
MEETING REPORTS

Highlights from the Society for Medicines Research symposium held September 23, 2004, in London, United Kingdom.

CNS Drug Discovery: Challenges and Solutions

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The World Health Organization predicts that central nervous system (CNS) disorders will become the major medical need of the 21st Century. There are two major drivers behind this: 1) the incidence of many CNS disorders (e.g., Alzheimer's disease, stroke and Parkinson's disease) increases exponentially after age 65 and 2) the number of people in the world over 65 is about to increase sharply because of a marked rise in fertility after World War II.¹ The need for effective CNS medicines is therefore increasing sharply. CNS is already the fastest growing therapeutic segment of the pharmaceutical market, with sales in excess of \$50 billion. Many of the top-selling drugs are in the CNS segment (Table I) and CNS medicines are predicted to account for a fifth of the sales of blockbuster drugs in 2007.

The rewards for successful CNS research and development are clearly high, but are associated with significant challenges. These are exemplified

Summary

The worldwide market for therapies for central nervous system (CNS) disorders was valued at around \$50 billion in 2001, and is set to grow sharply in the years ahead. This is because of a marked increase in the number of people aged over 65 (the "baby boomer" effect), which will lead to increased demand for more safe and effective medicines for CNS disorders. This one-day Society for Medicines Research symposium, held September 23, 2004, in London, United Kingdom, was organized by Dr. Alan M. Palmer (Pharmidex, London, U.K.) and Prof. F. Anne Stephenson (School of Pharmacy, University of London, U.K.). More than 100 delegates heard a scholarly and comprehensive review of the challenges currently facing CNS research and development, which was accompanied by consideration of a variety of innovative solution strategies. The meeting considered: 1) how to identify and validate targets for potential CNS drugs; 2) how to assess brain penetration (both *in vitro* and *in vivo*); 3) how to develop *in silico* methodologies to predict blood-brain barrier penetration; 4) how to assess therapeutic efficacy (both *in vitro* and *in vivo*); 5) how to establish reliable biomarkers to guide decision making; and 6) how to effectively apply magnetic resonance imaging to CNS drug discovery. © 2005 Prous Science. All rights reserved.

by the longer time it takes to get a CNS drug to market (13–16 years) compared with a non-CNS drug (10–12 years) and the higher attrition rate for the CNS drug candidates compared with non-CNS drug candidates. The underlying reasons were the focus of the Society for Medicines Research symposium held September 23, 2004, in London, United Kingdom, and were considered along with strategies to get CNS drugs to market faster, with less expenditure and with a higher probability of success.

Emergence of CNS drug discovery

Paul Whiting (MSD, U.K.) described how CNS drug discovery began in 1951 with Henri Laborit (a French neurosurgeon), who was so pleased with the "beatific quietude" caused by **chlorpromazine** that he recommended it for use in calming agitated patients. Two Parisian psychiatrists (Jean Delay and Piere Denikeer) observed clear-cut benefits in a surprising variety of patients: agitated, anxious patients, hyperactive manics

TABLE I: TOP SELLING CNS DRUGS

GENERIC NAME	BRAND NAME	THERAPEUTIC TARGET	DRUG TARGET	2001 SALES (\$ MILLIONS)
Paroxetine	<i>Paxil</i>	Depression	5-HT transporter	2,673
Sertraline	<i>Zoloft</i>	Depression	5-HT transporter	2,366
Fluoxetine	<i>Prozac</i>	Depression	5-HT transporter	1,990
Venlafaxine	<i>Effexor</i>	Depression	5-HT transporter/NA transporter	1,542
Citalopram	<i>Celexa</i>	Depression	5-HT transporter	714
Olanzapine	<i>Zyprexa</i>	Schizophrenia	DA receptors	3,087
Risperidone	<i>Risperdal</i>	Schizophrenia	DA and 5-HT receptors	1,845
Quetiapine	<i>Seroquel</i>	Schizophrenia	DA and 5-HT receptors	700
Bupropion	<i>Wellbutrin</i>	Depression	DA and NA transporters	931
Zolpidem	<i>Ambien</i>	Insomnia	GABA receptors	704
Zolpidem	<i>Stilnox</i>	Insomnia	GABA receptors	902

Modified from reference 9.

and schizophrenics, all became more manageable. The biochemical basis of this efficacy was subsequently elucidated by Arvid Carlsson in Sweden, who (in 1962) observed that chlorpromazine (and other neuroleptics) increase dopamine turnover. Carlsson therefore hypothesized that they work by blocking dopamine receptors. This was confirmed by many groups, and neuroleptic drugs have since provided enormous benefit in the management of schizophrenia. However, neuroleptics do have a number of serious limitations. Firstly, they are not always effective. Secondly, positive psychopathological symptoms may benefit more than negative or deficit symptoms. Thirdly, antipsychotics are generally associated with a variety of adverse neurological effects. A major advance in this area emerged in 1988 with the description, by Anthony Kane and colleagues in the United States, of a compound (**clozapine**) with a much-reduced propensity to induce adverse neurological effects. This has led to the emergence of a new generation of "atypical" antipsychotics in the 1990s (e.g., **risperidone** and **remoxipride**), which have been further refined in this decade, for example the partial D2 receptor agonist **aripiprazole** (Table II).

The approach of discovering drugs on the basis of behavioral changes in experimental animals is much less common today, largely because of the emergence of the approach of developing drugs on the basis of understanding disease pathophysiology was pio-

TABLE II: THREE GENERATIONS OF ANTIPSYCHOTIC DRUGS

First generation	Chlorpromazine (<i>Thorazine</i>) Fluphenazine (<i>Prolixin</i>) Haloperidol (<i>Haldol</i>) Perphenazine (<i>Trilafon</i>) Thioridazine (<i>Mellaril</i>) Thiothixene (<i>Navane</i>) Trifluoperazine (<i>Stelazine</i>)
Second generation	Clozapine (<i>Clozaril</i>) Olanzapine (<i>Zyprexa</i>) Quetiapine (<i>Seroquel</i>) Risperidone (<i>Risperdal</i>) Remoxipride (<i>Roxiam</i>) Ziprasidone (<i>Geodon</i>)
Third generation	Aripiprazole (<i>Abilify</i>)

neered in Asutria by Herbert Ehringer and Oleh Hornykiewicz, who in 1960 demonstrated that Parkinson's disease is associated with reduced concentrations of dopamine and its major metabolite (homovanillic acid) in the striatum. This loss was subsequently found to correlate with both cell loss from the substantia nigra and two of the three cardinal symptoms of Parkinson's disease (akinesia and tremor). This laid the basis for therapy with the precursor to dopamine, **L-dihydroxyphenylalanine**. This groundbreaking work stimulated a number of other groups across the world to begin to investigate the biochemical basis of other neurodegenerative diseases. A clear consequence of this effort came from three independent groups in the United Kingdom (led by David Bowen, Peter Davies and Elaine Perry), who in the mid 1970s demonstrated that the activity of the enzyme responsible for the synthesis of acetylcholine, choline acetyltransferase, was

reduced in Alzheimer's disease. It rapidly led to the hypothesis that the dementia associated with Alzheimer's disease occurs as a consequence of dysfunction of cholinergic neurons, which established the conceptual framework for the emergence of therapies to enhance cholinergic function. More than 25 years later, inhibitors of the enzyme responsible for acetylcholine catabolism, acetylcholinesterase (AChE), have become the most successful approach to treating the disease, with three such compounds (**donepezil**, **rivastigmine** and **galantamine**) now on the market for the symptomatic treatment of mild and moderate Alzheimer's disease. These compounds have a much better side-effect profile than the first generation of AChE inhibitors (Table III).² This rational approach to therapy contrasts markedly with therapies that were used prior to the AChE inhibitors, for example, hydergine, which was approved for the treatment of dementia despite

TABLE III: TWO GENERATIONS OF ACETYLCHOLINESTERASE INHIBITORS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

First generation	Physostigmine (<i>Eserine</i>) Tacrine (<i>Cognex</i> ®)
Second generation	Donepezil (<i>Aricept</i> ®) Rivastigmine (<i>Exelon</i> ®) Galantamine (<i>Reminyl</i> ®)

the fact that its mechanism of action was unknown.

Like other neurologic disorders, Alzheimer's disease has a characteristic pathology, and neurochemical and genetic studies have successfully presented a number of drug targets. By contrast, psychiatric diseases are much less tractable. Since there are no characteristic brain lesions, the biological basis is much less clear, the genetics are more complex and differential diagnosis is more ambiguous.

Challenges facing CNS R&D

There are many challenges in the process of discovering and developing new CNS medicines. These include the following: 1) the blood-brain barrier; 2) patient heterogeneity; 3) multiple molecular targets; 4) the predictive validity of experimental efficacy models; 5) establishing clinical proof of concept; and 6) establishing biomarkers of disease existence or disease progression.

Blood-brain barrier

The blood-brain barrier is the tight seal of cells that lines the blood vessels in the brain. It forms a serious challenge to CNS drug discovery, since crossing this barrier to achieve sufficient drug exposure to the molecular target is a necessary prerequisite for CNS activity/efficacy. Most small molecules and essentially all peptides and proteins do not cross the blood-brain barrier. Joan Abbott (King's College London, U.K.) reviewed both *in vivo* and *in vitro* approaches to assess brain penetration. The major *in vivo* model she focused on was *in situ* perfusion, which measures the rate of entry across brain endothelium. It therefore represents a kinetic measure. She argued that this was superior to the approach

of measuring brain penetration, which provides an indicator of brain partition, that is, brain/plasma ratio of compound, and is commonly used in CNS drug discovery. Caveats of the *in situ* perfusion technique are that it does not provide a full PK profile (i.e., C_{max} , half-life and AUC), and it does not take account of egress mechanisms (e.g., via P-glycoprotein). Cerebrospinal fluid concentrations probably give a better measure of free drug concentrations in the brain, but Peter Eddershaw (GlaxoSmithKline, U.K.) argued that the key compartment for a CNS active compound is brain interstitial fluid, which can be assessed by tissue microdialysis.³

Both Abbott and Eddershaw described *in vitro* models of blood-brain barrier function. These included primary cultures of endothelial cells, for example, bovine endothelial cells cocultured with astrocytes, which have been shown to correlate with *in vivo* brain penetration. However, the trans-endothelial electrical resistance (TEER) of such cells is low ($<100 \Omega\text{cm}^2$), which contrasts with the intact blood-brain barrier, where TEER is greater than $2000 \Omega\text{cm}^2$. Since the transmembrane resistance of Madin-Darby canine kidney (MDCK) cells is high (because of their tight junctions), these cells are being used increasingly in CNS drug discovery. Eddershaw described how MDCK cells transfected with human P-glycoprotein is now used routinely at GlaxoSmithKline and other pharmaceutical companies. This system permits assessment of both passive diffusion and active egress (via P-glycoprotein) in a single assay system.

A key validation of the assessment of the concentration of a compound in the brain is to establish relationships

with measures of receptor occupation and animal behavior. Such relationships were shown for one (undisclosed) compound on the basis of brain concentration, which provides important validation of this approach. This approach also seemed to hold true across a series of compounds on the basis of a good relationship between brain concentrations and receptor occupancy. However, a relationship between *ex vivo* binding and brain concentrations only became apparent when free concentrations in the brain were taken into account. Eddershaw went on to explore the physicochemical determinants of brain penetration. Numerous studies have highlighted the importance of lipophilicity in achieving brain penetration. Inclusion of other factors (such as H-bonding capacity and polar surface area) provides an improved relationship. Another important factor is the active egress of compounds out of the brain via carriers such as P-glycoprotein, which is the major cause of poor CNS penetration in lead optimization. The structure-activity relationship for this transporter is poorly understood, and attempts to improve brain exposure of drug molecules by overcoming its efflux remain largely empirical and, in many cases, unsuccessful.

Patient heterogeneity

Patient heterogeneity was clearly illustrated by Chas Bountra's (GlaxoSmithKline, U.K.) review of the progress and pitfalls associated with the discovery and development of new medicines for the treatment of pain. There are many types of pain: it can be acute (sprains and strains, postoperative, dysmenorrhea), chronic inflammatory (osteoarthritis, rheumatoid arthritis, chronic back, musculoskeletal) chronic neuropathic (postherpetic—neuralgia, diabetic neuropathy, cytotoxic neuropathy, phantom limb, fibromyalgia—or central pain), chronic visceral pain, headache (including acute migraine and cluster headaches) and cancer. The type, nature, duration and severity of the pain associated with these conditions shows great variation, reflecting heterogeneity in the underlying

ing pathophysiology. Neuropathic pain has become a particular target for drug discovery over recent years, largely because it represents a major unmet medical need.⁴

Multiple molecular targets

There are many molecular targets for any CNS disorder. Determining which are the best remains a challenge. Taking neuropathic pain as an example, four potential targets were considered in detail.

NK1 receptors

Although NK1 antagonists showed clear efficacy in a number of preclinical models of neuropathic pain, they were ineffective in the clinic. This included assessments of many types of pain, including dental pain, migraine, postherpetic neuralgia and osteoarthritis. Does this mean that NK1 receptors are not a good target or does it mean that the animal models have poor predictive validity? It is also possible that the compounds used had insufficient brain and spinal cord exposure.

Sodium channels

Sodium channels are essential for neurotransmission and are considered to play a role in the plastic changes associated with neuropathic pain.⁵ Two sodium channels (SNS and SNS2) were examined in detail using knockout animals. These studies suggested the involvement of SNS (but not SNS2) in development/maintenance of neuropathic pain. Whether selective SNS2 channel blockers provide the basis of an effective treatment for neuropathic pain remains to be seen. It is also not clear if it is sufficient to block just a single channel or whether other channels need to be blocked as well.

Vanilloid receptors

The transient receptor potential cation channel V1 (TRPV1) is expressed in peripheral nociceptive neurons and is subject to polymodal activation via various agents including capsaicin, noxious heat and low extracellular pH. TRPV1 is expressed on spinal and vagal afferents and is increased in patients with rectal hyper-

sensitivity, vulvodynia and esophagitis. In addition, TRPV1 knockout animals show reduced responses to jejunal mechanical and chemical stimuli. This suggests that TRPV1 antagonists will have utility in the treatment of pain. This is supported by evidence indicating a reduced "guarding response" to colorectal distention in humans and efficacy in experimental models of neuropathic pain. Whether this translates to efficacy in human neuropathic pain remains to be seen.

P2X7 channels

The P2X7 channel is the latest member of a superfamily of ATP-gated nonselective cation channels that are found on mast cells, microglia, macrophages, Schwann cells and endothelial cells. Their activation is associated with release of mature, biologically active interleukin-1 β . P2X7 channels are upregulated in dorsal root ganglia following nerve injury, and knockout animals are resistant to the development of inflammatory and neuropathic hypersensitivity, which suggests a role in initiating and/or maintaining chronic pain. P2X7 antagonists may therefore provide broad-spectrum analgesia. It remains to be established where in the CNS antagonists interact and whether this approach can demonstrate clear efficacy in the clinic.

Predictive validity of experimental efficacy data

Predicting that a compound will be effective in the clinic on the basis of preclinical data is a major challenge for CNS drug discovery. The throughput of *in vivo* models is not high, so there is a great need for reliable *in vitro* models of CNS disorders. Lars Sundstrom (Capsant, U.K.) described a new generation of *in vitro* models based on organotypic cultures of slices of rat brain, which retain functional connectivity and fundamental characteristics of the intact brain.⁶ New models have been developed for disorders associated with both acute (e.g., stroke and traumatic brain injury) and chronic neurodegenerative disorders (e.g., Alzheimer's disease). For traumatic brain injury, he described how organ-

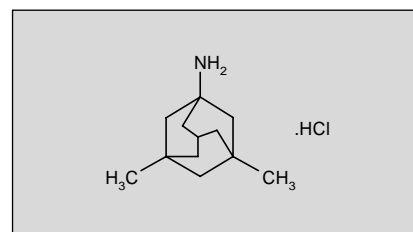


Fig. 1. Memantine (*Axura*, *Namenda*) is a moderate affinity NMDA-receptor antagonist that was recently approved in Europe and the United States for the treatment of moderate to severe Alzheimer's disease. It represents the first and only representative of a new class of drug for this disorder.

otypic slices grown on a silicone membrane were subjected to rapid deformation, which reproduced many of the changes seen in humans with severe head injury. For experimental stroke, the toxicity induced by hypoxia was attenuated by NMDA receptor antagonists, as expected. It was also apparent that the neuroprotective efficacy of a number of NMDA receptor antagonists was dependent on the redox state of the receptor; there was no efficacy when the receptor was in the reduced state, which may have contributed to the poor efficacy of NMDA receptor antagonists in clinical trials for stroke. The toxicity induced by amyloid peptide ("aged" for 72 hours with apolipoprotein E) was also sensitive to NMDA receptor antagonism (with **memantine**, Fig. 1).

The profile of neuroprotection observed in the organotypic cultures was very similar to that seen with *in vivo* models of stroke. However, the predictive value of these models is not clear, since the efficacy observed preclinically with NMDA and AMPA/kainate receptor antagonists was not reproduced in clinical trials. Similarly, the predictive validity of experimental models of neuropathic pain has been questioned because NK1 receptor antagonists, which showed efficacy in preclinical studies, were found to be ineffective in the clinic.

Thomas Rosahl (MSD, U.K.) suggested a powerful approach to drug discovery that linked molecular structure to behavior. He illustrated this by

a description of GABA_A receptor subtypes as targets for CNS disorders such as anxiety, pain, Alzheimer's disease and epilepsy. Benzodiazepines remain the major first-line treatment for most anxiety disorders. However, beside their beneficial anxiolytic, muscle relaxant and anticonvulsant effects, benzodiazepines also have several undesirable side effects, including an interaction with ethanol, and memory impairment, along with a propensity to cause tolerance and dependence. Benzodiazepines also have potential abuse liability. There are multiple GABA_A receptor subunits that can co-assemble in many possible pentameric permutations to form functional receptors. The most common combinations are: $\alpha_1\beta\gamma_2$, $\alpha_2\beta\gamma_2$, $\alpha_3\beta\gamma_2$ and $\alpha_5\beta\gamma_2$. Knowledge that the benzodiazepine binding site is formed by α and γ_2 subunits raised the possibility that the desirable and undesirable actions of benzodiazepines could be separated. Rosahl described the use of knockin mice carrying benzodiazepine binding site alterations to dissect out the various effects of benzodiazepines on individual GABA_A receptor subtypes. The resultant data supported the development of receptor subtype-selective benzodiazepines with similar anxiolytic properties but with an improved side-effect profile over the current generation of benzodiazepine drugs. Mice containing diazepam-insensitive α_1 -subtype (H101R) had substantially lower [³H]flumazenil binding, and flumazenil caused much less sedation than in wild-type animals. In addition, diazepam markedly increased explora-

tory behavior in the α_1 H101R animals; it had no such effect in wild-type animals. **L-838417**, an antagonist at the α_1 subtype and an agonist at the $\alpha_2/\alpha_3/\alpha_5$ subtypes (Fig. 2), was found to display anxiolytic activity in the elevated plus maze, but not to have sedating properties, on the basis of activity in the rotarod test. This compound increased locomotor activity in both wild-type and α_1 H101R mice.

On the basis of such studies, it was possible to establish that certain behavioral profiles of benzodiazepines are linked to particular subunits. Thus, sedative, amnesic and anticonvulsant effects are linked to the α_1 subunit-containing GABA_A receptors, anxiolytic, myorelaxant and anticonvulsant effects to the α_2 subunit-containing anxiolytic (myorelaxant), and antiabsence effects to the α_3 subunit-containing receptors and cognitive (myorelaxant) tolerance to sedative effects to receptors with α_5 subunits.⁷ This approach of developing anxiolytic compounds offers much potential for the development of new safe and effective medicines for CNS disorders.⁸ Indeed a retrospective evaluation of the knockout phenotypes for the targets of the 100 best-selling drugs has indicated that these phenotypes correlate well with known drug efficacy. This raises the prospect of mining the druggable genome with the aid of large-scale mouse knockout programs combined with phenotypic screens focused on identifying targets that modulate mammalian physiology in a therapeutically relevant manner.⁹ Large-scale knockout, gene trap and ENU mutagenesis programs have commenced, but they face significant challenges. For example, how can the predictive power of *in vivo* models be improved?

However, two technological breakthroughs have increased optimism that the transgenic approach will reap rich rewards. The first is the emergence of transgenic rats, which allows for more comprehensive assessment of efficacy and side-effect liability than is possible with mice. The second is the introduction of RNAi technology to CNS drug

discovery. An example of the benefits of this approach is illustrated by studies of NR1 knockout animals: the homozygote knockout is lethal, whereas the heterozygote has a normal phenotype. NR1 knockdown animals, by contrast, display a schizophrenia-like phenotype.¹⁰ Thirdly, drug-binding site alterations (knockin mice) provide detailed knowledge of drug-binding sites but leave gene product. Fourthly, "humanized" mouse models (knockin mice) have the mouse gene or parts of it replaced by its human counterpart, which allows assessment of drug effects in human proteins rather than mouse proteins. Finally, conditional transgenic and knockout mice permit temporal and spatial control of transgene expression or gene knockout, which can avoid lethality or compensation during development.

Establishing biomarkers of disease existence or disease progression

The cost and duration of getting a new medicine to market are both very high. Vincenzo Libri (Eli Lilly, U.K.) described how a typical CNS drug discovery program takes 13–16 years to get a compound to market. This breaks down to 4–5 years in preclinical research, 1–2 years in phase 1 clinical trials, 2–3 years in phase 2, 3–4 years in phase 3 and 1–2 years to achieve regulatory approval. The process typically costs \$800–1000 million and involves the synthesis and screening of 12,000 compounds, 80 of which are screened in detail, 10 of which are assessed in humans, with four involved in full clinical trials and one compound making it to market. Approaches to increase the probability of success and reduce expenditure are therefore highly desirable. Libri described how biomarkers have the potential to make a large contribution to CNS research and development. A biomarker can be defined as a laboratory or a physical sign used as a substitute for a clinically meaningful end point; changes induced by a therapy on a marker end point can be expected to reflect changes in a clinically meaningful end point. While marker end points may not be the true predictor of a genuine

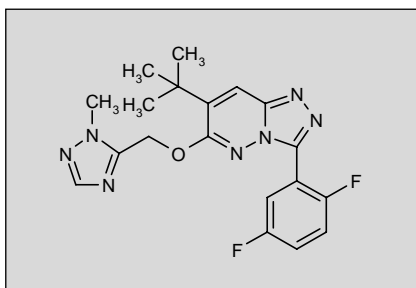


Fig. 2. L-838417 is an antagonist at the α_1 -subunit containing GABA_A receptor subtype and an agonist at the $\alpha_2/\alpha_3/\alpha_5$ subunit-containing subtypes.

clinical efficacy, they may provide initial indication on whether the intervention is sufficiently promising to justify the conduct of larger-scale, longer-term and more expensive clinical trials. Only reliable biomarkers can be used to guide decisions to progress compounds to further development. Useful biomarkers should be straightforward to assess in a noninvasive (or moderately invasive) fashion, be detectable in living subjects and generate reproducible and reliable results. Overall, biomarkers should correlate with disease pathophysiology (a disease-based surrogate marker) or be linked to the mechanism of action of a potential new therapy and therefore be of use in determining central penetration and/or optimal dose (a mechanism-based marker, or biomarker). Regardless of the process, the relation between marker end point and intervention should have a biological relevance. Biomarkers can also help improve diagnosis accuracy, reduce the sample size, duration and cost of clinical trials, and allow treatments to be assessed in situations where the use of primary outcomes would be excessively invasive, unethical, long or expensive.

There are very few good biomarkers of CNS disorders. Progress will be greatly facilitated by a validation process that investigates marker end points in both experimental animals and humans. Validation is also required for marker sensitivity, specificity, positive and negative predictive value, accuracy, likelihood ratio of positive and negative tests, discriminate validity, and sensitivity to change and to treatment difference. An accurate process of biomarker validation would establish whether marker end points actually support go/no-go decisions at early stages of CNS drug development. Validated biomarkers are needed for most (if not all) CNS disorders, but they are particularly needed for clinical trials in chronic neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease, where disease-modifying therapies are now under investigation.

Steve Williams (King's College London, U.K.) described the contribution that neuroimaging has made to CNS drug discovery. Positron emission tomography (PET) and magnetic resonance imaging (MRI) constitute the cornerstones of brain imaging, and they are both playing an increasingly important role in CNS research and development. In recent clinical trials, these modalities have been used not only to refine subject inclusion/exclusion criteria but also to evaluate whether a drug has reached the target organ and whether it has produced the desired biological effect.

In relation to drug discovery, the development of biomarkers is a key goal of neuroimaging research. Williams' talk focused on MRI imaging and described recent examples where imaging has helped to expedite go or no-go decisions for several putative therapies. These included the use of T2-weighted MRI in multiple sclerosis, which was used to expedite the approval of β seron by the U.S. FDA. It has also been used to "visualize" tissue atrophy in Alzheimer's disease by, for example, determining the total volume of cerebrospinal fluid, and the evolution of neurodegenerative changes in patients following a stroke.

MRI imaging has also made a significant contribution to patient inclusion in stroke trials. As mentioned above, heterogeneity within a patient population has been a major obstacle for clinical trials for CNS drug candidates. An effective approach to reduce the heterogeneity of the patient population in clinical trials for stroke was described. This involved visualizing the penumbra (which is amenable to neuroprotection) by using a combination of diffusion and perfusion weighted imaging. With this approach, it is possible to select patients with a cortical stroke with a clear "penumbra." This is the type of damage that best corresponds to that caused in experimental studies where there is occlusion of the middle cerebral artery. The perfusion/diffusion ratio therefore provides an important tool to ensure homogeneity of the patient population

in a clinical trial for stroke. Since longitudinal studies permit visualization of the evolution of the neurodegenerative process, it also provides a key tool to assess the efficacy of neuroprotective agents.

As well as to identify neurodegeneration, MRI has also been used to visualize the process of regeneration stimulated by grafted stem cells. This involved labeling the cells with tetramethylrhodamine and gadolinium chelated onto dextran chain prior to the graft.¹¹

Another exciting approach that has great potential utility is functional MRI, which takes advantage of the differential signals from deoxyHb and oxyHb. DeoxyHb is paramagnetic (reduced T2*) and Hb is diamagnetic (increased T2*). An increased signal corresponds with increased neuronal activity. This approach has been used to show brain activation occurring as a consequence of photic stimulation (visual cortex) and somatic stimulation (somatosensory cortex). It has also been used in studies of neuropathic pain (noxious esophageal stimulation) and working memory (which included the development of a virtual Morris water maze).

A rapidly emerging area of research is MRI imaging in experimental animals. Thus, for example, electrical stimulation of rat forepaw activates somatosensory cortex, and the increase in locomotor activity caused by the NMDA receptor antagonist **MK-801** is associated with a distinct pattern of activation in a number of cortical areas. Williams also described very elegant studies to establish the functional

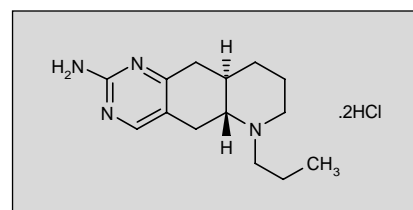


Fig. 3. Structure of quinelorane (LY-163502), a mixed D₂/D₃ dopamine receptor agonist.

specificity for novel antipsychotics. Using **quinlorane** (Fig. 3), which is a dopamine D₃ receptor agonist at low doses (~3 µg/kg) and a mixed D₂/D₃ agonist at higher doses (~30 µg/kg), he described studies investigating D₃ receptor activation. A low dose of quinlorane (3 µg/kg) evoked changes in locomotor activity that was different from that observed with a higher dose (3 µg/kg). This differential effect corresponded with differential activation of different brain regions in MRI studies. The increasing use of small animal scanners serves to strengthen the link between preclinical and clinical studies. Together, technological advances to improve resolution and combine technologies (e.g., PET and NMR dual acquisition) will mean imaging is set to play an ever increasing and important role in CNS research and development.

Conclusions

A number of CNS drugs have achieved blockbuster status (Table I). However, the need for CNS therapeutics remains high and looks set to increase substantially in the years ahead. To meet this need, it will be necessary for CNS drug discovery to become more efficient and effective. This meeting identified a number of the bottlenecks associated with getting a new CNS drug to market. These included our limited understanding of the mechanisms underlying most CNS disorders, the barrier to brain entry (the blood-brain barrier), patient heterogeneity in clinical trials, the existence of multiple molecular targets, the lack of experimental models of therapeutic efficacy with good predictive validity and the shortage of biomarkers to both

aid the diagnosis of CNS disorders and to provide an objective surrogate measure of disease progression. Considerable progress has been made in understanding the anatomical, cellular, molecular and pharmacokinetic basis of CNS drug action, which is leading to a more sophisticated regard for CNS drug discovery. With the massive increase in the number of people in the world with CNS disorders in the years ahead,¹ there is a clear and urgent need to translate this knowledge into safe and effective new medicines.

This Society for Medicines Research symposium can be viewed as a Webcast at www.prous.com/cns.

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Dr. Alan M. Palmer and Prof. F. Anne Stephenson are Conference Organizers and Committee Members of the Society for Medicines Research. The SMR Committee organizes conferences on behalf of the Society for Medicines Research four times a year. SMR symposia focus on research related to the discovery and development of new medicines and are usually held in London. Details about forthcoming meetings can be obtained from the SMR website: www.smr.org.uk or from: SMR Secretariat (secretariat@smr.org.uk). For correspondence in relation to this article, please contact: alan.palmer@pharmidex.com.

NEOSE AND BIOGENERIX ENTER OPTION AGREEMENT FOR GLYCOPEGYLATION TECHNOLOGY

Neose Technologies and BioGeneriX have entered into a supply and option agreement that, if the option is exercised, would result in the use of Neose's proprietary *GlycoPEGylation*TM technology to develop a long-acting, next-genera-

tion version of a currently marketed therapeutic protein. BioGeneriX and Neose will enter into an initial 3-month research period. Neose will receive a payment and supply of protein for research purposes. During the research period, BioGeneriX may choose to enter into a prenegotiated research, license and option agreement under which Neose would receive additional

upfront and research payments as well as royalties. Under the research, license and option agreement, BioGeneriX would have the right to an exclusive, worldwide license to use Neose's GlycoPEGylation technology to develop and commercialize a long-acting, next-generation version of the undisclosed therapeutic protein.