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Experimental medicine in psychiatry

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The recent allocation of £15 million by the MRC (Medical Research Council) specifically to support research in experimental medicine (defined as the ‘Investigation undertaken in human beings to identify mechanisms of pathophysiology or disease, or to test the validity and importance of new discoveries or treatments, relating where appropriate to model systems’) underlines the priority currently given to this area of research. The recent interest in experimental, sometimes called ‘translational’ medicine suggests that it is something new. However, the BAP (British Association Psychopharmacology) was established in 1974 to support experimental and translational medicine in the area of psychopharmacology by bringing together the preclinical and clinical arms of this research area. Through its meetings and journal the BAP has been at the forefront of translational medicine in its purest form – combining the knowledge gathered from preclinical and clinical science to provide synergy in the search for new treatments for some of the most devastating disorders known to man. Indeed it is difficult to name a society that does more to put the ‘translational’ into ‘translational medicine’ than the BAP and we have little doubt that psychopharmacology alone could generate world class research proposals that would account for all of the MRC allocation.

Another strong supporter of translational medicine is the pharmaceutical industry. Its driving force has been the large markets in psychiatry for medicines such as Risperidone (>\$2 billion annual sales) for the treatment of schizophrenia or Duloxetine (>\$1 billion annual sales) for depression. Consequently pharmaceutical companies have poured significant resources into discovering and developing new treatments for psychiatric disorders. On the pre-clinical side of the translational medicine equation, the combined resources of academia and industry have resulted in a phenomenal increase in fundamental knowledge, new experimental techniques and, indeed, whole new classes of candidate compounds. However, clinical translation of these findings directly to benefit psychiatric patients has so far been very limited and most of the medicines we think of as new – the atypical antipsychotics or the SSRIs (Selective Serotonin Reuptake Inhibitors), for example – were conceived as refinements of classical treatments. The failure, so far, of genuine innovation has been disappointing, and so merits closer examination. For example, preclinical and early clinical

studies suggested that NK-1 antagonists would be effective antidepressants. The first clinical study was also positive, but subsequent large Phase III studies were not. Uncertainty about the clinical efficacy of the compounds led to the termination of investment by the leading player. Unfortunately, placebo controlled trials in depression are difficult to conduct in patients with significant severity of depression, and placebo response rates are high so confounding detection of positive treatment effects. Such trials are also extremely expensive. Very promising candidate medicines may founder because of chance effects in very expensive clinical studies. There is an evident gap between the preclinical portfolio and such large scale clinical trials. The question is whether we can harness and exploit the strong clinical science base in the UK to fill this gap by generating translational data for new compounds, which would be highly predictive of subsequent clinical utility.

There should be no doubt about the unmet needs of the patients. Economically, more beds are occupied by patients with psychiatric disorders than any other patient group; schizophrenia alone costs the National Health Service in England and Wales about £2.9 billion each year. Add in the cost of lost working hours and benefit payments (about 95% of patients with schizophrenia are unemployed) the overall costs rocket. Thus, it would be foolish to doubt the potential benefits of investing in CNS (Central Nervous System) research and development. The existing global market for CNS drugs for 12 months to March 2004 was \$59.6 billion and with a 14% increase on the 12 months to March 2003 was the second fastest growing therapeutic category. Unfortunately, the costs of drug development (including lost opportunity costs) continue to spiral and the average cost of development of a new drug is estimated to be about \$900 million. Furthermore, the chance of success of a novel compound in Phase I reaching the market is 11% for all therapeutic categories and only 8% for CNS disorders. This makes the costs of CNS drug development particularly high and raises the question of why it is more difficult to discover and develop drugs for CNS disorders and why the success rate is not improving (Kola and Landis, 2004).

In the past 10 years there has been little improvement in the overall rate of novel compounds in development but there have been significant changes in the causes of attrition. In 1991, the

main reason for failure of a drug in clinical development was poor or unpredictable bioavailability and pharmacokinetics – a problem that accounted for 40% of all attrition. This issue has been successfully addressed by the introduction of comprehensive *in vitro* and *in vivo* drug metabolism and pharmacokinetic screening technologies at an early stage of the drug discovery process. Today the principal cause of failure in clinical development is lack of efficacy and safety (accounting for approximately 30% and 20% respectively of all failures) and this is a particular problem in CNS drug development which has a lower than average chance of success due to the poor translation from preclinical models to clinical response. The experience with NK-1 antagonists illustrates the problem. Consequently, it is increasingly recognized by the pharmaceutical industry that the introduction of experimental and translational medicine models at the interface between Phase 1 and Phase 2 clinical trials is the way forward in CNS drug development. Such studies bridge the gap between animal and human studies and aim to provide a faster route through clinical trials by providing a rapid Go/No-Go decision. The studies can use volunteers or small patient groups but importantly employ experimental design in a laboratory setting to introduce rigour and harder endpoints for measurement.

While this strategy commands a wide consensus, the tactics to enable its development are only now being thought through. If each pharmaceutical company attempts to develop and validate experimental medicine models using its own limited resources, progress in bringing the models to a state of readiness where they are effective decision-making tools in the drug discovery process will be very slow. For academia, the MRC investment of £15 million is welcome but psychiatric applications are unlikely to attract more than 10% of the sum available – just a single substantial programme grant for which many groups will no doubt compete. The fragmentation implied by this analysis is counter-productive at a fragile stage in the development of a new approach to this core problem. One solution is to have a coordinated effort across academia and industry. The pharmaceutical industry has a recent history of combining resources to develop technology in key areas of drug discovery. These ‘pre-competitive consortia’ are established with clear goals and objectives set and funded by the companies in the consortium. The advantages to the companies in the consortium are clear: new technology is more rapidly developed than can be achieved with in-house resources and at a

fraction of the cost. To date, such consortia have been formed around specialist biotechnology companies in the area of robotic and cell based screening, but in principle there is no reason why they should not be formed to support the development and validation of experimental medicine models, which will ultimately benefit drug development. However, the expertise in experimental medicine does not principally reside in biotechnology companies; it resides largely in clinical academic centres of excellence that have access to volunteers and patients to develop such models. Moreover, as the MRC call demonstrates, academic funding bodies also have a strong interest in developing experimental and translational science and making the most of its recent investment in clinical research facilities.

How then should academia and its principle funding bodies interact with industry to make significant progress in the development of experimental medicine, particularly in psychopharmacology? We believe the formation of a joint pre-competitive consortium with industry has a number of obvious (and some less obvious) advantages. The obvious advantages are efficiency of scale, coordination and funding that a pre-competitive consortium brings. The not so obvious advantages are the increased interaction between industry and academic scientists and the intangible benefit that accrues when each group achieves a better understanding of the other’s needs. Thus, such development work will increase the employment of the academic clinical research facilities that exist around the UK and offer important training and development opportunities for young scientists interested in clinical problems, who need to acquire the necessary skills to work and develop the area of experimental and translational medicine to its full potential. Such an approach requires vision and commitment to a long term project. It also requires increased cooperation between competing academic groups. To fund a large scale project of this kind will also require some brave decisions when it comes to investment. However, the ability and expertise to achieve these objectives is clearly available in the UK and with the right investment it can achieve international success which will provide both scientific insight and huge economic benefit. Ultimately, the benefit to society could be speed to launch new medicines and faster, more efficacious treatments. We certainly need them.

Reference

Kola I and Landis J (2004) *Nature Reviews Drug Discovery* 3: 711–715