EDITORIAL

Psychiatric drug discovery on the couch

The past two decades have been a barren time for the discovery of novel drugs for psychiatric disorders, in particular those that could revolutionize disease treatment. In our first 'Viewpoint' article this month, we present the opinions of experts from across the field of neuroscience on how the effectiveness of psychiatric drug discovery could be enhanced.

In March 1990, a cover of *Newsweek* pictured a capsule of Prozac (fluoxetine hydrochloride) with the description "A breakthrough drug for depression" — a reflection of the medical and public impact of the introduction of this pioneering selective serotonin reuptake inhibitor in 1988. However, although the new drugs introduced since 1990 for common psychiatric disorders such as depression and schizophrenia have been highly successful in market terms, it could be argued that none represents what might be considered a major breakthrough in disease treatment.

Indeed, compared with other therapeutic areas from a productivity and innovation perspective over the past two decades, new drugs for psychiatric disorders have been both few in number and based more on already established, rather than novel, mechanisms. For example, antidepressant pharmacotherapy is still dominated by neurotransmitter reuptake inhibitors. Similarly, for schizophrenia, the first-line therapies are atypical antipsychotics, the first of which, clozapine, was approved by the FDA in 1989 (it had been introduced in Europe in the 1970s, but was withdrawn owing to a link with a life-threatening blood disorder). Of course, if these drugs were considered to be optimal treatments, there would not be an important issue to discuss, but it is clear that there is still plenty of room for improvement with regard to efficacy, side effects and time to onset of therapeutic action.

So, what underlies the chronic shortfall in innovative psychiatric drugs, and what could be done to tackle this problem? These questions were considered at the first *Advances in Neuroscience for Medical Innovation* symposium held in November 2005, in which experts from across the field of neuroscience discussed research advances relevant to psychiatric disorders in areas ranging from molecular neurobiology to imaging, with a view to proposing steps that could be taken to improve the effectiveness of drug discovery for such disorders. Following the symposium, participants were invited to respond to five key questions relating to psychiatric drug discovery, covering reasons for the current lack of success and scientific advances related to neuronal plasticity, imaging, preclinical models and classification of patients. In this issue, we present their answers together with recommendations for addressing the issues and challenges identified (see the Viewpoint article on page 189).

With regards to the lack of success with novel approaches in particular, some of the reasons will be familiar to those working in other therapeutic areas, although these are compounded by the complexity of the central nervous system. For example, as is also the case for cancer, preclinical models of psychiatric disorders are increasingly viewed as unsatisfactory. In this case, however, this might not just be because of the challenge of modelling even some aspects of a disorder such as schizophrenia in a rodent, but also because current models have often been validated using existing drugs, perhaps reducing the likelihood of discovering agents with novel mechanisms of action.

Other barriers to success are more distinctly associated with psychiatric drug discovery in particular. For example, diagnosis of psychiatric disorders is currently based on subjective assessments of a collection of signs and symptoms. Furthermore, disorders such as depression are heterogeneous, with poorly characterized and complex aetiology, and the placebo effect in clinical trials can be more than 30%. So, it is not surprising that large-scale trials of drugs with new mechanisms of action have failed to reproduce promising effects seen in preclinical and early clinical trials, as occurred with the neurokinin receptor 1 antagonist aprepitant, one of the few conceptually novel antidepressants to make it as far as Phase III trials in recent years.

With these reasons in mind, and noting that the optimization of the established psychiatric drug classes seems to have reached a limit, the recommendations of the symposium have a theme: a fundamental rethink of psychiatric drug discovery, from the initial discovery strategy, to the type of preclinical models, to the classification and selection of patients in clinical trials, is needed. As the answers of the participants illustrate, concerted efforts not only to better translate basic research into therapeutic applications as in other disease areas, but also to better integrate advances in molecular, cellular and systems-level knowledge of psychiatric disorders, could be the key to the success of such a rethink in revitalizing innovative drug discovery in the field.