MEETING REPORT

Highlights of the Society for Medicines Research symposium held on June 6, 2007, at the Eli Lilly Research Centre in Surrey, U.K.

Neurodegenerative Disorders and their Treatment

by Eric Karran and Alan M. Palmer

Summary

This Society for Medicines Research symposium was held on June 6, 2007, at the Eli Lilly Research Centre in Windlesham, Surrey, United Kingdom. The meeting, organized by Eric Karran and Alan Palmer, reviewed the progress made, and the challenges still to be overcome, in discovering safe and effective therapies for the most common chronic neurodegenerative diseases: Alzheimer's disease, Parkinson's disease and multiple sclerosis. Progress in establishing effective pharmacotherapy for acute neurodegenerative disorders (stroke and traumatic brain injury) was also reviewed. © 2007 Prous Science. All rights reserved.

Neurodegenerative disorders represent a challenging unmet medical need. As the incidence of chronic neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, increases with age, the expected demographic change to a more elderly population will increase considerably the socioeconomic burden of these devastating conditions. While current treatments are palliative only, with increasing understanding of the biological basis of these disorders, there is now a realistic prospect for drugs that slow, or even halt, the process of neurodegeneration. This meeting reviewed the progress made in the discovery and development of medicines to treat neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), traumatic brain injury (TBI), stroke and multiple sclerosis (MS), and considered future prospects for effective pharmacotherapy, including the possibility of slowing, or even halting, the course of neurodegenerative disorders.

Jill Richardson (GlaxoSmithKline, Harlow, Essex, U.K.) set the scene for the meeting with a comprehensive overview of the incidence and prevalence of AD, PD and MS. By 2050, the prevalence of AD will have tripled, to 1.5 million patients in Italy, the United Kingdom, Spain, Germany and France combined (compared with nearly 15 million patients in the United States). In the same regions, PD is predicted to have a prevalence of 1.1 million, with MS not that far behind with 0.5 million. Recombinant interferons have been approved in many countries for treatment of relapsing-remitting MS, but, despite claims to the contrary, their ability to modify disease course has not been clearly established.[1] By contrast, no disease-modifying therapies are yet available for AD and PD. Symptomatic drugs are on the market, but they are associated with serious side effects in PD and provide only modest improve-

ments in cognitive status in patients with probable AD.

The deposition of amyloid in the brains of AD patients, as well as the strong human genetic links to amyloid pathology, has made the amyloid cascade hypothesis[2] a central theme in the CNS drug discovery efforts of many pharmaceutical companies. As a consequence, several potential therapies are currently in late-stage clinical testing for AD. These include Myriad's *Flurizan*™ (**tarenflurbil**), Neurochem's *Alzhemed*™ (**tramiprosate**), Wyeth/Elan's anti-Aβ antibody **bapineuzumab**, Lilly's anti-Aβ antibody **LY-2062430** and Lilly's γ-secretase inhibitor **LY-450139**.

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GlaxoSmithKline are working on therapies to reduce beta amyloid (Aβ) production, including inhibitors of BACE1 (β-APP cleaving enzyme-1) and have demonstrated, for the first time, *in vivo* Aβ-lowering efficacy in the TAST-TM transgenic mouse model with a BACE inhibitor administered via the oral route. In addition to therapies targeting amyloid deposition, GlaxoSmithKline are also seeking targets and agents to ameliorate the inflammatory response seen in the brains of AD patients.

For PD, the discovery in 2004 of Leucine Rich Repeat Kinase-2 (LRRK2) as a gene responsible for autosomal dominant disease[3] has stimulated research into the cellular mechanisms that result in the destruction of dopaminergic cells in PD with the promise of uncovering new targets amenable to therapeutic intervention. Current estimates suggest that LRRK2 is responsible for about 2% of all PD patients but can rise to greater than 10% in certain populations, such as Ashkenazi Jews.

Chronic neurodegenerative diseases

Alzheimer's disease

Roger Bullock (Kingshill Research Centre, Swindon, U.K.) gave a provocative talk on AD from a clinical perspective. While preclinical research tends to progress in a largely reductionist manner, AD presents itself clinically as a complex disorder so it could well be that certain therapies will work with certain subtypes of AD but not others. It is unlikely that a therapy targeting a single biochemical pathway (such as Aβ) will of itself be sufficient to halt the disease. Indeed, there are very few diseases where a single therapy is able to effect a "cure." It is also wise to remember that some of the processes being targeted may be physiologically important—for example, there is a literature that supports the case for a role of Aβ in synaptic activity and the expression of synaptic AMPA receptors. Likewise, while the

tau protein can be hyperphosphorylated in AD, phosphorylation of tau is a normal process that regulates its binding to and stabilization of microtubules. Hence, therapeutics aimed at reducing tau phosphorylation may have unwanted side effects. Finally, attention was drawn to the limitations of the clinical instruments used (e.g., the ADAS-cog) and how they may be inappropriate to the new therapeutic approaches coming into the clinical arena as it lacks an assessment of how cognitive decline affects the activities of daily living. The various types of clinical trial design that will be employed to determine whether any therapeutic intervention modifies the progression of the disease or affects just the symptoms are also theoretical constructs without real-life validation.

The two pathological hallmarks of AD are the presence of extracellular amyloid plaques and the intracellular deposition of "tangles" that are comprised of hyperphosphorylated tau protein in a paired helical conformation.[4] Tau is a microtubule stabilizing protein that is required for the intracellular transport of organelles within neurons. It is now known that mutations in tau that result in inherited fronto-temporal dementia and parkinsonism linked to Chromosome 17 cause both neuronal loss and patterns of abnormal tau deposition that are similar to those seen in AD.[5] Thus, it is likely that tau abnormalities in AD result in neuronal loss and it follows that approaches that intervene in the biochemical pathways that result in hyperphosphorylated tau may prove to be effective therapies for the disease. Lit-Fui Lau (Pfizer, Groton, Connecticut, U.S.A.) presented upon Pfizer's efforts to find selective inhibitors of cyclin-dependent kinase 5 (CDK5), a kinase that has been implicated in the hyperphosphorylation of tau. Lau described two compounds (**CP-668863** and **CP-681301**) that are potent and selective inhibitors of CDK5. CP-668863 has a K_i = 2.9 nM vs. CDK5, being 5.7-fold and 103-fold selective vs. CDK2 and glycogen synthase kinase (GSK)-3β, respectively.

CP-681301 has a K_i = 13.7 nM, being 2.8-fold and 40-fold selective vs. CDK2 and GSK-3β, respectively.

In CHO cells stably transfected with p25, CDK5 and tau, CP-681301 and CP-668863 had IC_{50} values of 513 nM and 470 nM, respectively. In co-crystallization studies with CDK2, CP-668863 bound within the ATP binding pocket and acts mechanistically as a competitive inhibitor.

While the *in vitro* and cellular activities of both compounds are very promising, demonstrating relevant *in vivo* efficacy has been challenging. Both compounds are highly brain permeable. No effects were seen with the compounds on endogenous tau phosphorylation in mice, although the relevance of this to AD pathology is questionable. When CP-668863 was infused via a miniosmotic pump for 6 weeks in inducible p25 tau mice, astrogliosis and caspase 3 cleavage— markers of activation of inflammation and apoptosis—were reduced. However, the variability of the model precluded a robust assessment of the effects of the compound on tau phosphorylation. In summary, these compounds are very good tools with which to dissect the role of CDK5 in models of tau phosphorylation and further studies in *in vivo* models of tau pathology are required to understand their potential for *in vivo* efficacy.

Parkinson's disease

Alan Crossman (University of Manchester, U.K.) reviewed current

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CP-681301
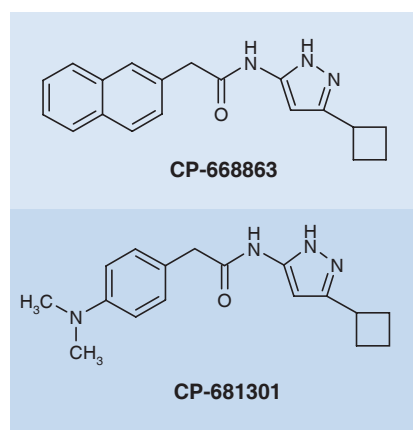
pharmacotherapy for PD. This disorder of movement is characterized by muscle rigidity, tremor, a slowing of physical movement (bradykinesia) and, in extreme cases, a complete loss of movement (akinesia). The primary symptoms occur as a consequence of the loss of dopamine neurons from substantia nigra of the ventral midbrain and the associated loss of dopamine innervation of the neostriatum (caudate nucleus and putamen). Secondary symptoms may include the loss of cognitive function, along with subtle language problems. The development of rational therapies to treat movement disorders, such as PD, depends heavily upon elucidation of the underlying neuronal changes that are responsible for the emergent symptoms. Professor Crossman reviewed changes in the neural pathways of movement disorders, particularly PD, along with the involvement of particular neurotransmitters and receptors.

Parkinsonism and various involuntary movement disorders (dyskinesias) can be replicated in animals better than any other functional neurological disorders, providing the opportunity to elucidate their mechanisms at the cellular and molecular levels and to identify novel therapeutic targets. In PD, the loss of dopamine neurons from the substantia nigra of the ventral midbrain and the associated loss of dopamine innervation in the neostriatum (caudate nucleus and putamen) are readily modeled in experimental animals using a range of neurotoxins, such as 6-hydroxydopamine (6-OHDA) and 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP).

Using a histological section that showed the key brain nuclei involved in the main symptomatology of PD, the mechanism of action and side effects of the main therapies available were explored. Drawing heavily on the direct (D_1-mediated) and indirect (D_2-mediated) pathways from the putamen to the globus pallidus external and internal segments as a model of basal ganglia connectivity, the effects of current dopamine-based therapies could be rationalized as the imbalance of excitatory (glutamate and aspartate) and inhibitory (γ-aminobutyric acid) regulation of the subthalamic nucleus. Currently, L-dihydroxyphenylalanine (L-DOPA) is still the gold-standard therapy for PD but, while its initial pharmacological effect in PD is dramatic, the period for which L-DOPA therapy successfully treats the symptoms of PD (tremor and bradykinesia) diminishes with duration of treatment. The dyskinesias and freezing that patients taking L-DOPA suffer represent serious side effects and treating these iatrogenic problems is currently an area of active research.

The basal ganglia have a rich diversity of different receptors (including opioid, nicotinic, muscarinic, adrenergic, histaminergic, serotonergic and adenosinergic receptors) and neuropeptides, particularly enkephalin. Because of this, a wide range of agents have been tested in models of PD, such as the MPTP-toxin model. In particular, the μ-opioid receptor appears to play a role in the development of the dyskinetic state which is often associated with increases in the mRNA for pre-proenkephalin B. In summary, therapies that halt the progression of PD are clearly the long-term objective for research into PD therapeutics, but in the interim agents that allow longer use of existing agents without incurring the serious side effects currently seen would also be of significant benefit to patients. Such compounds include the recently launched methyl-esterified form of L-DOPA (**melevodopa**) and the monoamine oxidase type B inhibitor **rasagiline**. A number of dopamine receptor agonists continue to progress through clinical trials. In terms of nondopaminergic treatments, $α_2$-adrenergic receptor antagonists and adenosine A_{2A} receptor antagonists remain in clinical trials.[6]

Cellular and regenerative approaches to the treatment of PD were reviewed by Stephen Dunnett (Cardiff University, Wales, U.K.). Transplantation of embryonic dopamine cells into the 6-OHDA lesioned rat and MPTP lesioned monkey striatum were the first model systems in which functional recovery after neurotransplantation in the brain was clearly demonstrated. Such studies have been the major driver of neurotransplantation research over the last 30 years. They also led to clinical studies. Early trials used tissue from the adrenal glands, but symptoms showed little improvement; this procedure is no longer used. Embryonic nigral grafts were shown to alleviate simple motor asymmetries and restore lateralized motor learning mediated by the affected striatum in experimental animals. Grafted into the neostriatum, the tissue produces dopamine and so, in theory, makes up for the loss of the normal dopamine-producing cells that occurs in PD. However, the use of embryonic dopamine tissue for the treatment of PD has been severely hampered by their relatively poor survival once implanted. This has been observed in both animal models of PD and in PD patients and is considered a major factor in the incomplete recovery seen in many clinical trials. Another serious constraint of using fetal material is its dependency on obtaining graft tissues from elective abortion, which will inevitably encounter significant practical difficulties in tissue availability, ethical acceptability and quality control. There is consequently an active search to identify a more suitable and robust donor source, with adult stem cells being the current hottest option.

In has generally been assumed that fetal tissue grafts work by replacement of the lost dopamine cells and their afferent regulation of striatal activation, but in recent years, it has become apparent that other regenerative mechanisms may play a role. Support for such a mechanism is provided by the intrinsic plasticity of forebrain dopamine systems. In early PD, symptoms only become apparent once denervation exceeds approximately 70%. The challenge then is to augment this functional compensation by stimulating structural plasticity. Several stem cell and trophic factor strategies almost certainly exert their effects via promoting sprouting and reorganization

within host systems. But this leaves the major issue of how to deliver large trophic factor molecules (such as glial-derived neurotrophic factor [GDNF]) across the blood–brain barrier to structures deep within the brain. Following proof of the neuroprotective concept with central injection of trophic factors, caspase inhibitors etc., sustainable delivery using new gene therapy strategies is under active development (e.g., GDNF via adeno-associated virus or lentiviral vectors).

Although clear success of the initial clinical trials of nigral and adrenal transplants in patients with PD was not demonstrated, many of the critical factors are identified and under active investigation. The promise of neural transplantation in PD has therefore not yet been realized. Nonetheless, it has proven to be a powerful tool for studying basic biology, functional organization and plasticity of central dopamine systems.[7]

Multiple sclerosis

Kenneth J. Smith (King's College London, U.K.) considered strategies to prevent axonal degeneration in MS. The creeping paralysis that characterizes MS, particularly in its progressive forms, is caused by degeneration of neuronal axons. However, the mechanism(s) responsible for such degenerative changes are not yet known. Pathological studies suggest a role for inflammation or inflammatory mediators or both. These include the free radical nitric oxide (NO). NO is a reactive and potentially toxic agent and it has been shown that NO-mediated axonal damage can result in axonal degeneration, especially if the axons are electrically active while exposed to NO.

The cause of the degeneration is not fully understood, but the available evidence suggests that the NO exposure inhibits mitochondrial function so that ATP production is impaired. The ATP-dependent sodium/potassium pump therefore fails to cope with the enhanced sodium ion entry due to the electrical activity, and so the intra-axonal sodium ion concentration rises.

Professor Smith suggested that high concentration of sodium in the axon permits the sodium/calcium exchange molecule to operate in reverse mode, importing damaging calcium ions that eventually activate endogenous degradative enzymes resulting in axonal degeneration.

Our understanding of the potential role of sodium channels in MS has grown substantially in recent years.[8] The channels have long had a recognized role in the symptomatology of MS, but now also have suspected roles in causing permanent axonal destruction, and a potential role in modulating the intensity of immune activity.[9] Sodium channels might also provide an avenue to achieve axonal and neuronal protection in MS, thereby impeding the otherwise relentless advance of permanent neurological deficit. The symptoms of MS are largely determined by the conduction properties of axons and these, in turn, are largely determined by sodium channels. The number, subtype and distribution of the sodium channels are all important, together with the way that channel function is modified by local factors, such as those resulting from inflammation (e.g., NO). Suspicion is growing that sodium channels may also contribute to the axonal degeneration primarily responsible for permanent neurological deficits. The proposed mechanism involves intra-axonal sodium accumulation which promotes reverse action of the sodium/calcium exchanger and thereby a lethal rise in intra-axonal calcium. Partial blockade of sodium channels protects axons from degeneration in experimental models of MS.

A prediction of the above hypothesis, is that axons will be protected from degeneration by partial blockade of axonal sodium channels, thereby limiting sodium entry. Professor Smith found that the sodium channel blocking agents **flecainide** and **lidocaine** can protect axons from NO-mediated degeneration in experimental models of MS, including rats with chronic relapsing experimental autoimmune encephalomyelitis (CR-EAE). Daily

administration of flecainide, from either 3 days prior to, or 7 days following, immunization, was effective in significantly reducing the magnitude of neurological deficit, and increasing the number of functional axons assessed electrophysiologically at the end of the trial; it also increased the number of surviving axons within the spinal dorsal columns. These findings indicate that sodium channel blocking agents may provide a novel approach for axonal protection in patients with MS. **Lamotrigine**, a phenyltriazine, is a use-dependent blocker of sodium channels that is widely used as a broad-spectrum antiepileptic drug.

Therefore, on the basis of lamotrigine's widespread use in the clinic and demonstration of its efficacy in EAE models of MS, Professor Smith and his colleagues have initiated a clinical trial in patients with secondary progressive MS to establish if lamotrigine slows disease progression.

Acute brain injury

There are two major causes of acute brain injury: stroke and traumatic brain injury (TBI).

Stroke

Michael J. O'Neill, (Eli Lilly & Company Ltd, Windlesham, Surrey, U.K.) described how a stroke is caused by the interruption of the flow of blood to the brain by thrombosis and/or detachment of a previously formed clot (embolus). This can lead to cerebral ischemia of varying duration which, in turn, causes a delayed loss of neurons in both experimental animals and humans. As well as constituting the third greatest cause of mortality in industrialized countries, stroke represents the single most common cause of

Lamotrigine
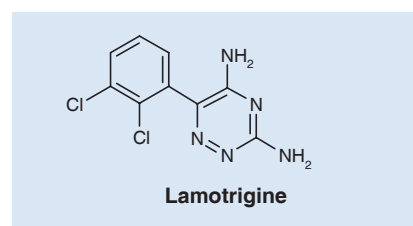
severe disability. A compelling mechanism to account for the secondary injury is that cerebral ischemia causes substantial elevations in the interstitial concentrations of excitatory amino acids (EAAs), principally aspartate and glutamate, which in turn overactivate EAA receptor-operated channels leading (either directly or indirectly) to a massive increase in cytosolic concentrations of free Ca^{2+} and, ultimately, cell death. This understanding of the underlying mechanism of neurodegeneration led to a major effort to use EAA receptor antagonists, particularly *N*-methyl-D-aspartate receptor (NMDA) blockers, to treat stroke. Both competitive and noncompetitive NMDA antagonists reduced the infarct volume (volume of brain damage) produced in rodents by middle cerebral artery occlusion (MCAO) when given before or immediately after occlusion. These antagonists comprise noncompetitive blockers of the ion channel associated with the NMDA receptor (e.g., **aptiganel** [*Cerestat*]), competitive antagonists of the glutamate recognition site of the NMDA receptor (e.g., **selfotel**) or of the glycine recognition site (e.g., ACEA-1021 [**licostinel**], GV-150526 [**gavestinel**]), antagonists at the polyamine site (e.g., **eliprodil**), Based on the preclinical data, many EAA receptor antagonists progressed to clinical trials, but all were later abandoned because of poor side effect profiles or failure to

Aptiganel

Selfotel

demonstrate clear efficacy, or a combination of both.[10] An analysis of a number of such compounds has established that many had very poor therapeutic ratios.[11] Several other approaches to therapy were then tried, including sodium and calcium channels blockers, along with inhibitors of nitric oxide synthase and caspase as well as antiinflammatory agents. Recently the free radical trapping agent, NXY-059 (**disufenton**; *Cerovive*) was evaluated in two large, multicenter trials. In spite of data in experimental models that followed many of the guidelines of the Stroke Therapy Academic Industry Roundtable (STAIR) group, the compound failed to show efficacy in the clinic. The first Stroke-Acute-Ischaemic-NXY-Treatment (SAINT-I) trial reinvigorated enthusiasm in neuroprotection, but the SAINT-II trial did not replicate the positive effect on the same primary prespecified outcome measure.[12] Despite setbacks from clinical trials, acute brain injury from stroke remains a major cause of mortality and disability and so novel approaches to reduce brain injury or enhance recovery of function are desperately needed.

Traumatic brain injury

Edward Dixon, (University of Pittsburgh, Pennsylvania, U.S.A.) considered treatment prospects for TBI. This type of brain damage, predominately affecting the young, is caused by a blow or jolt to the head that disrupts the function of the brain. Mortality is often high and many survivors suffer from emotional, cognitive and motor disturbances and thus a decreased quality of life. Recent data indicates that approximately 1.4 million people sustain a TBI each year in the United States. Of those, 50,000 die, 235,000 are hospitalized and 1.1 million are treated and released from an emergency department. An estimated 5.3 million Americans are living today with disability related to TBI; the incidence in the European Union is similar to that in the U.S.

TBI causes neurodegenerative changes in the brain that are dependent on the severity and location of impact.

Some of these changes are similar to those seen in AD and PD. Thus, AD-like changes include increases in $A\beta_{1-42}$ and cholinergic hypofunction. PD-like changes include synuclein pathology and impaired dopamine neurotransmission.

In recent years, there has been a rapid increase in the number of pharmacological targets evaluated in experimental models of TBI. These include excitotoxicity, oxidative injury, inflammation, proteolysis and mitochondrial dysfunction. Blockade of a number of such targets have shown neuroprotective efficacy, assessed on the basis of improved cognitive and motor outcome and decreased loss of brain tissue. However, such preclinical promise has not met with success in the clinical arena. Several promising compounds, particularly NMDA receptor antagonists, have failed to show clear efficacy in clinical trials.[13] The appetite for such trials has therefore waned in recent years.

Because of this, alternative treatment strategies are now emerging to attenuate TBI-induced neurodegeneration and/or improve recovery after brain injury. These include growth factors and stem cell transplantation, as well as compounds that target second messenger cascades and a variety of neurotransmitter modulators.

Successful phase III clinical trials for TBI have been limited. Future success will require a more comprehensive preclinical effort and greater synchrony between animal and human experimental designs. In summary, TBI may induce or accelerate brain neurodegeneration. Pharmacological treatments should be developed to target both early and late time points.

TBI is a complex and multifaceted disorder that is associated with pronounced neurodegenerative change that evolves over days, weeks or months. Although pharmacotherapy has not yet succeeded in slowing the progress of neurodegeneration, moderate hypothermia has been shown to be of benefit.[14]
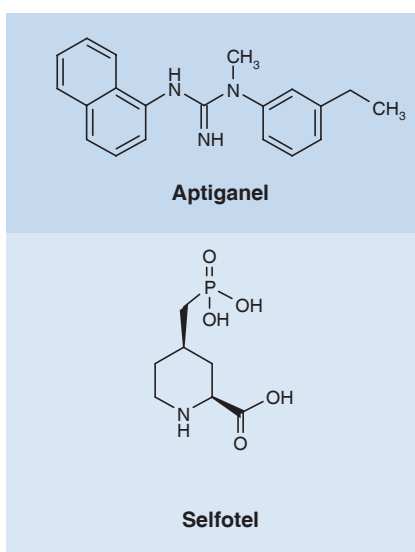
Conclusions

Neurodegenerative disorders can be subdivided into those where neurodegenerative change runs a slow progressive course, but where the cause of the disease is largely unknown; such disorders include AD, PD and MS, as well as Huntington's disease, Lewy Body dementia and motor neuron disease. The other type of neurodegenerative disorder is associated with a sudden burst of neurodegenerative change that is followed by a cascade of secondary neurodegeneration. Such disorders include stroke, TBI and spinal cord trauma and so the cause of the neurodegenerative changes is known. Symptomatic therapies for AD, PD and MS exist, but their usefulness is limited. A major goal of most pharmaceutical companies is to discover drugs that slow or halt the progress of neurodegenerative change. However, it is important that lessons are learned from the many failed neuroprotection studies undertaken for stroke and TBI. Most of these targeted the NMDA receptor and, with a total 9,000 patients examined in such trials, no therapeutically useful agent has emerged, with the possible exception of magnesium for treatment of subarachnoid hemorrhage.[15]

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