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## Special issue on CNS experimental medicine

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The past 5 years have seen unprecedented changes in the approach to developing new therapeutic drug treatments. Perhaps the most significant changes have taken place in the area of clinical development with a move away from determining efficacy exclusively in traditional phase II clinical trials in patients, to earlier development phases in which efficacy is inferred from experimental studies with healthy volunteers and/or surrogate patient groups. It is not difficult to identify the drivers for such change. In the last decade the cost of drug development has been subject to double-digit year-on-year inflation while the rate of productivity of new drugs remains stubbornly low at approximately 10 per year and falling (Munos, 2009). Moreover, with the development and opportunity costs of each new drug now in excess of £1 billion (DiMasi et al. 2003; Munos, 2009) and the revenues from highly profitable drugs dwindling due to patent expiry, it is little wonder that the outlook for the pharmaceutical industry is increasingly uncertain and the mood is sombre. Nowhere has this been more profoundly experienced than in psychiatry where two large Pharma companies, GlaxoSmithKline and AstraZeneca, recently announced the closure of their discovery research divisions (Miller, 2010). From a commercial business perspective the reasons for these withdrawals are very clear: the prospect of a significant return on capital invested in the discovery of drugs for psychiatric disorders is too low compared with other therapeutic areas to warrant further investment.

Thus, despite significant advances in our understanding of brain chemistry, circuitry and function in the last 20 years, these developments have not been sufficient to enable rational development of drug therapies for psychiatric disorders. Part of the problem stems from the empirical observation that promising effects of novel compounds in animals do not reliably predict efficacious effects in patients (Pangalos et al., 2007). This lack of translation from animal models to clinical efficacy makes it difficult to generate human models of psychiatric disease that provide a stepping stone to the large, expensive phase III patient trials required for drug registration. Ironically, however, just as large Pharma companies are reconsidering their commitment to discovering and developing new treatments for psychiatric disorders new approaches to developing and validating human experimental medicine models of the disorders are finally emerging. In this special issue leading researchers review new advances in experimental medicine models and approaches in the areas of anxiety,

depression, schizophrenia, cognitive disorders, drug addiction and sleep disorders. They also provide an evaluation of the latest advances in functional magnetic resonance imaging (fMRI), pharmacofMRI (pfMRI) and electroencephalography (EEG) as well emerging technologies such as magnetoencephalography (MEG). These articles articulate some of the latest theories, techniques and technologies that are now being brought to bear in this challenging area. They also highlight recent advances in areas where real progress has been made and the directions that hold significant promise for future drug development in psychiatry.

Progress in the development of experimental medicine approaches is particularly apparent in the area of depression. Approximately 14% of the Western European population have a lifetime history of any mood disorder (Alonso et al., 2004). The extent of this problem is also reflected in the large worldwide sales of antidepressants (more than US\$19.4 billion in 2007) (CNS Drug Discoveries: Depression, 2008). They are often less than perfect drugs with a significant side effect burden such as sleep disturbance or sexual dysfunction (Hansen et al., 2005). However, perhaps the greatest problem is that a significant proportion of patients are 'treatment resistant': their depression is not significantly relieved by two or more courses of treatment with different antidepressants (Howland et al., 2011). Consequently the need for new treatments is undeniable, but in this area the standard animal models of tail suspension, forced swimming and mild chronic stress lack the precision and sophistication required to model such a complex disorder as depression.

The traditional theory of antidepressant drug action postulates that treatment with an antidepressant, e.g. a selective serotonin reuptake inhibitor (SSRI), results in downstream neuroadaptive changes which take some time to occur but eventually lead to an elevation in mood. More recently, Harmer et al. (2011a) have proposed that antidepressants

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act within a few days to reduce the emotional negative bias characteristic of depressed mood and that this change in cognition eventually improves mood (Pringle et al., 2010). In the present issue Harmer et al. (2011a) review how this hypothesis has stood up to empirical scrutiny with marketed antidepressants and treatments that had promising effects in animal models of depression, but subsequently failed in clinical trials. In a second article in the current issue Harmer et al. (2011b) report that aglomelatine, a new treatment for depression with a novel mechanism of action and fewer side effects than traditional antidepressants, also modulates emotional processing in ways similar to existing antidepressants. In a related article Murphy and Mackay (2011) describe how fMRI, in particular the BOLD response may be used with EEG and MEG to provide further insights into how antidepressants and other drugs affect brain systems. Although each of these technologies can provide information on drug action, Murphy and Mackay describe how synergy may be achieved by drawing upon the unique properties of each.

On a similar theme, Alhaj et al. (2011) suggest that EEG can both provide data relating to neural activity that may be abnormal in certain psychiatric disorders and predict which patients may respond to particular treatments. They illustrate the utility of EEG with reference to depression and its ability to increase the 'signal-to-noise' ratio in early clinical trials. Thus, they show that baseline measures of EEG alpha power, alpha asymmetry and theta power in the anterior cingulate cortex are predictive of patients who are likely to respond to treatment. By selecting only those patients who are likely to respond, the signal-to-noise ratio inherent particularly in early clinical trials for depression can be significantly improved. Predicting treatment response using fMRI, MEG or EEG may seem like a diagnostic luxury only available in specialist centres but as with all new technologies early adoption leads to miniaturization and a fall in production costs. Consequently, it may, in the not too distant future, become routine for physicians who are treating patients with more severe depression to take advantage of these new technologies to identify a suitable treatment for their particular form of depressive disorder.

Recently, there has been an increasing trend to treat generalized anxiety disorder (GAD) with antidepressants. Although not formally evaluated, the common drug regime in clinical practice is to initially combine a benzodiazepine drug with an antidepressant. The benzodiazepine is normally tapered off after 2–3 weeks treatment when the antidepressant becomes more effective (Rickels and Rynn, 2002; Rickels et al., 1993; Uhlenhuth et al., 1999). As Bailey et al. (2011a) point out in the current issue these drugs have a number of limitations and there is a clear need to develop more efficacious treatments for GAD. One of the core symptoms of GAD is irrational 'worry', and this symptom, and others, is reliably induced in both patients and healthy volunteers by breathing 7.5% CO<sub>2</sub> gas for 20 minutes. Bailey et al. (2011a) review the published literature from their own laboratory and others and consider if the 7.5% CO<sub>2</sub> experimental medicine model can be considered a validated model of GAD. In a related paper Bailey et al. (2011b) report preliminary evidence that the corticotrophin-releasing factor (CRF)<sub>1</sub> receptor antagonist R317573 has anxiolytic-like effects in the 7.5%

CO<sub>2</sub> model. These data suggest, for the first time, that drugs other than benzodiazepines have robust anxiolytic effects in this model.

Koychev et al. (2011) provide a very useful overview of how different types of biomarker can be used in drug development and the criteria by which they can be validated. Against this background they review the problem of identifying effective new principles of treatment in schizophrenia early in development using the experimental medicine approach. New treatments are badly needed because existing antipsychotics, although effective against psychotic symptoms, have little effect on the impairments of motivation and social and intellectual functioning associated with the disorder. Koychev et al. review new ideas about the molecular and cognitive processes that underlie the difficult-to-treat symptoms and whether biomarkers of these processes could be used to detect novel drug efficacy in healthy volunteers. They review the validity of several potential cognitive and EEG biomarkers. One novel concept is that biomarkers might be especially sensitive in identifying efficacy in healthy volunteers selected for some of the cognitive and personality characteristics of schizophrenia; these features are increasingly understood to be continuously distributed in the general population personality trait called schizotypy (van Os et al., 2000). In this way some of the confidence associated with efficacy in clinical trials could be brought into phase I studies while eliminating some of the problems of recruiting patients free of substance misuse and the effect of pre-existing treatment.

In other therapeutic areas such as sleep disorders, drug addiction and cognitive disorders, translation from animal models to human volunteer or patient models may be more readily achievable. Paterson et al. (2011) describe how sleep is controlled by two separate processes the circadian process and homeostatic, or sleep-dependent recovery (the S-process). As they illustrate, all animals have innate circadian clocks that are dependent on particular genes. Polymorphisms of these genes particularly those involved in setting the period and timing of circadian rhythms have been found in human sleep disorders. The S-process is wake-dependent and increases as the amount of time since last sleep increases. In humans these processes interact to promote sleep when both are high and maintain sleep when the circadian process is high and the S-process is declining during the night. Complaints of insomnia can arise when either of these processes is perturbed by, for example, arousal, anxiety or transcontinental air travel. Furthermore, sleep and wakefulness are controlled by a network of brain nuclei that integrate these homeostatic and circadian regulations and which can be influenced by pharmacological treatment. Given the conserved nature of sleep processes across species translation between animals and man is readily achievable and has led to more widespread development of sleep promoting therapies.

Similarly, the promise of human behavioural biomarkers in addiction is growing with a greater understanding of reward and incentive processes in animals. Duka et al. (2011) describe several theoretical frameworks that have been developed to better understand those processes and mechanisms potentially involved in addiction. The various 'theories of addiction' place different emphases on the

components thought to be involved in drug addiction, e.g. craving or drug value, but find common ground in the role of Pavlovian or associative learning between cues and environments in-play as addiction develops and during relapse. Duka and colleagues review and evaluate these behavioural processes and their relationship to addiction identifying critical brain structures associated with the behaviours in animal studies and relate these to results from human imaging studies.

Antonova et al. (2011) consider the value of taking a well-characterized animal model of spatial learning, the Morris water maze, and translating it to humans using a virtual reality technique combined with fMRI to determine the elements of spatial learning, acquisition and/or retrieval, that activate particular brain areas. Good concordance with the results from animal experiments emerged showing that both during acquisition and retrieval of novel spatial locations the hippocampus was activated. Moreover, the muscarinic receptor antagonist, scopolamine, impaired the accuracy of encoding and/or retrieving spatial locations and also reduced hippocampal activations compared with placebo. Interestingly the behavioural measure of accuracy was more variable between participants than the hippocampal activations and deactivations under placebo and scopolamine treatments. These results demonstrate the value of fMRI in determining test sensitivity and echo similar findings with exposure to fearful faces. While behavioural responses to fearful faces tend to habituate with continued exposure, the activation levels of the amygdala remain constant (see Harmer et al., 2011).

The results reported and opinions expressed in this issue show that we remain some way from a fully validated portfolio of experimental medicine models for evaluating the effects of new chemical entities in early development for psychiatric disorders. However, significant progress has been made in a number of areas and the experimental medicine models that have been developed to evaluate antidepressants and anxiolytics have already been deployed in a phase I setting to provide an early evaluation of efficacy. Moreover, the combination of behavioural and fMRI techniques employed in these models provide a road map for the development of new experimental medicine models in the future. It only remains for us to thank the authors of this special issue for their excellent contributions and the referees whose comments and insights have further strengthened the manuscripts to provide a state of the art review and critique of this rapidly developing area of experimental medicine.

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