreased prefrontal activity, while patients with greater cognitive impairment with low prefrontal and high hippocampal baseline activity had increased prefrontal activity. Dr. Miettinen concluded that mild AD is



Rivastigmine tartrate

a heterogeneous state in which responses to acetylcholinesterase inhibitors are linked to the level of attentional dysfunction.

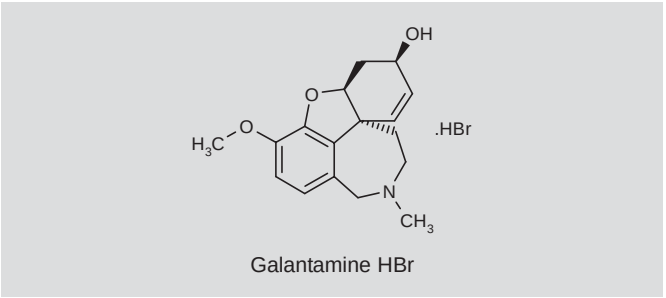
M. Navratilova of Masaryk University Hospital in Brno followed with a discussion of a study of nutritional support in patients with AD and vascular dementia (33). She began by discussing the association of AD with malnutrition, an association with many potential causes, including patients not cooperating, the difficulty in observing patients' nutritional status and a shortage of dietary nurses on site at institutions. The processes behind the association between AD and malnutrition are somewhat mysterious, with theories including changes in energy expenditure, metabolic changes, changes in growth hormone secretion (an idea not supported by available data) and atrophy of the cerebral cortex.

Dr. Navratilova was part of a team that conducted a study of nutritional status in 7 nursing homes which included 102 patients with AD and 65 with vascular dementia. The primary assessment tool was the Mini Nutritional Assessment (MNA). It was found that the MNA was correlated with the MMSE and that MNA scores were lower in AD compared to vascular dementia patients. While energy intake was similar between AD and vascular dementia patients, body mass index (BMI) was significantly lower in the AD group, and BMI was significantly correlated with the MNA. Food components –proteins, saccharides– also differed between groups. After 1 year, study subjects were randomized to receive nutritional support or not. MMSE scores revealed significant slowing of deterioration in AD patients given nutritional support, although nutritional support did not affect survival. The early implementation of nutritional support in AD patients may therefore be an important means of improving patient quality of life.

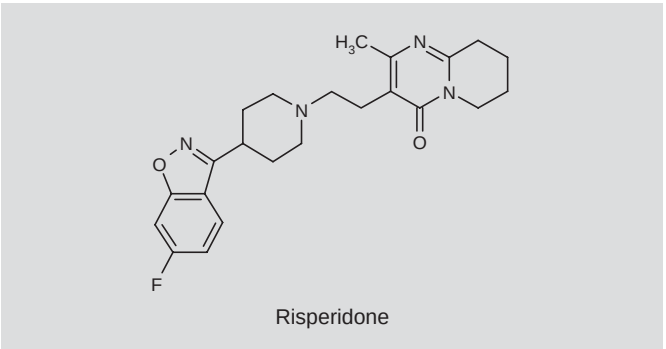
Yvonne Freund-Levi of the Karolinska Institute began the following talk by noting that 50-90% of AD patients have behavioral and psychological symptoms in dementia (BPSD) (34). The study conducted by her team compared the effects of **galantamine** and **risperidone** on these symptoms in 100 patients, 91 of whom completed 12 weeks of treatment. The phase II study was open and randomized. Both treatments were associated with improvement, and the time of resource use from the caregiver declined in both groups. Risperidone, however, was found to have better effects on the Neuropsychiatric Inventory (NPI) domains of irritability, aggressive behavior and aberrant motor behavior compared to galantamine, suggesting a patient population in which the drug may be preferable. Trends toward a treatment advantage with galantamine were seen on the NPI domains of apathy/indifference and sleep.

The effects of **EHT-0202**, a $GABA_A$ receptor modulator from ExonHit Therapeutics, were detailed by Laurent Desire (35). The drug has been found to stimulate the production of sAPPα, which is neuroprotective. Other properties suggesting its applicability in AD have also been noted. It reduced brain and CSF $A\beta_{42}$ in vivo, and in aged rats undergoing the Barnes test, EHT-0202 improved the complex behaviors of homing and foraging. The results of toxicology and drug metabolism and pharmacology (DMPK) studies suggested its evaluation in humans.

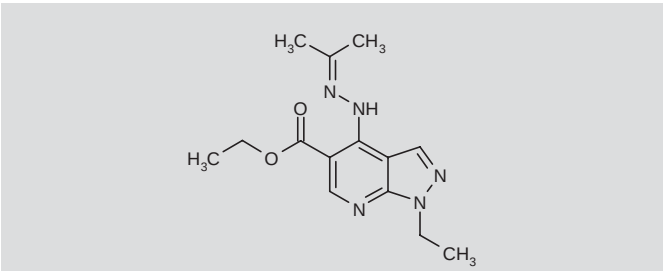
Indeed, over 130 healthy volunteers have been evaluated in phase I studies assessing single and multiple doses, the effects of food and 10-day treatment in elderly volunteers. In these studies, tolerated



Galantamine HBr



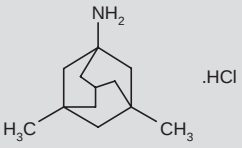
Risperidone



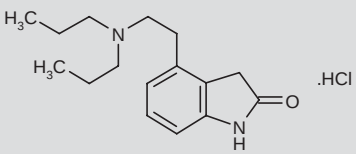
EHT-0202

doses corresponded to exposure levels compatible with pharmacological properties. In a study in 12 subjects, EHT-0202 was found to counter the effects of scopolamine on cognition. EHT-0202 is presently under investigation in a multicenter, randomized, double-blind, placebo-controlled phase IIa trial with a duration of 3 months. Doses of 40 and 80 mg b.i.d. are being evaluated as add-on therapy to acetylcholinesterase inhibitor therapy. The primary goals are to investigate safety and tolerability, with a secondary endpoint of the effects on cognitive function. Results are expected in the fourth quarter of this year.

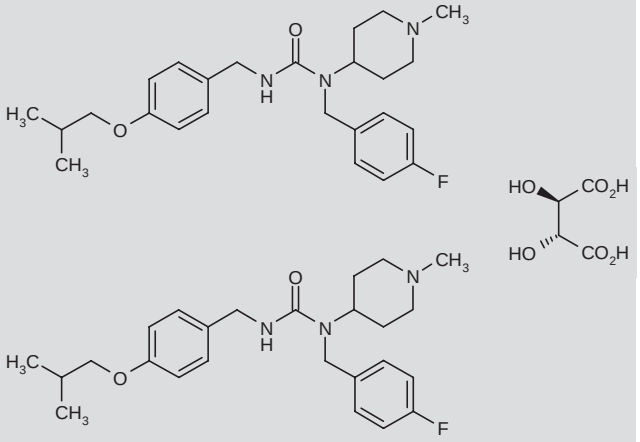
In the last clinical study presented, Elisabet Londos of Lund University showed how **memantine** proved beneficial in patients with PD dementia or dementia with Lewy bodies (36, 37). The randomized, double-blind, 24-week trial compared memantine and placebo in 75 patients enrolled at 4 centers. Memantine was associated with a significant improvement on the Clinical Global Impression of Change (CGIC) evaluation compared to placebo, with 27% and 0% of the memantine and placebo groups, respectively, achieving a moderate or marked clinical improvement. MMSE scores did not differ between groups. Memantine was also safe, with no differences between groups in adverse events or withdrawals due to adverse



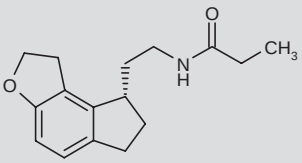
Memantine HCl



Ropinirole hydrochloride



Pimavanserin tartrate



Ramelteon

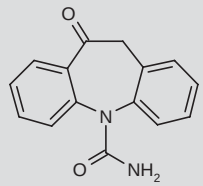
events. These varieties of dementia may be added to the list of indications in which memantine is in active clinical development.

NEW TREATMENT CANDIDATES: CLINICAL INVESTIGATIONS

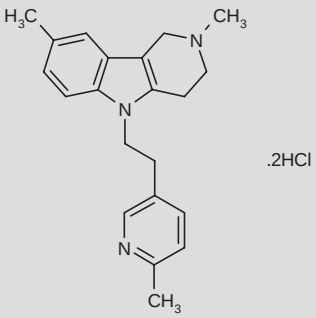
The effects of prolonged-release (PR) and immediate-release (IR) formulations of the dopamine D_2 agonist **ropinirole hydrochloride** on symptom control in patients with advanced PD were evaluated in a recent study supported by GlaxoSmithKline. Patients who participated in the 24-week PREPARED study (ROP105323) were randomized to receive either adjunctive ropinirole PR (2-24 mg/day) or ropinirole IR (0.75-24 mg/day). At week 24 last observation carried forward (LOCF), the primary endpoint (maintenance of 20% or greater reduction in "off" time over two consecutive visits) was met by 66% of patients receiving ropinirole PR compared to 51% on ropinirole IR treatment ($P = 0.009$). Unified Parkinson's Disease Rating Scale (UPDRS) scores and total motor scores displayed a significant improvement in the PR compared to IR ropinirole-treated groups ($P = 0.022$). The most frequently reported adverse events were nausea (15% and 18%, respectively), dyskinesia (11% and 6%, respectively) and dizziness (10% and 6%, respectively) in the ropinirole PR- and IR-treated patients, respectively. The authors of the study concluded that adjunctive ropinirole PR treatment was well tolerated overall and demonstrated improved symptom control compared to ropinirole IP in patients with advanced PD (38). Ropinirole is currently in phase III trials for major depression and in phase II trials for the treatment of fibromyalgia.

Pimavanserin (Acadia Pharmaceuticals) is a selective 5-HT_{2A} receptor antagonist being developed for psychosis, insomnia and schizophrenia and which has entered phase III investigation in psychosis in patients with PD. Data from clinical studies have shown that the drug is safe in PD patients and may improve psychosis. In a randomized, double-blind, dose-escalation study, 60 patients were treated for 28 days with placebo or pimavanserin with doses started at 20 mg daily and elevated to 40 and 60 mg depending on individual responses. There was no significant difference between the placebo and pimavanserin groups in the absolute mean change from baseline on the UPDRS Parts II and III, indicating no worsening of parkinsonism with pimavanserin. Psychosis scores were generally improved more with pimavanserin than with placebo, and significant improvements in psychosis were seen on the Scale for the Assessment of Positive Symptoms (SAPS) combination score (hallucination and delusion) compared to placebo. A significant improvement in UPDRS Part I (mentation, behavior and mood) was also seen with pimavanserin compared to placebo. Pimavanserin was safe and well tolerated, with most adverse events of mild to moderate severity and few motor function adverse events reported (39). Safety is also being evaluated in an open-label extension study including patients with PD and psychosis who participated in a previous clinical trial of pimavanserin. Patients started treatment with 20 mg/day and could receive 40 mg after 2 weeks and 60 mg after 4 weeks. Preliminary data in 39 patients show pimavanserin to be well tolerated at doses up to 60 mg and for a period up to 48 months. The small number of motor function adverse events suggested that the treatment did not worsen parkinsonism symptoms, and the most common adverse events were those expected in this patient population. Only one serious adverse event was considered possibly related to treatment (rhabdomylolysis) (40).

Takeda's **ramelteon** (Rozerem™), approved in the U.S. for the treatment of insomnia, has been investigated in a double-blind, placebo-controlled, crossover study in patients with PD with sleep disturbances, which are common in this patient population. Fifteen patients were enrolled in the study and data on 4 subjects completing the study were presented. Among other assessments, sleep/wake cycle and day/night activity patterns were assessed over 1 week via actimetry. The active treatment significantly reduced the



Oxcarbazepine



Dimebolin hydrochloride

activity count/minute and significantly decreased Abnormal Involuntary Movement Scale (AIMS) scores compared to placebo. Interestingly, a strong trend towards increased recall scores on the Hopkins Verbal Learning Test was also seen with ramelteon. Other measures were not affected by ramelteon, including the UPDRS, The Neuropsychiatric Inventory and the Epworth Sleepiness Scale. This appears to be the first study of the drug in PD patients (41).

The sodium channel blocker **oxcarbazepine**, launched in 1990 by Novartis for epilepsy, was found to provide meaningful pain relief in a trial in patients with idiopathic PD. The study included 27 patients who received an initial oxcarbazepine dose of 150 mg/day which was doubled weekly over 4 weeks up to 1200 mg/day. The following 8 weeks evaluated fixed-dose treatment. Mean visual analog scale (VAS) score, the primary efficacy variable, significantly fell after 12 weeks compared to baseline (from 67.1 to 42.5). The most common adverse events were drowsiness and dizziness, and there were no serious adverse events. Larger trials are needed to validate these findings (42). Oxcarbazepine was previously in development for diabetic neuropathic pain, but investigation in this indication was discontinued.

A multicenter study (DIMOND) in 91 patients with mild to moderate Huntington's disease produced results encouraging further evaluation of **dimebolin hydrochloride** in this indication. The compound is in phase II investigation for Huntington's disease and in phase III for AD at Medivation. Patients enrolled in the present randomized study received dimebolin 20 mg t.i.d. or placebo for 90 days. The primary outcome of the completion of the treatment period at the target dose was achieved by 87% of patients in the dimebolin group and by 82% of those in the placebo group. Adverse events were also less frequent in the dimebolin group (70% vs. 80%), and the active treatment was deemed safe and well tolerated. A significant improvement in MMSE scores was seen with dimebolin, with an improvement of nearly 1 point from baseline at 90 days. An improvement of 1.9 points was seen in patients with greater cognitive impairment at baseline. A trend towards an improvement on the behavior component of the United Huntington's Disease Rating Scale was also seen, while there was no effect on the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) with dimebolin (43).

E.U.-FUNDED ALZHEIMER'S DISEASE PROJECTS

A series of presentations given on the first morning of the conference before the plenary lectures described several AD research projects funded by the E.U. under Framework Programmes 6 and 7 (FP6 and FP7). The 7th Framework Programme for Research and Technological Development is the E.U.'s main instrument for funding research in Europe and covers the years 2007-2013. The sixth program ran from 2002 to 2006.

A number of the projects are focused on clarifying the causes of AD and the identification of targets and therapeutic agents to act on them. ADIT is one such project which includes centers of excellence from 6 E.U. countries and is focused on the amyloidogenic hypothesis of AD. ADIT is one of three large collaborative research projects in AD funded by FP6 (44). The FP7 project Neuro.GSK3 is exploring GSK-3 kinases in neuronal plasticity and neurodegeneration and has three aims: 1) to define the role of GSK-3 isozymes in synaptic plasticity and identify up- and downstream signaling partners; 2) to define the roles of GSK-3 isozymes in the metabolism of amyloid and tau and their effects on synaptic and neuronal degeneration in mouse models of AD and frontotemporal dementia; and 3) to develop compounds and tools to manipulate GSK-3 activity in brain in vivo (45). Nine research partners and a drug development company are participating in the MEMOSAD Project, which, in stages, is intended to identify toxic Aβ and tau species responsible for memory loss in AD; to determine how toxic Aβ oligomers affect tau metabolism, the combined effects of Aβ and tau pathology in animal models and the relevance of tau in Aβ-induced toxic effects; and to identify novel candidate therapeutic targets (46). The FP7 project MEMOLOAD is intended to elucidate the molecular mechanisms by which accumulation of Aβ in the brain results in impaired synaptic plasticity and memory loss. Seven research groups are involved in the project, which has as output goals the identification of new drug targets and the development of novel peptidomimetic compounds that neutralize the effects of harmful Aβ species (47). Another team has developed a two-color single-molecule fluorescence methodology to provide information on the early oligomers formed during the formation of amyloid fibrils; these oligomeric species may be the critical pathological species in some amyloid disorders (48).

Several projects are related to biomarker discovery and detection. One of them, AddNeuroMed, is a cross-European AD biomarker discovery platform with both preclinical and clinical components, the latter of which has assessed over 700 subjects. A proteomic approach revealed a potential blood biomarker that correlates with neuroimaging measures and clinical measures of severity (49).

NeuroTAS project members are working on a lab-on-chip prototype for a miniaturized system to be used in diagnostics for the early stage of AD and other neurodegenerative diseases or as a point-of-

care instrument for patient follow-up. The effort involves the use of microfluidics to increase sensitivity for the detection of biomarkers in early stages (50).

cNEUPRO aims to use advanced proteomic tools to discover novel neurochemical dementia biomarkers in blood and CSF for the early diagnosis of AD and prediction of the disease. The first research and development module is dedicated to be the discovery of novel protein biomarkers, while the second module is intended to improve the performance of current CSF-based neurochemical dementia diagnostics by establishing European standard operating procedures (51).

Immuno-polymerase chain reaction (iPCR) and immunoprecipitation are being used to develop an assay for Aβ oligomers in CSF and blood in the EDAR project. EDAR includes 11 partners from 6 countries and began in 2007 (52).

The Neuroscreen Project is to develop a specific iPCR application for the differential diagnosis of AD, PD and Creutzfeldt-Jakob disease via detection of specific direct and indirect amyloid-related markers in the CSF and/or blood (53).

Among other diverse efforts are those of a team studying the immunological reactions to different serotypes of adeno-associated virus (AAV) in a project aimed at facilitating the development of vectors targeted to different cell types in the brain (54).

As discussed above, the MimoVax vaccine program, utilizing AFFiRiS' AFFITOPE® technology, is targeting truncated and modified forms of the Aβ peptide that causes AD. Experiments in human APP mice have demonstrated reduced amyloid plaque load and associated alterations in the brain with a MimoVax vaccine (55).

The LipiDiDiet Project includes 16 specialists from Europe and Israel and has 60 months of E.U. funding to explore the benefit of nutritional lipids on neuronal and cognitive performance in aging, AD and vascular dementia. The project includes a basic research arm to develop advanced nutritional formulations, a clinical section to evaluate formulations in a large, multicenter clinical trial and to assess population-based and diet-related risk factors, and a production arm to improve the quality and production processes and product features for consumers (56).

BrainNet Europe (BNE) is a network of 19 brain banks created to acquire and distribute well-characterized and high-quality CNS tissues for basic research in neuroscience. The brain bank also has among its goals the development of standards for tissue handling, safety aspects, quality control and ethics (57).

Lastly, a 3-year PhD training program for scientists focusing on AD was created by a consortium of AD scientists from 10 universities and 8 companies and named NEURAD. The consortium includes scientists involved in the comparative analysis of transgenic mouse models of AD, in novel therapeutic strategies and in clinical therapy studies, efforts from which the students will benefit (58).

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