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MEETING REPORT

NEWS FROM THE 10TH INTERNATIONAL CONFERENCE ON ALZHEIMER'S AND PARKINSON'S DISEASES (AD/PD)

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SUMMARY

Barcelona was the setting for this year's International Conference on Alzheimer's and Parkinson's Diseases (AD/PD), the 10th installment of the biennial congress, held on March 9-13, 2011. Consistent with the previous meeting in Prague, a great breadth and depth of new information was provided on the diagnosis and treatment of Alzheimer's disease, Parkinson's disease and related disorders. The oral and poster sessions have been mined for data on the newest treatments that have shown therapeutic potential in early investigations. Also highlighted are presentations on new compounds for imaging in Alzheimer's disease, as well as an oral session that provided greater context for the ongoing search for understanding and conquering these diseases.

INTRODUCTION

A synopsis of the first symposium held at the congress, Challenges and Potential Treatments in AD and PD, sets the stage for an overview of new compounds in early development for imaging and treating Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS).

"Why have we failed to find a cure for AD?" asked Amos Korczyn in the first talk, which highlighted conceptual obstacles hindering these efforts (1). One problem is the search for a magic bullet, the emphasis on many simple solutions for a complex problem. Simple solutions are undermined by incorrect assumptions. The first of these assumptions is that AD is easy to diagnose. AD is not a single entity, but has multiple facets, and clinical diagnosis is frequently inaccurate. A second assumption concerns pathology as the gold standard for diagnosis, when pathology cannot diagnose dementia; plaques and tangles can be seen in nondemented subjects and plaque load does not correlate with dementia severity, among other limitations. That plaques and tangles occur in elderly individuals without dementia points to a third incorrect assumption: AD is defined by characteristic histological changes. The question remains as to whether amyloid plaques, neurofibrillary tangles, synaptic loss, cholinergic depletion or hippocampal degeneration are responsible for cognitive decline. It is also incorrectly assumed that sporadic AD follows the same pathological route as familial presenile AD. How β-amyloid (Aβ) is related to sporadic AD is uncertain; it appears unlikely that AD is due to enhanced Aβ production, as it is inconsistent with reduced cerebrospinal fluid Aβ concentrations. AD is associated with Aβ deposits by definition, implying that the disease is caused by Aβ, but Aβ deposition could just be an epiphenomenon in sporadic AD.

A further dubious assumption highlighted by Dr. Korczyn is that transgenic animal models mimic the important steps in human neurodegenerative processes. Animal models are limited by several factors, including the absence of consistent neuronal loss, the lack of an inflammatory response, the lack of consistent tau deposition and the absence of progressive cognitive impairment. Also incorrect is the notion that a cure will result from eliminating the amyloid load in the brain. Therapies targeting amyloid or tau are aimed at downstream markers, which are not necessarily pathologically important. The idea that AD is a homogeneous disease entity is also mistaken; almost all dementias are mixed dementia. The differentiation of AD and vascular dementia is impossible, as the two entities share risk factors, phenomenology, evolution and therapy.

Dr. Korczyn concluded that curative therapy is unlikely, that preventive therapy should start early and that therapy should be directed against many targets simultaneously.

Fabrizio Stocchi reviewed new treatment strategies for PD, beginning with the deficiencies of L-dopa, notably its short half-life and the unreliable exposure after administration (2). **IPX-066** (a combination of carbidopa and levodopa) represents an improvement in levodopa delivery, with a longer half-life, and is headed for phase III development. The dopaminergic agent **pardoprunox hydrochloride** demonstrated efficacy in the MPTP marmoset model, with a duration of action longer than levodopa, and entered phase III development, but has been hindered by side effects. The compound has

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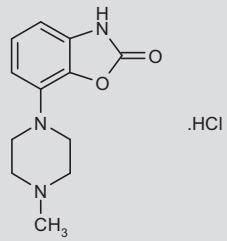
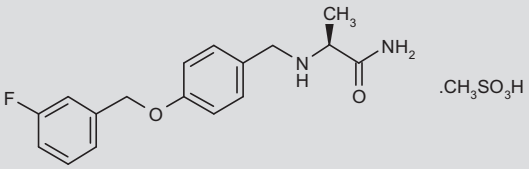
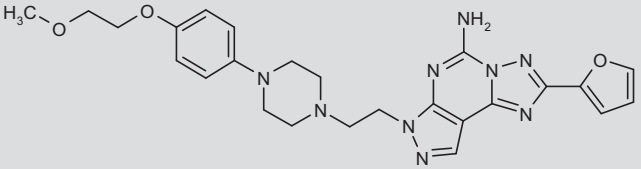


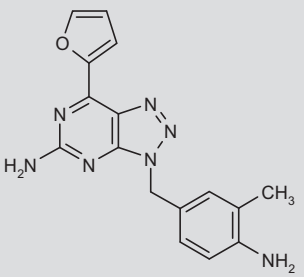
Pardoprunox hydrochloride



Safinamide mesilate



Preladenant



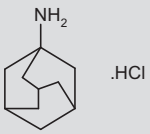
Vipadenant

been evaluated in a pilot study as an add-on treatment to levodopa therapy for treating dyskinesia. A treatment that may reach the market this year is the dopamine uptake inhibitor and monoamine oxidase type B (MAO) B inhibitor **safinamide mesilate** as adjunctive treatment with a dopamine agonist or levodopa. Nondopaminergic therapies under investigation include the adenosine A_{2A} receptor antagonist **preladenant**, which is undergoing phase III evaluation in early, de novo patients and in patients with fluctuations. Another agent with the same mechanism of action, **vipadenant**, showed promise in clinical studies but was discontinued.

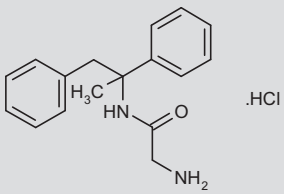
Other mechanisms of action with potential for PD treatment include NMDA receptor antagonism, represented by **amantadine hydrochloride**, **remacemide hydrochloride** and **riluzole** (Rilutek®). AMPA receptor antagonism is represented by **talampanel**, which may reduce levodopa-induced dyskinesia and is in phase II development. Lastly, the metabotropic glutamate $mGlu_5$ receptor antagonist **AFQ-056** has demonstrated antidyskinetic effects and is in phase II development for PD.

Anthony Schapira discussed the prodrome of PD, noting that the PD process begins years before diagnosis (3). A variety of genetic mutations have been linked to the risk for the disease, but multiple other factors have been implicated in its pathogenesis, including environmental factors, oxidative stress, mitochondrial dysfunction, intracellular calcium homeostasis, excitotoxicity, inflammation, protein dysfunction, apoptosis and autophagy. How long is the presymptomatic period of PD? Answers vary, with clinical clues suggesting 3-8 years, pathological clues suggesting 7-8 years, imaging clues suggesting 7-8 years and genetic causes perhaps existing for decades. Establishing risk for PD requires assessment of clinical features, genetic mutations, imaging markers and biochemical markers. The prodrome may not only help identify patients at risk, but therapeutic targets as well, and attacking multiple targets is likely to be of greater benefit than focusing on a single one.

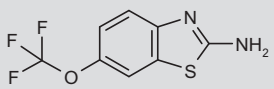
Raymond Bartus followed with a description of the development of **CERE-120**, which is intended to improve the control of motor symptoms in moderate to late stages of PD (4). Neurotrophic factors offer the potential for repairing damaged neurons, restoring function and protecting against continued degeneration and disease progression, but their delivery has been problematic. CERE-120 is intended to solve the delivery problems by employing an adeno-associated virus type 2 vector to encode a modified human neurturin (*NRTN*) gene. Efficacy has been seen with CERE-120 in rodent and monkey models of PD, as well as controlled protein expression, with an orderly dose response. In addition, no side effects have been seen in rats and monkeys followed for up to 1 year. Three clinical trials have been completed and a revised double-blind phase IIb study with sham surgery control is ongoing. No safety issues have arisen in 60 subjects treated thus far. In a previous double-blind trial with sham surgery control, proof of concept was achieved (significant improvement in Unified Parkinson's Disease Rating Scale [UPDRS] motor off scores), although efficacy through 12 months was insufficient for FDA registration. The results provided the first evidence of a clinical benefit for gene therapy in PD. Further evidence of CERE-120 proof of concept was also derived from autopsy studies. Other studies related to the dosing approach used for CERE-120 pointed to the importance of administration to the substantia nigra. This appeared to be without toxicity in rat studies. A revised phase I/II protocol including intraputaminal and intranigral administration was devised, with two dose cohorts. No serious adverse events, surgical complications, unexpected adverse events or weight loss were seen



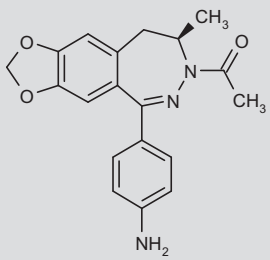
Amantadine hydrochloride



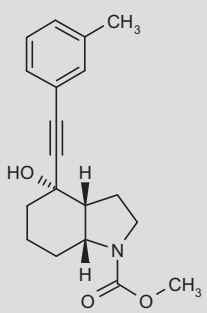
Remacemide hydrochloride



Riluzole



Talampanel



AFQ-056

in the phase I portion. Dosing from the ongoing phase II portion in 52 subjects given the high dose from phase I is to be completed in the summer of 2011 and topline data are expected in the fourth quarter of 2012.

The approach of treating or preventing AD by immunization targeting Aβ was discussed by Jean-Marc Orgogozo, focusing on **CAD-106** (5). The first phase II trial evaluating the approach assessed the effects of **AN-1792**, with neuropathological findings of total plaque removal providing proof of concept. Subacute meningoencephalitis was observed in some immunized patients, however, and development of the agent was discontinued. An active immunization vaccine targeting Aβ protein is in development as part of a collaboration between Lundbeck and Pharmexa; preclinical proof of concept has been obtained. CAD-106 induces Aβ-specific antibodies without stimulating Aβ-reactive T cells. The vaccine has been associated with reduced amyloid burden in the brains of transgenic APP mice, with larger effects seen with longer treatment and initiation at an earlier age. Experiments in mice also indicated that CAD-106 does not induce microhemorrhages. In rhesus monkeys, CAD-106 induced monkey Aβ antibodies, protecting against the toxicity of $A\beta_{1\text{-}42}$ and fibrillar $A\beta_{1\text{-}40}$.

In the first-in-man study in elderly AD patients, CAD-106 was administered at doses of 50 μg at weeks 0, 6 and 18 or 150 μg at weeks 0, 2 and 6. There were no deaths and no differences in serious adverse events between subjects treated with CAD-106 or placebo. Most adverse events were mild. An Aβ IgG response was noted in 16 of 24 subjects in the 50-μg cohort and in 18 of 22 individuals in the 150-μg cohort, with double the level of Aβ-specific IgG antibodies seen in the higher dose group. There were no cases of meningoencephalitis. These doses are being investigated in two ongoing trials evaluating two injection schedules in patients with mild AD.

The last presentation at the symposium, given by Alireza Atri, was an assessment of the value of long-term observational patient cohort (LTOC) studies of combination therapy (a cholinesterase inhibitor plus memantine) for AD (6). Randomized, controlled trials are the gold standard for determining the efficacy of anti-dementia interventions for regulatory approval within the shortest time. Such trials reveal signals of drug benefit in a leveraged population and minimize adverse effects. LTOC studies are pragmatic studies of clinical effectiveness, last years, are conducted in a naturalistic patient care setting and have a high external validity. They provide information on long-term clinical trajectory and endpoints, and a long-term risk–benefit balance.

The approaches mark the difference between efficacy, determining whether an intervention can work, and effectiveness, determining whether it works in normal practice. Dr. Atri noted that long-term studies are necessary, as AD is a chronic and progressive disease, and short-term studies are not suited to assess the real-world clinical and economic impact of treatments. Practical and ethical constraints have meant that few randomized, controlled trials are over a year in length. In addition to longer durations and larger populations, the inclusion of real patients in LTOC studies reveals the impact of comorbidities, concurrent medications and treatment adherence. LTOC studies are also less expensive than randomized, controlled trials.

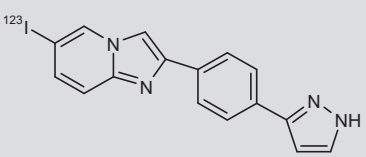
A review of published data indicates that LTOC studies in AD support the short-term data from randomized, controlled trials, showing that the cholinesterase inhibitor and memantine combination is

superior to a cholinesterase inhibitor alone in reducing cognitive and functional decline and in delaying the time to nursing home admission. Benefits increased over time.

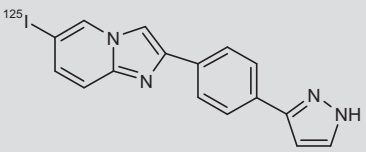
LTOC studies are nevertheless limited by the lack of randomization, selection factors associated with long-term drug exposure, which may influence results, and by the fact that adjustment for baseline variables may not fully control for potentially confounding factors. It was concluded that randomized, controlled trials are indeed the gold standard, but are a means and not an end. As they are limited by ethical and practical considerations, they can be usefully augmented by naturalistic LTOC studies providing pragmatic, long-term data on treatment effects. LTOCs can also inform the design of randomized, controlled studies. Finally, Dr. Atri called for the creation of an international cooperative network to coordinate and pool similar LTOC studies.

NEW IMAGING CANDIDATES

Noninvasive SPECT imaging could be used to detect pathological changes in the brain signifying prodromal AD and to evaluate responses to treatment. A suitable tracer is required, but some candidate tracers have been limited by short half-lives and production procedures limiting availability. For this reason, scientists at Daiichi Sankyo and FUJIFILM RI Pharma synthesized [^{123}I]-labeled DRM-106, **123I-DRM-106**, which binds Aβ. Studies were performed using **125I-DRM-106** (123I, $t_{1/2}$ = 13.2 hours; 125I, $t_{1/2}$ = 59 days). In vitro binding assessments showed dissociation constants for synthetic $A\beta_{1\text{-}40}$ fibrils of 1.5 and 140 nmol/L for high- and low-affinity binding sites, respectively. K_d values for the high- and low-affinity binding sites for brain homogenates from transgenic mice expressing mutant amyloid precursor protein (APP Tg2576) were 4.2 and 264 nmol/L, respectively. For frontal cortex homogenates from one patient with AD K_d values were 4.3 and 101 nmol/L, respectively, for the high- and low-affinity binding sites, and K_d values for homogenates from a second patient were 2.8 and 109 nmol/L, respectively. Specific binding of 125I-DRM-106 increased with the amount of Aβ in brain homogenates. In normal rats, 125I-DRM-106 crossed the blood–brain barrier and was rapidly washed out. Amyloid plaques were also labeled via injection of Tg2576 mice with 125I-DRM-106, and its accumulation correlated with thioflavin-S and Congo red staining. The results indicated the potential of 125I-DRM-106 as a candidate for noninvasive SPECT imaging of amyloid plaque in the brain of AD patients (7). The agents have been described in the patent literature (WO 2007063946; JP 2009007348).



123I-DRM-106



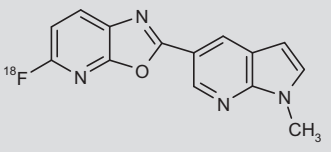
125I-DRM-106

Merck & Co.'s novel PET tracer **[^{18}F]-MK-3328** exhibited a favorable pharmacological profile in a recent study and is expected to be further evaluated in clinical settings for the detection of Aβ plaques in the brain of patients with AD. Cortical tissues from three subjects with AD and three age-matched healthy individuals were used in in vitro binding and autoradiographic analyses with [^{18}F]-MK-3328. The agent bound to Aβ plaques with K_d and B_{max} values of 17 and 1600 nM, respectively. Autoradiographic data demonstrated punctate binding of the compound on Aβ plaques in brain slices obtained from the frontal cortex of patients with AD. This binding was not displaced significantly by the MAO-B (flavin-containing) inhibitor lazabemide. Evaluation of the biodistribution and dosimetry of [^{18}F]-MK-3328 following delivery of the tracer (at approximately 145 MBq) in healthy volunteers revealed a favorable effective dose of 18.2 mSv/MBq. The agent displayed distribution volume ratio values that were comparable with those obtained with florbetapir, florbetaben and Pittsburgh compound B ([^{11}C]-PIB) (8).

NEW TREATMENT CANDIDATES

Alzheimer's disease

Noscira researchers have screened marine natural products in an attempt to identify compounds with neuroprotective activity. Among molecules isolated from *Streptomyces* species demonstrating antioxidant activity, **NPM-01** was selected as the prototype and protected neuroblastoma cells from H_2O_2-induced death with an EC_{50} of 19 nM. A time- and concentration-dependent reduction in $A\beta_{40}$ secretion was also observed with NPM-01 in an APP751-transfected cell line. This correlated with an increase in soluble sAPPα, suggesting that the effect is mediated by activation of α-secretase. An active medicinal chemistry program developed to improve the properties of the chemical series yielded over 250 compounds. For the most potent compounds, EC_{50} values for increase in sAPPα ranged from

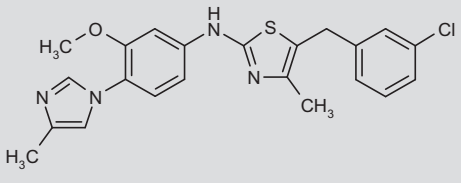


[^{18}F]-MK-3328

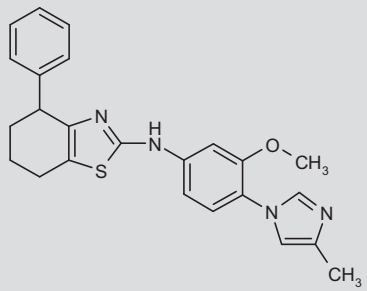
40 nM to 300 nM and maximum effects on sAPPα (amount over 100% basal level) ranged from 140% to 360%. The data are currently being evaluated in order to synthesize compounds with good potency and efficiency for the treatment and/or prevention of oxidative stress-induced disorders, particularly neurodegenerative diseases such as AD (9).

Although its function in the brain is unknown, the Klotho protein has been linked to several processes related to aging in animal studies. Decreased Klotho expression has been identified in the brain of aged animals and in mouse models of AD. Klotho was found to induce maturation in primary oligodendrocyte precursor cells and the brains of Klotho knockout mice displayed decreased myelin protein expression. These and other findings led investigators at Beth Israel Deaconess Medical Center, Boston University School of Medicine, Harvard Medical School and the University of Texas at Dallas to the hypothesis that Klotho has a neuroprotective function, and its age-dependent reduction can lead to neurodegeneration. Upregulation of Klotho expression or secretion may therefore be beneficial. On this basis, high-throughput screening using a Klotho promoter-driven luciferase system was undertaken to identify compounds that increase Klotho expression. The lead compounds with the greatest potency were **LDN-0187608** (EC_{50} = 0.05 μM) and **LDN-0192753** (EC_{50} = 0.02 μM). Further investigation will be directed towards determining if these or related compounds can ameliorate the hypothesized effects of decreased Klotho on myelin repair. Such activity may be useful in treating not only AD, but also other neurodegenerative diseases, such as multiple sclerosis (10).

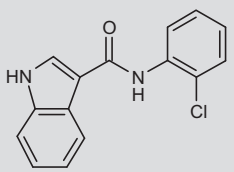
Roche disclosed the development of novel compounds that act as modulators rather than inhibitors of the activity of γ-secretase for the treatment of AD. The agents act by shifting the formation of toxic $Aβ_{42}$ to shorter nontoxic Aβ fragments and are expected to overcome the toxicity in the thymus, gut and spleen seen with γ-secretase inhibitors. Structure–activity relationship optimization of a lead compound belonging to the aminothiazole class led to the identification of compounds [**I**] and [**II**], which acted as potent modulators of the activity of γ-secretase, with respective IC_{50} values of 127 and 30 nM against $Aβ_{42}$ in rat primary neurons. Pharmacokinetic analysis in rats revealed half-lives of 2.5 and 2.6 hours and oral bioavailabilities of 64% and 25%, respectively, for [I] and [II] (11). Compounds [I] and [II] have been described in the patent literature (WO 2008138753 and WO 2009087127, respectively).



[I]



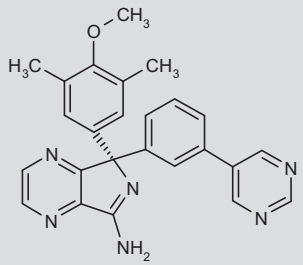
[II]



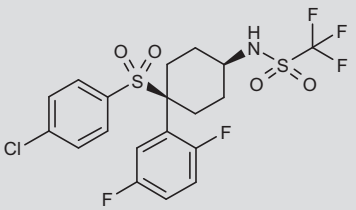
LDN-0187608

The Laboratory for Experimental Alzheimer Drugs (LEAD) at Harvard Medical School and Brigham & Women's Hospital has sought γ-secretase inhibitors that do not affect Notch signaling in the hope of discovering compounds for the treatment of AD that lower Aβ production without Notch-related adverse effects. Evaluation of over 1,000 novel compounds resulted in the identification of Notch-sparing molecules that selectively block Aβ production. A preliminary compound, **AD-749**, showed cellular IC_{50} values of 89 nM for $Aβ_{1-42}$, 88 nM for $Aβ_{1-40}$ and 34.3 μM for Notch (Notch:$Aβ_{1-42}$ ratio = 386). The agent was also characterized by a brain:plasma ratio of 0.4, a half-life of 2 hours and an oral bioavailability of 45%; it was nontoxic, displayed excellent solubility and had a reasonable molecular weight. When administered to female hAPP(751)SL transgenic mice for 7 days, Aβ levels were reduced in the hippocampus (10-38% and 33-54%, respectively, at 50 and 100 mg/kg p.o.) and cortex (6-33% at 50 mg/kg p.o.), but not in cerebrospinal fluid, and there were no observable side effects. Next-generation compounds have been identified, including **AD-861** (cellular $Aβ_{1-42}$ IC_{50} = 4 nM; Notch IC_{50} = 2.4 μM; Notch:$Aβ_{1-42}$ ratio = 370) and **AD-1038** (cellular $Aβ_{1-42}$ IC_{50} = 2 nM; Notch IC_{50} = 1.6 μM; Notch:$Aβ_{1-42}$ = ratio 800) (12).

Preclinical data on the ability of two of AstraZeneca's inhibitors of β-secretase 1 (β-site amyloid precursor protein cleaving enzyme 1) to inhibit Aβ production were detailed at the meeting. In SH-SY5Y cells, **AZ-13** reduced secreted soluble APPβ in a concentration-dependent manner, with an IC_{50} of 12 nM. In SH-SY5Y cells overexpressing wild-type isoform APP695 (APP695wt), incubation with AZ-13 resulted in a concentration-dependent reduction of secreted $APPβ_{40}$, with an IC_{50} of 5 nM. Concentration-dependent reductions in secreted $Aβ_{40}$ were also seen in primary murine cortical neurons



AZ-13



MRK-560

treated overnight with AZ-13, with an IC_{50} of 34 nM. In addition, concentration-dependent decreases in soluble APPβ and Aβ were observed in brain and plasma in C57BL/6 mice given a single oral dose of AZ-13 (13). AZ-13 has been described in the patent literature (WO 2011002409).

In guinea pigs, oral gavage with **AZ-78** was associated with concentration-dependent reductions in plasma and brain $APPβ_{40}$ and $APPβ_{42}$, with good brain penetration of the compound observed. Maximum reductions in plasma Aβ (70-80%) occurred after 3 hours, while maximum reduction of brain Aβ (40-50%) was noted after 1.5 hours. A concentration- and time-dependent decrease of Aβ in cerebrospinal fluid was also seen in guinea pigs, with the effect in cerebrospinal fluid slightly delayed compared to that in the brain (14).

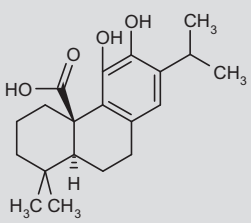
AZ-13 and AZ-78 also demonstrated selectivity for human β-secretase 1 over human β-secretase 2 and human cathepsin D in TR-FRET assays, as well as good permeability in human Caco-2 cells (15).

To generate novel compounds targeting the advanced glycosylation end product-specific receptor (RAGE, AGER) for the treatment of AD, Medifron researchers, in collaboration with the Seoul National University, analyzed the pharmacophores of patented compounds and established a pharmacophoric model. Based on the model, 700 compounds were designed, synthesized and evaluated in in vitro assays (luciferase reporter assay, artificial blood–brain barrier assay) for RAGE antagonism. Promising compounds were then assessed for efficacy in double transgenic mice (APPswe/PS1Ed9). These tests led to the selection of a lead compound, **CKH-66**, for further evaluation. Oral administration of CKH-66 for 4 weeks to transgenic mice was associated with significant reductions in Aβ in the brain and Congo red staining of hippocampal slices revealed reduced plaque burden; recovery was also seen in Y-maze and fear conditioning memory tests (16).

The γ-secretase inhibitor **MRK-560** has demonstrated efficacy and tolerability in vivo, unlike many other γ-secretase inhibitors, which display mechanism-based toxicity due to disturbed Notch signaling. Studies conducted by scientists from AstraZeneca, the Karolinska Institutet and Flanders Interuniversity for Biotechnology have shown that this may be due to the fact that MRK-560 displays a preference for γ-secretases containing presenilin-1 (PS-1) over those containing presenilin-2 (PS-2). MRK-560 displayed greater potency in inhibiting Aβ formation and Notch intracellular domain (NICD) formation in HEK 293 cells overexpressing PS-1 than in cells overexpressing PS-2. Binding studies in membranes prepared from both types of cells showed that MRK-560 was more efficient in displacing the competing γ-secretase inhibitor [^{3}H]-DBZ in cells overexpressing PS-1; [^{3}H]-DBZ displacement was partial, suggesting a different binding interaction of the compounds with γ-secretase (17).

When MRK-560 was administered to wild-type and *PS2* knockout mice once daily for 4 days, the two groups of animals displayed similar levels of exposure and Aβ reductions in brain and plasma. However, *PS2* knockout mice displayed goblet cell metaplasia, thymus atrophy and depletion of the splenic marginal zone, while the agent was well tolerated in wild-type mice. In addition, greater inhibition of Notch signaling was seen in jejuna of *PS2* knockout mice than in wild-type mice. By displaying a preference for γ-secretase containing PS-1, MRK-560 may be effective without affecting essential PS-2-mediated γ-secretase signaling in the periphery (18).

Researchers from Iran University of Medical Sciences presented preclinical results suggesting that **carnosic acid** may protect against neurodegeneration in AD. Vehicle or carnosic acid was administered to rats at 10 mg/kg i.p. 1 hour before bilateral intrahippocampal injection of Aβ protein (4 μL of a solution of 1.5 nmol/μL) or sham opera-



Carnosic acid

tion at 3-4 hours after the operation (carnosic acid 3 mg/kg i.p.) and each afternoon for 12 days. Pretreatment with 10 mg/kg i.p. carnosic acid led to decreased cell death and reduced levels of caspase-3 -positive neurons in the CA1 region of the hippocampus in lesioned rats compared with the levels in vehicle-treated lesioned rats (19).

NeuroPhage's **NPT-001**, a filamentous bacteriophage M13 which binds to Aβ, has been shown to disaggregate Aβ plaque in vitro and to reduce Aβ plaque in four different APP-overexpressing transgenic mouse models. The duration of such effects and whether they are associated with functional improvement were assessed in 19-month-old female Tg2576 mice receiving bilateral intrahippocampal injections of NPT-001. Dense core Aβ plaque was significantly reduced at 1, 2 and 3 weeks after injection with NPT-001 compared to vehicle treatment, while diffuse Aβ plaque was reduced significantly at week 2. Aβ plaque was also reduced with NPT-001 in the cortex. Synaptophysin staining was decreased in vehicle-treated transgenic mice compared to wild-type mice, but was significantly increased at week 2 in hippocampus and cortex in transgenic mice treated with NPT-001. Evaluation of locomotor activity revealed a decrease in hyperactivity in transgenic mice administered NPT-001, while a Y-maze test revealed a trend towards an improvement in spatial working memory. There were no adverse effects observed with NPT-001 treatment. A phase I study is being planned in patients with AD, which will include an amyloid imaging agent to provide evidence of treatment activity (20).

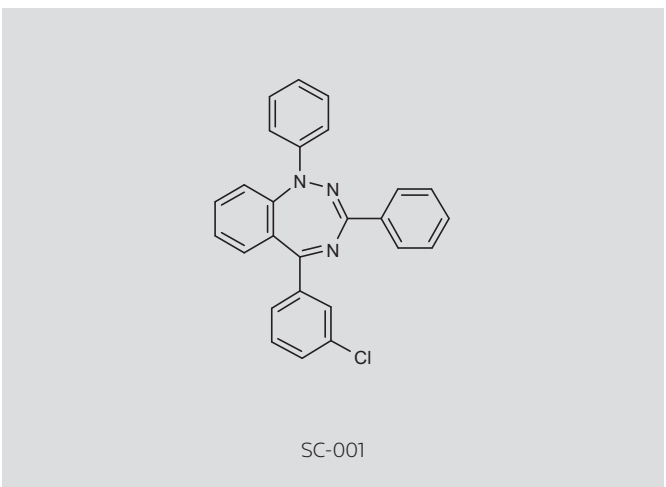
Parkinson's disease

Screening of a library of 400 chemically diverse compounds at the Spanish Consejo Superior de Investigaciones Científicas (CSIC) led to the identification of **SC-001**, a glycogen synthase kinase-3 (GSK-3) inhibitor that may hold potential as a therapeutic candidate for the treatment of PD. In in vitro enzymatic assays, SC-001 inhibited the activity of GSK-3 with an IC_{50} of 3.38 μM. At 10 μM, it significantly protected SH-SY5Y cells from 6-hydroxydopamine (6-OHDA)-induced death and exhibited neuroprotective and antiinflammatory effects in neuronal HT22 cells treated with 100 μM glutamate and in glial cell cultures challenged with 10 μg/mL lipopolysaccharide (LPS), respectively. In vivo injection of SC-001 (15 nmol) into the substantia nigra pars compacta of adult rats challenged with LPS (10 μg) was associated with a reduction in the susceptibility of neurons to LPS-induced toxicity (21).

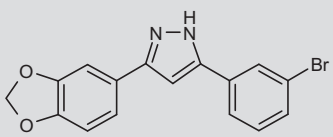
Investigators from Ludwig-Maximilians-Universitat and Max-Planck-Gesellschaft described the results of a screening effort to identify compounds capable of inhibiting protein aggregation with potential for the treatment of PD. Primary screening using scanning for intensely fluorescent targets (SIFT) and cell culture assays led to the identification of **ANLE-138b**, which inhibited the disease-associated form of prion protein, PrPSc, by 84% at 0.2 μM in cell culture. In prion-infected mice, ANLE-138b administered orally reduced PrPSc accumulation by 57-108%, reduced neuronal cell death and prolonged survival. Assessment of pharmacokinetics in mice revealed good blood–brain barrier penetration (serum:brain ratio of 1:3) following administration of 1 mg i.p. and 1 or 5 mg p.o., as well as excellent oral bioavailability. In the MPTP model of PD, ANLE-138b inhibited dopaminergic cell death in the substantia nigra at 5 mg/day p.o., while in α-synuclein transgenic mice, the compound reduced α-synuclein deposition in the brainstem, improved rotarod performance and prolonged survival. No toxicity was observed at the doses used. The findings indicate promise for the treatment of neurodegenerative disorders (22). ANLE-138b has been described in the patent literature (WO 2010000372).

Amyotrophic lateral sclerosis

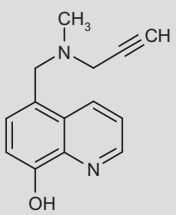
Varinel's multifunctional neuroprotective iron-chelating agent **M-30** (VAR-10300) is being investigated for its beneficial activity in treating AD. A team of investigators has also reported its potential for the treatment of ALS. M-30 was developed at the Technion Israel



SC-001



ANLE-138b



M-30

Institute of Technology in collaboration with the Weizmann Institute of Science, and displays a unique combination of pharmacological activities, including selective iron chelation, selective irreversible inhibition of MAO-A and -B, neurotrophic properties and antiapoptotic properties.

In the motor neuron-like cell line NSC-34, exposure to M-30 was associated with increased transferrin receptor protein (TfR) expression, increased expression of neuromodulin (growth-associated protein 43, GAP-43) and increased NSC-34 cell differentiation, as well as increased protein kinase C (PKC) and mitogen-activated protein kinase (MAPK, ERK-1/2). The neuritogenic effects of the agent were reduced by inhibitors of PKC and MAPK/ERK in NSC-34 cells. M-30 also upregulated the expression of hypoxia-inducible factor 1-α (HIF-1-α) and HIF-regulated genes, including *ENO1*, *VEGF* and *BDNF*. In the SOD1-G93A transgenic mouse model of ALS, M-30 1 mg/kg 4 times weekly significantly improved survival (from 124 to 134 days), improved motor deficits and delayed the onset of motor dysfunction. Furthermore, the compound reduced iron accumulation in the spinal cord in the SOD1-G93A model, while increasing motor neuron survival and attenuating astrocyte activation in the lumbar spinal cord (23).

DISCLOSURES

The author states no conflicts of interest.

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