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REVIEW

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Challenges and opportunities for drug discovery in psychiatric disorders: the drug hunters' perspective

Erik H. F. Wong[1], Frank Yocca[1], Mark A. Smith[2] and Chi-Ming Lee[3]

[1] *CNS & Pain Discovery Research, AstraZeneca Pharmaceuticals, Wilmington, DE, USA*
[2] *Early Clinical Development, AstraZeneca Pharmaceuticals, Wilmington, DE, USA*
[3] *Translational Science, AstraZeneca Pharmaceuticals, Wilmington, DE, USA*

Abstract

Innovation is essential for the identification of novel pharmacological therapies to meet the treatment needs of patients with psychiatric disorders. However, over the last 20 yr, in spite of major investments targets falling outside the classical aminergic mechanisms have shown diminished returns. The disappointments are traced to failures in the target identification and target validation effort, as reflected by the poor ability of current bioassays and animal models to predict efficacy and side-effects. Mismatch between disease biology and how psychiatric diseases are categorized has resulted in clinical trials of highly specific agents in heterogeneous patients, leading to variable treatment effects and failed studies. As drug hunters, one sees the opportunity to overhaul the pharmaceutical research and development (R&D) process. Improvements in both preclinical and clinical translational research need to be considered. Linking pharmacodynamic markers with disease biology should provide more predictive and innovative early clinical trials which in turn will increase the success rate of discovering new medicines. However, to exploit these exciting scientific discoveries, pharmaceutical companies need to question the conventional drug research and development model which is silo-driven, non-integrative across the confines of a company, non-disclosing across the pharmaceutical industry, and often independent from academia. This leads to huge redundancy in effort and lack of contextual learning in real time. Nevertheless, there are signs that drug discovery in the 21st century will see more intentional government, academic and industrial collaborations to overcome the above challenges that could eventually link mechanistic disease biology to segments of patients, affording them the benefits of rational and targeted therapy.

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Introduction

From 1950 to 2008, the US Food and Drug Administration (FDA) approved 1222 new drugs [new molecular entities (NMEs) including biologicals] (Munos, 2009). It is alarming that although the level of investment in pharmaceutical research and development (R&D) efforts has increased dramatically over this period to the point of spending over US$50 billion in 2009 (Paul *et al.* 2010), the number of new drugs that are approved annually (about 25) is no greater now than 50 yr ago, i.e. scale is not matched by productivity (Garnier, 2008; Paul *et al.* 2010). Indeed, in 2009, in spite of said investment, of the 25 new drugs approved for marketing in the USA, only two are from the psychiatry portfolio (Hughes, 2010). This is further compounded by the high rate of failure in CNS drug discovery and in particular the attempts to introduce first-in-class therapeutics with an unprecedented mode of action (Agid *et al.* 2007; Conn & Roth, 2008; Kola & Hazuda, 2005; Munos, 2009). While the success rate for development of drugs for CNS and oncology are similarly low (8% *vs.* 5%), in spite of the immense social cost incurred, psychiatry continues to suffer from lack of funding in basic research relative to other

Address for correspondence: Dr E. H. F. Wong, CNS Discovery, AstraZeneca Pharmaceuticals, 1800 Concord Pike, Wilmington, DE 19850, USA.
Tel.: +1 302 885 4709 *Fax*: +1 302 886 1584
Email: erik.wong@astrazeneca.com

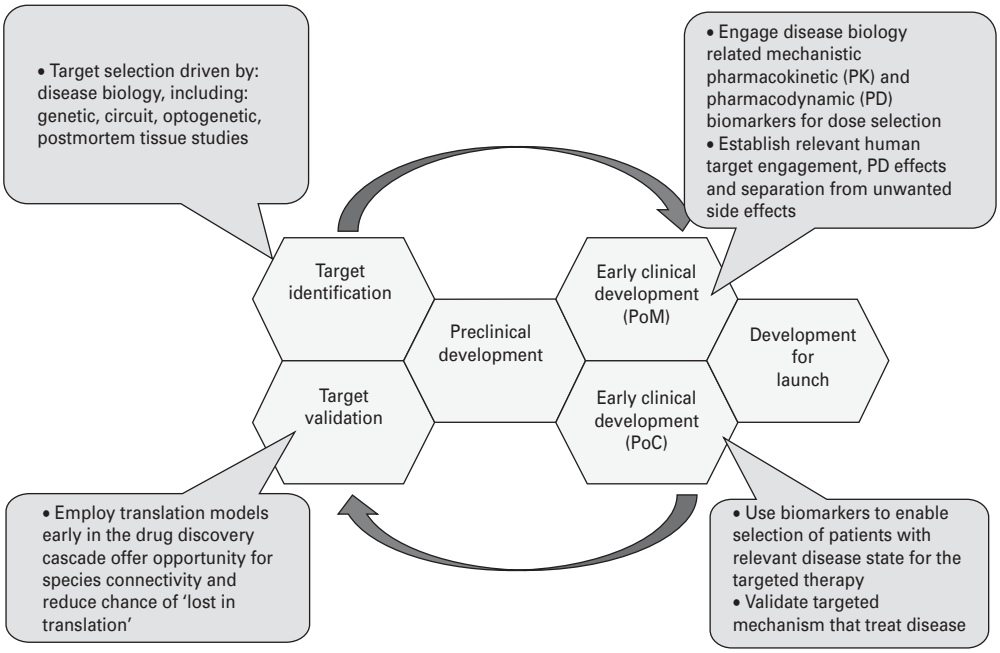

Fig. 1. Drug discovery and development is a reiterative process.

therapeutic areas (Insel, 2008; Kola & Landis, 2004; Anon., 2010). Although it is recognized that part of the increased R&D investment is to address the increasing regulatory demand on drug safety, one must address the question of how pharmaceutical R&D productivity can be improved to sustain this industry, and how to overcome the hurdles in order to identify the next generation of pharmacotherapies for psychiatric disorders.

The process of drug discovery encompasses a period of intense R&D effort that typically spans 13–15 yr, and involves: (i) search for a target to start a programme or project, (ii) lead generation and optimization steps to allow candidate drug selection, and (iii) human testing to achieve proofs of mechanism, principle and concept, hopefully leading to regulatory approval (Fig. 1). While the above figure outlines some of the clear milestones in the current R&D process, it can be classified simply in terms of two steps, i.e. target identification and target validation. For target identification, the intention is to explore rationally the connection between manipulations of a target to intended clinical actions. One might consider a target beyond its usual molecular description to a set of mechanisms with physiology and pathological relevance. The choice of a novel target often depends on the level of insights from novel biological principle, yet to show clinical values (Campbell *et al.* 2010; Insel, 2009*b*; Millan, 2006). Target validation charts the progress of the painstaking process to develop molecules with a target product profile including: appropriate pharmacology, acceptable therapeutic index in preclinical models and subsequent validation in clinical settings in volunteers and patients. This review will outline both preclinical and clinical challenges in the current R&D model, discuss the recent developments in technological and methodological strategies to mitigate risk of failure and suggest options to harness innovation to identify the next generation of novel psychotherapeutic agents.

Target identification and validation: challenges and opportunities

Since the dawn of psychotherapeutics nearly 60 yr ago (Ban, 2006), target identification has arguably been 'accidental and opportunistic'. A classic example is the serendipitous observation of tuberculosis patients becoming 'cheerful' after administration of the antibiotic iproniazid. Soon after this astute clinical observation, Zeller showed that iproniazid slowed the breakdown of norepinephrine, serotonin and dopamine via inhibition of monoamine oxidase. Through the use of animal models, testing and development of various putative monoaminergic antidepressants continues to this day, e.g. selective norepinephrine reuptake inhibitor (NRI) (Wong *et al.* 2000). Thus, with very few exceptions over the past 50 yr, discovery of

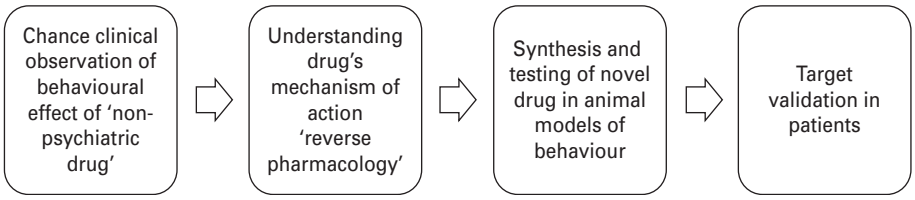

Fig. 2. The classical process of drug discovery based on 'reverse pharmacology'.

psychiatric drugs has followed a sequence beginning with a chance observation in the laboratory or clinic, followed by research to understand the neurochemical mechanism of action responsible for the behavioural effects of the original drug (i.e. 'reverse pharmacology'), and then synthesis and testing of the putative new drug in rodent models to ensure that it mimicked the behavioural effects of the original drug (Fig. 2).

Lessons in 'reverse pharmacology': MK-801 and NMDA antagonists

A good example of the reverse pharmacology process is the serendipitous observation of muscle relaxant action from dye molecules that led to the identification of chlordiazepoxide, one of the most successful anxiolytics in the market (Ban, 2006; Sternbach, 1979). Availability of a wave of 'animal models for psychiatric behaviours' (Crawley & Goodwin, 1980; Cryan & Slattery, 2007; Porsolt *et al.* 1977) has encouraged extensive *in-vivo* screening, with the aim of identifying agents with desirable behavioural effects (e.g. anxiolysis). In the early 1980s, attempts to recapitulate the desirable anti-anxiety action of benzodiazepines led to the synthesis of over 240 analogs of dibenzocycloheptenimines, and gave rise to MK-801, with an interesting spectrum of potent anxiolytic, sympathomimetic and anticonvulsant action (Clineschmidt *et al.* 1982).

Tritium labelling of MK-801 allowed identification of high-affinity, saturable, brain regional specific-binding sites (Bowery *et al.* 1992; Wong *et al.* 1986, 1988) that are sensitive to modulation by endogenous ligands and divalent cations (Bakker *et al.* 1991; Foster & Wong, 1987; Wong *et al.* 1987, 1988). This culminated in identifying MK-801 as a non-competitive glutamate NMDA receptor antagonist (Anis *et al.* 1983; Kemp *et al.* 1987). These findings drove a heightened interest in the biology of neurodegenerative disorders in general, and stroke research in particular (Rothman & Olney, 1995; Wong & Kemp, 1991).

Unfortunately, MK-801 had psychotomimetic properties precluding its testing in these various disorders. In this regard it was very similar to the dissociative anaesthetics such as phencyclidine and ketamine which had long been known to produce psychotic symptoms in surgical patients. However, the recognition that it and related psychotomimetic drugs such as phencyclidine and ketamine were all NMDA receptor antagonists (Anis *et al.* 1983; Zukin & Zukin, 1979) was another example of 'reverse pharmacology' that generated a paradigm shift in schizophrenia drug development to focus attention on glutamate. Metabotropic glutamate receptors and glycine reuptake inhibitors are being tested in schizophrenia as a result of these original clinical observations and reverse pharmacology (Moghaddam, 2003; Olney, 2003).

A surprising turn of the NMDA story arose from another unexpected clinical observation, this time involving mood rather than psychosis. Berman and colleagues noticed a very rapid, mood-elevating effect of ketamine while conducting a cognition study in depressed patients (Berman *et al.* 2000). This astute observation has subsequently been confirmed by other investigators and triggered a number of drug companies to 're-profile' their NMDA antagonists from former stroke programmes as potential rapid-onset antidepressants. For example, in a small ($n = 30$ subjects) but well-controlled study, the NR2B subunit selective NMDA antagonist, CP-101,606 was administered intravenously to patients with treatment-refractory depression and shown to have a very robust and rapid antidepressant effect (Preskorn *et al.* 2008). Dissociative side-effects of CP-101,606 were mild lending hope that it may be possible to develop well-tolerated NMDA antagonists which nevertheless have robust antidepressant effects.

Single-target *vs.* multiple-target drugs: clozapine

Some of the most innovative drugs, including the atypical antipsychotics clozapine and quetiapine, were discovered based on their performance in animal models of efficacy and side-effects without regard to their mechanism of action or molecular binding parameters. It was only later that it was discovered just how complex their pharmacology proved to be.

While there is no doubt that the identification of the genes coding for specific receptors and their subtypes has made drug discovery more rational over the past 30 yr, it has also intentionally or unintentionally driven the pursuit of ever more selective drugs. While these single-target agents (STAs) may have reduced side-effects compared to their 'dirty' multi-target agent (MTA) ancestors, improved efficacy has been an elusive goal (Millan, 2006; Roth *et al.* 2004). For example, reverse pharmacology has increased the confidence that manipulation of monoaminergic transporters by STAs such as selective serotonin reuptake inhibitors (SSRIs), or selective NRIs has a good chance of producing antidepressant action with improved tolerability (Wong *et al.* 2000, 2008), but efficacy is no better than imipramine.

Similarly, since the discovery of a unique MTA such as clozapine, attempts to recapitulate their pharmacological signature has delivered a number of second-generation antipsychotics (Meltzer, 2004). However, efforts to determine whether more selective agents show antipsychotic efficacy has been disappointing. Specific 5-HT_{2A} antagonists such as MDL-100907 did not show clinical efficacy in Phase III trials of acute schizophrenia in spite of showing efficacy in many preclinical models of antipsychotic activity (de Paulis, 2001). Although the latter interpretation could be complicated by the fact that these compounds worked on reversals of PCP and amphetamine-induced locomotor activity, and not in conditioned avoidance and apomorphine-induced climbing, indicating the need for a battery of tests to render a conclusion on preclinical efficacy. Nevertheless, selective agents that target other receptors to which clozapine bind, such as D_4, have not proven efficacious on their own (Corrigan *et al.* 2004). Perhaps predictability is too difficult when preclinical testing invariably uses a healthy, lissencephalic, rodent brain for *in-vitro* and *in-vivo* analysis. One then expect the results to predict efficacy in a chronic dosing regimen, in a complex diseased human. There are many review articles discussing the lack of predictability of current animal models (Agid *et al.* 2007; Chadman *et al.* 2009; Cryan *et al.* 2002; Cryan & Slattery, 2007), although the issues of acute preclinical testing *vs.* chronic dosing and the cross-species mismatch continue to receive limited attention.

Opportunities to identify novel drug targets based on disease biology

In the last decade, large-scale candidate gene and genome-wide association studies have generated a growing list of 'risk' genes for psychiatric illnesses. A key finding of these genetics studies in psychiatry is that multiple risk genes were identified, each making a small contribution to the disease (Manolio *et al.* 2009). This has led to an increasing interest in pre-competitive private–public partnership to pool resources (including large cohort samples and multiple analytical technologies) to validate risk genes and understand how they relate to disease pathophysiology and abnormal behaviour (Insel & Cuthbert, 2009; Spedding *et al.* 2005). These human genome-based approaches of understanding the location and function of specific gene products and their relevance to disease pathophysiology have rewarded the field of biological psychiatry with some novel target ideas (Berton & Nestler, 2006; Conn & Roth, 2008; Covington *et al.* 2010; Schloesser *et al.* 2008). They have enriched our understanding of the psychopharmacology of the cholinergic, glutamatergic and peptidergic mechanisms and continued to fuel novel target exploration (Beaulieu *et al.* 2009; Conn & Roth, 2008; Mathew *et al.* 2008; Roth, 2006). For example, the *DISC1* (disrupted-in-schizophrenia1) gene is shown to be a major risk factor in familial schizophrenia and bipolar disorder. Polymorphism studies of *DISC1* (e.g. Leu607Phe) point to changes in synaptic functions that could lead to alteration in cortical circuits (Eastwood *et al.* 2009; Harrison & Weinberger, 2005).

The recent advances in optogenetics using light-activated channel rhodopsin 2 to activate specific neuronal pathways with cell-type selectivity and millisecond temporal precision in conscious 'behaving' transgenic animals will provide an unprecedented opportunity to study how selective activation of cholinergic, GABAergic and glutamatergic neurons in amygdala and striatum can modulate normal or abnormal endophenotypes in transgenic animals carrying different psychiatric risk genes (Arenkiel *et al.* 2007), and potentially support a new target validation strategy.

STAs: conventional target biology *vs.* clinical reality – 'lost in translation'

The rational drug design process has driven the recent wave of unprecedented targets (Covington *et al.* 2010; Mathew *et al.* 2008). However, in spite of achieving the appropriate selectivity, CNS penetration and safety characteristics, and even 'efficacy' in preclinical models, many novel drug candidates failed to survive the target validation process. For cases involving development of non-sedating anxiolytics, it is clear that the

prevailing rodent models used to rule out sedation simply do not predict this in humans (Atack, 2003, 2010). What started off as a single-minded search for non-sedating anxiolytics as a commercial concept (i.e. target product profile), soon evolved into the need to manage other patient requirements such as onset of action, tolerance, dependence, abuse liability and psychomotor functioning (D'Hulst *et al.* 2009; Rudolph *et al*. 1999). Accurate measurement of sedation requires objective endpoints such as saccadic eye velocity and EEG (de Haas *et al.* 2007). Interesting, it is somewhat challenging to measure efficacy of anxiolytics in normal volunteers exposed to stress. While objective effects of benzodiazepines on the sympathetic nervous system and hypothalamic–pituitary–adrenal (HPA) axis are readily apparent, less so are their effects on subjective reports of anxiety (Fries *et al.* 2006). Non-selective benzodiazepines do attenuate subjective anxiety in response to inhalation of CO_2, but so do sedating GABA modulators such as zolpidem (Bailey *et al.* 2009). Thus it has been surprisingly difficult to verify the hypothesis that selective GABA modulators are anxiolytic with a better tolerability profile than non-selective GABA modulators by translational models in normal volunteers. In this case, it seems that Phase II trials in anxious patients are necessary to test the hypothesis adequately.

Beyond the difficulties inherent in the clinical target validation process, biological validation in animals has been disappointing. For example, the CRF_1 receptor is engaged in stress, control of the HPA axis, regulation of mood, and induction of anxious and depressed states (Binder & Nemeroff, 2010; Millan, 2006), but development of selective central CRF_1 receptor antagonists across multiple companies has so far been frustrated by lack of efficacy. This is the case in spite of careful attention to CNS exposure, and well documented evidence of receptor occupancy for CP-316,311 (Binneman *et al.* 2008). In that study, Phase 1 pharmacokinetic (PK) data gave steady-state mean serum trough concentrations of $\sim$980 ng/ml generated from a dosage of CP-316,311 used in a well designed Phase 2 study. These levels exceeded the upper end of *in-vitro* (human CRH_1 receptor affinity: 0.4–1.7 ng/ml) projections for required clinically efficacious serum exposures. Perhaps this is a drug still looking for the relevant therapeutic indication. Similar situations occurred for an NK_1 receptor antagonist in depression – aprepitant (Herpfer & Lieb, 2005).

There is also increasing evidence that activity in preclinical cognition models are poor predictors of efficacy in patients. An example of this is the result from a selective histamine H_3 inverse agonist, MK-0249 (Egan *et al.* 2009). There is ample preclinical evidence that as an autoreceptor, H_3 inverse agonism is able to regulate release of histamine, acetylcholine, dopamine and other transmitters engaged in cognition. In spite of clear efficacy in rodent models of attention, recognition memory (e.g. novel object recognition) and working memory, clinical trials employing a dose of MK-0249 with a similar plasma exposure value that achieved blockade of $>85\%$ of H_3 receptors in human brain, failed to improve cognition in schizophrenia patients. Indeed, elevating target occupancy by increasing drug dosage more often dials up mechanism based side-effects rather than improving efficacy. Perhaps the validity of these cognitive models remains experimental, and activity across a spectrum of cognition models will be required to model the complexity of human cognition.

These failures need to be reconciled in terms of (i) complex diseases requiring multi-target therapy, and (ii) the need to segment patient populations so that the biological processes can be measured in a clinical setting, without being overwhelmed by 'noise' or placebo effects. The fact that all major psychiatric diseases are heterogeneous, triggered by a complex pattern of genetic, epigenetic, developmental and environmental factors, is a human reality (Baghai *et al.* 2007; Hasler *et al.* 2004; Millan, 2006). It may be unreasonable to expect any STA that manipulates an individual neurotransmitter system to impact the complex pathological human brain to the point of delivering robust clinical effects.

MTAs for complex disorders

The examples of 'lost in translation' are not helped by the fact that the current definition of psychiatry diseases according to DSM-IV criteria is far from biological (APA, 1994). By definition, current clinical trial criteria do not engage any rules of segmentation or biomarkers that oncology therapy enjoys [e.g. human epidermal growth factor receptor (HER2) for breast cancer and CD20 in B cells pathology for chronic lymphoblastic leukaemia]. In depression, in addition to correction of the mood component, there are many other treatment demands: anxiety, insomnia, circadian desynchronization, cognitive impairment, motor retardation, pain and sexual dysfunction (Morilak & Frazer, 2007). Indeed, one observes in the presentation of anxiety disorders, depression, bipolar disorder, and schizophrenia a constellation of symptoms, but with a dissimilar degree of pattern expression (Millan, 2009; table 1 of Wong *et al.* 2008). This indicates that the current disease classification is not biological but

symptom-based without a uniform presentation in space and time, and therapeutic correction with STAs, however well meaning, is insufficient (Millan, 2006, Wong *et al*. 2008, 2010). Pragmatically, it seems logical that a treatment algorithm that can engage multi-targets has a better chance of showing efficacy in these complex disorders under the current clinical diagnostic scheme (Keiser *et al.* 2009; Millan, 2006; Roth *et al.* 2004). It seems logical to meet this treatment demand by MTAs, as has been shown with the second-generation antipsychotics (Meltzer, 2004), or via a combination of a SSRI plus other agents (Millan, 2006, 2009; Wong *et al.* 2008, 2010). From the drug discovery point of view, the medicinal chemistry challenge for a multi-target approach is problematic (Morphy *et al.* 2004; Wong *et al.* 2008). Beyond the standard multi-target approach, one can see there are a number of variations on a theme ranging from (i) combination of STAs with an established biological principle that has an appropriate safety profile (fig. 2 of Wong *et al.* 2008), to (ii) combination of a SSRI plus adjunctive agents (e.g. fluoxetine, aripiprazole), to (iii) a continuation of the long-tried practice of polypharmacy with its success and limitations. These approaches seem pedestrian in the face of high-powered neuroscience advances, but until clinical trial design and patient segmentation can improve to the point of matching disease phenotype to circuit-based deficits, such multiple-treatment algorithms might be practical and necessary (Fig. 1; Wong *et al.* 2008). The value of using two agents simultaneously, or in series as an add-on adjunctive approach deserves attention (Blier *et al.* 2009; Millan, 2009).

Translational science for target validation: connecting biology to clinical practice and back

To improve the productivity of R&D investment, the FDA 'Critical Path' and the NIH 'Roadmap' all emphasized the importance of 'translation' science, both as an attitude and a practice (Insel, 2009*a*). Translational research is defined as 'the transfer of knowledge gained from basic research to new and improved methods of preventing, diagnosing, or treating disease, as well as the transfer of clinical insights into hypotheses that can be tested and validated in the basic research laboratory' (Hall, 2002).

The goal of translational medicine is to provide a better understanding of human disease by connecting basic and clinical research at every stage of the drug R&D process, and to answer the question: is the drug safe and efficacious for the targeted disease population? It is a data-driven, two-way re-iterative process where the discovery and development of therapy is complemented by the pursuit to understand human diseases. In forward translation, one will use preclinical findings to guide clinical studies and the development plan (e.g. disease indications, patient populations, dose selection, dosing regimen). In back translation, one will use clinical data to 'humanize' and improve preclinical drug discovery (e.g. identify and validate drug targets, understand disease mechanisms, develop predictive models/biomarkers). Therefore, by investing in 'forward and back translation' studies, one aims to optimize and transform the entire drug development portfolio and not just each drug candidate (Fig. 1).

Using translational tools to enhance dose prediction across species

The first challenge in target validation is to determine the effective dose. The blood–brain barrier (BBB), which regulates the passage of compounds into and out of the brain, is critical for the normal functioning of the CNS but it also presents a significant challenge to delivery of CNS drugs into the brain. It is known that drug transporters and metabolic pathways can be highly polymorphic at the BBB within and across different species, which have contributed to the less than robust estimation of drug levels in brain based on plasma exposure. Positron emission tomography (PET) is increasingly being applied to measure the biodistribution and brain concentration of a CNS drug (Farde, 1996; Fischman *et al.* 1997; Halldin *et al.* 2001). This can be achieved by microdosing or target occupancy studies to enable compound and dose selection for clinical studies (Lee & Farde, 2006). If it can be demonstrated that the drug is not getting into the targeted regions of the brain or not binding to the targeted receptor at the expected level, such human target validation exercise should be terminated without going through the time and expense of a conventional clinical trial. For instance, in micro-dosing studies, clear differences can be seen in the biodistribution of three related 5-HT_{1B} antagonists (Fig. 3). Compound AZ10419580 which showed poor distribution into the brain was terminated for further development as an antidepressant. Molecular imaging can also provide evidence of proof of concept or to reject a target (Wong *et al.* 2009). On the one hand, for typical D_2 antagonist antipsychotics, a therapeutic response can be expected with 65–80% D_2 receptor occupancy thus qualifying it as a proof of concept biomarker (Farde *et al.* 1988). On the other hand, in the case of the NK_1 antagonist aprepitant, because clinical

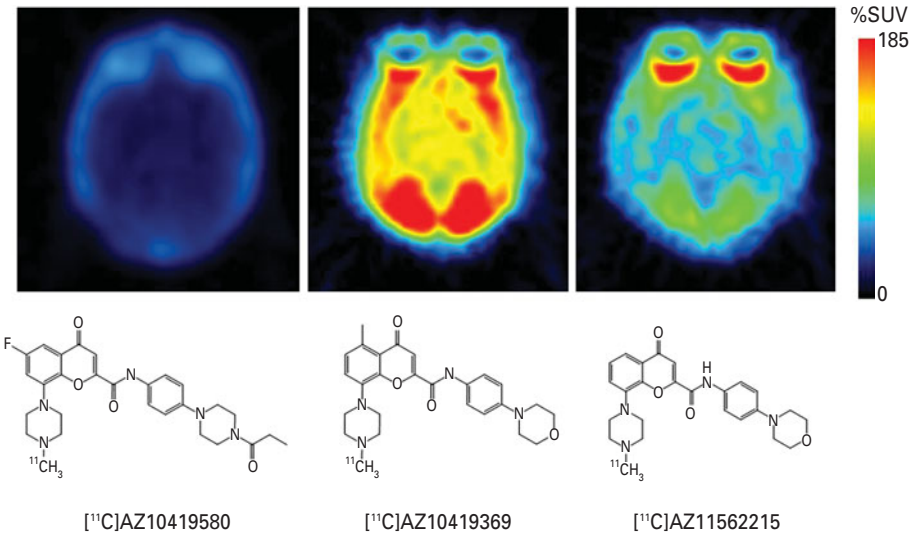

Fig. 3. Summation PET images showing radioactivity distribution for three 5-HT_{1B} radioligands in a horizontal section of cynomolgus monkey brain. The images represent integrated radioactivity from 9 to 93 min after radioligand injection. Regional radioactivity concentrations were decay-corrected, normalized to injected radioactivity and body weight – expressed in % of standard uptake value (%SUV) (J. Andersson *et al.* unpublished data). [^{11}C]AZ10419369 showed much higher uptake in 5-HT_{1B} receptor-rich regions (e.g. occipital cortex) than related analogues [^{11}C]AZ11562215 or [^{11}C]10419580.

doses which occupied 80–90% of NK_1 receptor throughout the treatment period were not effective, the NK_1 receptor by itself was rejected as an antidepressant target (Keller *et al.* 2006).

After establishing that the drug reaches the brain, it is important to determine if it has a pharmacodynamic (PD) effect to confirm that the dose is right. In this regard, electrophysiology and functional magnetic resonance imaging (fMRI) are increasingly being utilized as non-invasive translational PD markers in psychiatry. Scalp-recorded electroencephalography (EEG), magnetoencephalography (MEG) and event-related potentials (ERPs) can provide continuous non-invasive measures of brain electrical activity in healthy volunteers and patients. Moreover, several specific electrophysiological measures are pre-attentional (e.g. P50, mismatch negativity) and do not require attentional or purposeful actions of the test subject (Naatanen & Kahkonen, 2009). This is advantageous over neuropsychological evaluations, which are affected by an individual's vigilance and motivational state. There is a strong face validity and mechanistic homology among rodents, primates and humans for a battery of EEG/ERP components, supporting valuable preclinical to clinical translation. An example is the cross-species measurement of schizophrenia-related sensorimotor gating deficit using pre-pulse inhibition (PPI) of startle paradigm (Light & Braff, 1999; Swerdlow *et al.* 2008). As a complementary translational tool, fMRI can be used to reflect changes in regional blood flow as a surrogate for neuronal responses after drug administration in animals and humans (pharmacological MRI) (Ketter & Wang, 2002; Mayberg *et al.* 1997).

One can also capitalize on the complementarity of these translational tools by integrating them appropriately. For instance, the complementarity between anatomic [computerized tomography (CT) and magnetic resonance imaging (MRI)] and molecular (PET) imaging is well established and routinely used. In the past decade there have been increasing efforts to combine high temporal resolution EEG/MEG with fMRI (high spatial resolution), to enhance the localization of functional activity in the brain (Horwitz & Poeppel, 2002). This has been applied in language processing and is expected to be increasingly applied in psychiatric disorders (Mulert *et al.* 2008; Vitacco *et al.* 2002). Most recently, some prototypes of a MRI/PET scanner for rodent and human brains have been built to acquire morphological and functional data simultaneously and may offer higher resolution and more versatile translational tools for the future (Herzog *et al.* 2010).

Most of the PD methodologies (e.g. quantitative EEG, ERP, fMRI, PET) are typically developed singularly and pursued by distinct laboratories. In the

future, multimodal behavioural analysis should also be considered. While no one physiological measurement can afford predictive power for currently classified psychiatric illnesses, the blending of multiple measurements in parallel integrated across space and time could be a powerful approach for the future. Indeed, there are encouraging signs that some of the technological challenges are being worked out (fMRI and EEG, MRI/PET, fMRI and behavioural tests, etc.). Further, data acquisition demands are also being resolved through machine learning practices that have been migrating from the computer field to neuroscience application (Brammer, 2009). Perhaps these contextual neuroscience approaches could be the way of the future!

By combining translational PK and PD measurements, it is possible to address PK/PD relationships that can help establish a valid dose range for clinical studies intended to establish efficacy (Binneman *et al.* 2008; Farde *et al.* 1988; Keller *et al.* 2006). Gabrielsson *et al.* (2009) described strategic approaches to integrate preclinical and clinical PD/PK information in order to estimate relevant clinical doses and provide insight into potential adverse effects across species.

Thus during Phase I testing of a novel compound, it is important to establish proof of mechanism by demonstrating that a certain dose not only has acceptable tolerability but also has biological activity as evidence by its PD response in humans. This is to ensure that the proper study dose is determined to prevent false negatives from occurring in Phase IIA studies in patients because the target has not been engaged sufficiently.

Developing disease biology-based preclinical models to improve predictiveness of drugs in clinical studies

Currently, most commonly used preclinical animal models are pharmacologically based (e.g. amphetamine- and phencyclidine-induced locomotory activity tests for antipsychotics and forced swim test for antidepressants) rather than disease biology-based. This makes it difficult if not impossible to develop translational biomarkers with sufficient construct validity to predict the benefits and risks of a candidate drug in human clinical studies (Cryan *et al.* 2002). With increasing understanding of the functions of neuronal circuitries in the brain, the association between a molecular target and psychiatric relevant behaviour becomes measureable. For instance, anhedonia (decreased motivation for and sensitivity to rewarding experiences) is a core symptom for several psychiatric disorders (including depression and schizophrenia); the cortico-striatal-limbic system is an important circuitry in mood regulation (Price & Drevets, 2010). In rodents, anhedonia-like behaviour is traditionally assessed by reward-seeking activities such as lever pressing and sweet solution preference, which have face validity but insufficient construct validity. The recent finding that anhedonia, but not other symptoms of depression or anxiety, is correlated with reduced nucleus accumbens (NAc) responses to rewards, reduced NAc volume and decreased resting activity in the rostral anterior cingulate cortex, indicates that the neurobiological mechanism underlying anhedonia can potentially be tracked by these objective translational measures (Wacker *et al.* 2009). Increasing construct validity through such translational studies across multiple *in-vivo* models across species will significantly enhance our understanding of the relationship between brain circuits and disease phenotypes and will likely increase their predictiveness in future clinical studies, particularly for candidate drugs which demonstrated convergent activities across multiple disease relevant models.

Paradigm shift from 'single disease entity' to 'multiple domains of pathology'

On average, a marketed psychiatric drug is efficacious in approximately half of the patients who take it. One reason for this low response rate is the artificial grouping of heterogeneous syndromes with different pathophysiological mechanisms into one disorder. For instance, in schizophrenia, at least three primary domains of pathology have been recognized: positive symptoms (psychosis), negative symptoms and cognitive deficits. The current antipsychotics, typically dopamine D_2 receptor blockers, provide relief for many schizophrenia patients from psychosis but still leave them with persistent negative symptoms, significant cognitive deficits and poor executive functioning. Emerging evidence suggests that these deficits appear to be associated with glutamatergic dysfunction (Javitt, 2008; Moghaddam, 2003). The identification of specific and reliable biomarkers reflecting glutamatergic dysfunction will enable the selection of schizophrenia patients who will benefit more from pharmacotherapies targeting glutamatergic pathways. Thus, by increasing the mechanistic understanding of disease and matching the right treatments to the right patients, one could move from one-size-fits-all to targeted therapy and increase the benefit-risk ratio for patients (Wong *et al.* 2008).

As evidence for specific 'pathological domains' increases, there is an increased use of objective

translational tools to define the relevant endophenotypes/intermediate phenotypes. An endophenotype is a biological or behavioural feature (in non-affected subjects or patients) that reflects a discrete biological system, and as such is thought to be more closely related to a specific gene than the broad clinical phenotype (Insel & Cuthbert, 2009). It is expected to augment the discriminating power of genetic association and linkage studies, as well as facilitating the development of new therapeutics targeting subsets of complex phenotypes (Gottesman & Gould, 2003; Meyer-Lindenberg & Weinberger, 2006; Tan *et al.* 2008). An example of an endophenotype is deficient sensorimotor gating, i.e. a reduction in the brain's ability to filter excessive sensory information and generate appropriate motor responses. For instance, schizophrenia patients and their first-degree relatives exhibit a smaller reduction in the startle response than control subjects when a strong unexpected startle stimulus is preceded ~50–150 ms by a lower intensity prestimulus (generally referred to as PPI). These deficits impact sensory processing, cognition and functional outcome. It should be noted that impaired sensorimotor function is not specific to schizophrenia. PPI deficits can also be seen in bipolar disorder (Giakoumaki *et al.* 2007). Indeed, substantial genetic overlap has been reported for schizophrenia and bipolar disorders (Le-Niculescu *et al.* 2007; Lichtenstein *et al.* 2009; Moskvina *et al.* 2009; Purcell *et al.* 2009). Thus, PPI will provide a homologous measure for a specific 'pathological domain' (diminshed sensorimotor gating) within a complex phenotype. It can be used translationally across preclinical and clinical studies to identify and confirm drug candidates that will improve sensorimotor gating in schizophrenia as well as bipolar patients.

Strengthening pharmacogenetic research to facilitate personalized healthcare in psychiatry

The goal of personalized healthcare in psychiatry is to personalize the diagnosis and treatment of patients in order to maximize efficacy and minimize risk of adverse effects as well as reduce trial-and-error prescribing. It is hoped that by studying a patient's genetic profile, physicians will be able to detect susceptibility to certain ailments and suggest effective preventive or therapeutic measures tailored to both patient and disease (Flordellis, 2005). Since drug targets, signalling pathways and metabolic pathways can be highly polymorphic, genetic biomarkers that discern different endophenotypes/patient populations in relation to PK or PD parameters will enable clinical trials to become more effective. For instance, biomarkers that predict the likelihood of a disease event or more rapid disease progression or treatment response can increase the likelihood of detecting therapeutic benefits in a shorter time with fewer subjects (Scharfetter, 2004).

For example, since the primary target of SSRIs is the serotonin transporter (5-HTT), the inter-individual variation in clinical response to a SSRI may be related to inter-subject variability in 5-HTT expression (Spigset & Martensson, 1999). A relatively common polymorphism in the human *5-HTT* gene (SLC6A4) resulting in the short (s) and long (l) variants in the promoter region of the gene has been studied extensively. This 5-HTTLPR polymorphism impacts *5-HTT* gene transcriptional efficiency and expression in transfected cells, the s allele associated with lower transcription, expression and activity of the 5-HTT (Mancama & Kerwin, 2003). Individuals homozygous for the s allele are associated with heightened anxiety and more readily develop affective illness than the l allele carriers (Lesch & Mossner, 1998). Multiple studies in Caucasian subjects have reported differences in the efficacy and time of onset of SSRIs associated with variations in this 5-HTTLPR polymorphism and those with the l/l genotype have a more favourable and earlier onset response to SSRI treatments than the s allele carriers, although there are also some conflicting data (Kato *et al.* 2005; Luddington *et al.* 2009).

Patients with the genotype combination s/s (5-HTTLPR polymorphism of SLC6A4) and the G/G (-1018C/G polymorphism of the *5-HT$_{1A}$* receptor gene) appear to have the worst outcome compared to those patients carrying other combinations (Arias *et al.* 2005). Interestingly, based on the inverse relationship of 5-HT$_{1A}$ autoreceptor density (determined by PET) with amygdala reactivity (revealed by fMRI), it has been suggested that a reduced capacity for negative feedback regulation of 5-HT release is associated with increased amygdala reactivity (Fisher *et al.* 2006). Thus, an increase in 5-HT$_{1A}$ autoreceptor availability may contribute to the risk of depression and the down-regulation of 5-HT$_{1A}$ receptor may contribute to the therapeutic efficacy of antidepressant drugs (Richardson-Jones *et al.* 2010). This hypothesis is supported by recent pharmacogenetic data. A relatively common polymorphism (-1018C/G) in the promoter region of 5-HT$_{1A}$ has been reported to impact *5-HT$_{1A}$* receptor gene expression (Lemonde *et al.* 2003). Unlike the C/C allele, the G/G allele does not permit the binding of a transcriptional repressor and thus resulted in substantially higher levels of 5-HT$_{1A}$ autoreceptor expression. The G/G allele is over-represented in major

depressive disorder (MDD) patients especially in those with delayed response to SSRIs and non-responders. Therefore, it is conceivable that 5-HT_{1A} autoreceptor expression can be used to stratify patients – those with higher receptor expression are more likely to be non-responders (Richardson-Jones *et al.* 2010). Future clinical studies in depression should consider monitoring 5-HT_{1A} expression by genetics, PET or functional response measurements.

Genetic predisposition only provides information about relative risk as the expression of the full disease phenotype is influenced by other factors. Most psychiatric diseases are caused by a combination of genetic and environmental factors (e.g. stress) and their interactions (Insel & Cuthbert, 2009; Uher & McGuffin, 2009). Recent evidence suggests that a combination of genetic vulnerability and major life stressors contribute to the development of depression (Caspi *et al.* 2003; Risch *et al*. 2009). Most notably, individuals who are homozygous for the short (s) allele in the promoter region of the serotonin transporter gene (*5-HTTLPR*), and thus with a lower expression of the 5-HTT, have higher rates of depression and more suicidality as a function of exposure to increasing levels of stressful life event than those who are homozygous for the long (l) allele. Interestingly, mice with diminished function of the *5-HTT* gene exhibited greater increases in ACTH in response to stress. Hypercortisolaemia has been postulated to damage hippocampal neurons, which in turn may be involved in the pathogenesis of depression. Indeed, 40–60% of MDD patients have elevated cortisol. Circulating, urinary or salivary cortisol/cortisone levels; abnormal dexamethasone suppression profiles and genetic polymorphisms in HPA axis and contributing neuroendocrine pathways (e.g. 5-HTTLPR, FKBP5, NR3C1) are potential indicators of HPA axis functioning and stress reactivity (Gotlib *et al.* 2008). These should be evaluated as potential biomarkers to stratify patients who might be more responsive to a targeted 'anti-cortisol' therapy.

Environmental factors can influence phenotypes via epigenetic mechanisms such as covalent modification of DNA and histones as well as expression of regulatory microRNAs, which in turn can affect the expression of drug transporter, drug-metabolizing enzymes and drug targets (Nestler, 2009). Thus pharmaco-epigenetics provides another translational avenue for understanding and regulating inter-individual variation in drug response in addition to genetic polymorphism (Gomez & Ingelman-Sundberg, 2009; Tsankova *et al.* 2007). The antidepressant actions of histone deacetylase inhibitors provides an example for a potential role of epigenetic regulation of disease phenotype in depression (Covington *et al.* 2009).

Building an integrated disease biology-led, mechanism-based translational approach to increase the productivity of psychiatric R&D investment

Given the above challenges, one way to increase psychiatric R&D productivity is to shift from the 'more shots on goal' strategy (with an over-emphasis of *in-vitro* high throughput screening) to a 'higher quality targets and compounds' paradigm by putting a focus investment into an integrative disease biology-led, mechanism-based translational approach. Such an approach will include:

- securing high-quality control and disease human tissue resources to understand disease pathology;
- understanding disease pathophysiology/target mechanisms and their linkage with disease relevant endophenotypes;
- developing more predictive disease biology-based translational models to assess drug efficacy and safety which takes into account the appropriate translation from recombinant to native systems, from *in-vitro* to *in-vivo* perturbed models, from pre-clinical animal to clinical human studies and from healthy volunteers to patients;
- developing and qualifying biomarkers to provide robust quantifiable physiological, biochemical and behavioural indices that can be readily measured and translated in both animal models and human subjects to support patient segmentation;
- introducing early phase human clinical translational studies to:
  - select the most promising drug candidates,
  - identify appropriate dose range and dosing regimen,
  - validate targets/biomarker/models,
  - early clinical testing of therapeutic hypothesis in small homogeneous population defined by relevant biomarkers

While EEG and fMRI clearly have a role to play as PD biomarkers to verify dose predictions, a longer term goal is to develop and validate them as disease-related surrogate endpoints that could provide objective measures or predictors of efficacy. Although recent studies suggest high potential value for psychiatric patient stratification and proof of principle confirmation of a variety of EEG-related biomarkers [e.g. mismatch negativity (MMN), ERN, P300, and derived endpoints such as theta cordance, IDAP, gamma

coherence], these all require further validation and alignment with other clinical and preclinical efficacy measures. Careful coordination of internal effort with external academic collaboration is likely to be necessary to realize utility of EEG in this context as a potential competitive advantage.

MRI can help to focus in on the abnormal neural circuitry underlying mood and anxiety disorders. Accumulating data suggests that various, proven treatments for depression share a common ability to attenuate subgenual cingulate activity (Ressler & Mayberg, 2007). Thus it would be of interest to determine whether decreased activity in this area in response to a novel drug predicts antidepressant activity. Similarly, it has been argued that depression and anxiety may be explained by an underlying problem in emotional processing in that there is a bias to interpret affective and threat stimuli in an exaggerated, negative light. Overly focusing on these negative biases serves to maintain the disorder. These negative cognitions are the basis for one treatment of depression, namely cognitive behavioural therapy (CBT). MRI can be a very powerful tool to uncover the circuitry involved in this negative emotional cognition. Harmer has shown convincingly that subchronic treatment with either serotonin- or norepinephrine-specific reuptake blockers attenuate the activation of the amygdala, limbic cortical areas, etc. activated by fearful faces (Harmer, 2010). Additional studies have shown that lorazepam attenuates activation in the amygdala and insula to the emotional test battery (Paulus *et al.* 2005). However, further validation work needs to be done with novel drug classes before we can consider fMRI biomarkers as surrogates of antidepressant/anxiolytic activity.

A different R&D model

Thus it is recognized that there are relatively few qualified/validated translational biomarkers for psychiatric diseases. However, there is an increasing commitment and collaborative effort between the pharmaceutical industry, academia and government agencies to advance translational science in the precompetitive space via an iterative learning approach (i.e. test, learn and confirm). It is encouraging that many companies are active participants in these public–private partnerships such as the Alzheimer's disease Neuroimaging Initiative, the Biomarker consortium, the Innovative Medicine Initiative, and the P1vital consortium. For example, in the case of the European Innovative Medicine Initiative (IMI) – Novel Methods leading to New Medications in Depression and Schizophrenia (NEWMEDS), the challenges to psychiatric drug development are being addressed in three distinct yet integrated ways, namely system-based animal models, translational measurements and patient stratification work packages. This public and private collaboration differentiates itself from other models in that it is a government-initiated, industry friendly process, with the European Union recognizing an industry with unsustainable failures in clinical development, and companies realizing that the silo-driven mentality is outdated. As an example of 'Open Innovation' it offers an unprecedented construct for academia and industry to work together to tackle some of the most profound issues confounding the psychiatric drug discovery process, over a 5-yr period, with funding from government and in-kind contribution from industry (Hughes, 2009). Indeed, the perceived secrecy in industrial research is addressed intentionally by IMI through a mandate to share *all* findings by timely publication and presentation at public forum. This signals a change of mentality in the R&D community in recognizing the need to break down barriers to address the present and future needs of psychiatric drug discovery and development. One such contract research organization (CRO) that is helping to facilitate this process is P1vital. They have organized and conducted cooperative studies between a consortium of international drug companies and various academic centres in Great Britain to validate several CNS biomarker paradigms. Increased confidence in the biomarker is established by testing various proven psychotherapeutic drug classes in the model. This can then provide the validation necessary prior to testing a novel compound in the same model.

These efforts will help to identify and validate biomarkers, which will enable data-driven risk assessment and decision-making in early phase human clinical trials (Kola, 2008). We believe that for novel targets and novel therapeutic approaches, it will be more efficient and effective to change the drug development mind set from purely 'planning for success' mentality to 'weeding out programmes early with poor success potential' using early phase clinical studies (Kola, 2008; Paul *et al.* 2010).

Conclusions

This review has outlined former practices, current challenges and future opportunities in translational science. The case for a focused investment in translational research should not be viewed as too academic or industrial. Rather it should be viewed as a sincere,

timely and necessary effort to achieve effective communication and integration of knowledge in these pioneering fields. As transformational technologies evolve, one should not overlook the biological learning obtained from STAs and MTAs. Failure to focus on the unmet medical needs of the patient and default to purely economic considerations can too easily lead to an exit strategy for psychiatry drug discovery to the detriment of the mental health community. The urgency to maintain timelines or make very quick returns on investment can sometimes stifle the translational science activities necessary to discovering the next breakthroughs. The opportunities highlighted, while exciting, are multi-dimensional and are clearly beyond the resource capability of a single research institute or company. Rather they call for visionary thinking to create new R&D models that engage interested partners across academia, industry and government. This should lead to creation of an innovative research framework with internal retooling of competence and external partnership at a pre-competitive level to enhance future psychiatric drug discovery and development. It is envisioned that through focused investment and attention to translational science, the success rate of discovering new medicines for psychiatric diseases will increase and thereby transform psychiatric practice from empirical to a more personalized approach to the benefit of patients.

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Statement of Interest

All authors are employees of AstraZeneca Pharmaceuticals LP and are involved in the discovery and development of drugs for psychiatric disorders.

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