Opportunities and Challenges of Psychiatric Drug Discovery: Roles for Scientists in Academic, Industry, and Government Settings

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Despite significant progress in understanding the biological systems and mechanisms involved in CNS disorders, use of this knowledge to realize practical gains in psychiatric care has been slow. To gain further insight into the reasons for failure and success in CNS drug discovery, preclinical predictors of success and failure for CNS drug discovery were evaluated for drugs developed for schizophrenia, depression, and anxiety. Specifically, we examined the success rate for drugs that had entered at least the later stages of preclinical research. Almost 500 compounds (140 antipsychotic; 211 antidepressant; 143 anxiolytic) were classified based on their molecular target(s) and evaluated based on preclinical validation, whether preclinical studies predicted clinical efficacy, and whether the compound displayed greater efficacy than 'conventional treatment'. Results varied with indication but suggest that preclinical models have modest to good ability to predict overall clinical efficacy and adverse effect liability but are less able to predict efficacy greater than conventional treatment. In order to fully realize the potential therapeutic impact of recent basic science discoveries, it will be critical to increase attention on rigorous target validation at each step of the drug discovery process and focus efforts on developing new tools and clinical models that can be used for proof-of-concept studies in early clinical development. Also, increased attention should be focused on the development of early predictors of adverse effects of candidate compounds.

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INTRODUCTION

Over the past decade, we have witnessed unparalleled advances in our understanding of the basic biological processes that contribute to many human disorders, although a detailed understanding of the etiology of complex psychiatric disorders remains elusive. The highly celebrated elucidation of the sequence of the human genome (Venter *et al*, 2001) and other recent advances promise to provide unprecedented opportunities for breakthrough discoveries leading to fundamental new insights into the functions of biological systems. These advances in turn will create unique opportunities to translate basic science advances into new therapeutic options for psychiatric diseases.

Despite this progress in understanding biological systems and mechanisms of disease, use of this knowledge to realize practical gains in psychiatric care has been slow. In fact, (see Tables 1–3; Roth *et al*, 2004) the five most widely prescribed psychiatric medications (sertraline, olanzapine, venlafaxine, risperidone, and quetiapine) share mechanisms of action with drugs discovered many decades ago (eg olanzapine, risperidone, and quetiapine with clozapine from the 1950s, venlafaxine with the tricyclic antidepressants in the 1950s, and sertraline with zimelidine in 1977). This lag between advances in basic biology and advances in therapeutics has occurred despite an enormous investment in biomedical research. The budget of the US National Institutes of Health was doubled in the late 1990s and early 2000s, while total spending by pharmaceutical companies for research and development grew from \$2 to \$32 billion between 1980 and 2002.

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Historical Paradigms used for Psychiatric Drug Discovery

This decrease in the introduction of fundamentally new drugs into clinical practice during a time of increased

knowledge and research spending stems in part from a fundamental shift in the basic paradigms used for drug discovery. In the early era of psychiatric drug discovery, all of the advances arose through serendipity (Ayd, 1991). Thus, for example, the antipsychotic actions of chlorpromazine were discovered by chance when it was used as a preanesthetic agent in psychiatric patients (Delay *et al*, 1954). The antimanic actions of lithium (Cade, 1949) and various anticonvulsants were also based on chance preclinical and clinical observations. Once a clinically effective compound was identified, thousands of derivatives were synthesized and then screened in preclinical models before being advanced to clinical trials. In many cases, preclinical models do not reliably predict relative therapeutic efficacy (Tables 1–3). Thus, clozapine, the first atypical antipsychotic drug, was developed as a chlorpromazine analogue and was initially rejected as an antipsychotic drug because it failed to induce catalepsy in rodents. In terms of antipsychotic drug discovery, with the possible exceptions of aripiprazole and the substituted benzamides, a major goal has been to create clozapine mimetics devoid of the more serious side effects of clozapine. This goal has been largely successfully reached, although none of the currently available atypical antipsychotic drugs fully recapitulate the spectrum of clinical efficacies of clozapine (Meltzer *et al*, 2003). As well, many of the currently available medications carry the risk of serious and potentially fatal adverse side effects, including weight gain and associated metabolic disturbances. Only in the past year has evidence for potential clinical efficacy of agents that act by a fundamentally different mechanism emerged (Patil *et al*, 2007).

For anxiety and depression, the history is much the same. Thus, SSRIs, for example, share a mechanism of action with zimelidine which was discovered to be clinically effective for treating depression in the late 1970s (Benkert *et al*, 1977), while the more recently launched SNRIs recapitulate the actions of the tricyclic antidepressants. Likewise, the most clinically effective treatments for the anxiety disorders remain the benzodiazepines (discovered in the 1950s) and various antidepressants including tricyclics and SSRIs.

More recently, molecular target-based approaches have been adopted by pharmaceutical companies and, although progress has been slow, there have been some intriguing recent successes using these approaches (Tables 1–3) wherein novel therapeutic options have been discovered. These include the observations that (1) agomelatine (a melatonin-1/2 receptor agonist and 5HT_{2C} antagonist) has antidepressant actions, (2) neurokinin-3 antagonists may be antipsychotic, and (3) mGluR2/3 agonists may be anxiolytic as well as antipsychotic. In each of these cases, there was scant preclinical evidence available to indicate that these would provide validated targets for drug discovery (Tables 1–3). Importantly, detailed study of the neurobiology and neuropharmacology of these particular molecular targets as they relate to the above psychiatric indications has been minimal—at least as far as NIH-funded research is concerned. Indeed a search of the NIH CRISP database reveals only two RO1-type grants linking the melatonin system with depression, none linking NK-3 receptors and schizophrenia, and only three RO1 grants linking mGluRs and anxiety or schizophrenia. This is disappointing in light of the critical need for NIH-funded scientists to translate

such fundamental neuroscience discoveries to more detailed understanding of drug effects on brain systems, as a bridge to help further our understanding of human diseases.

The Problem of the Gap Between Traditional Academic Science and Industrial Drug Discovery

A major challenge facing today's biomedical research community is the translation of newly gained knowledge into fundamentally new therapeutics. The complexity of this task requires the combined efforts of outstanding scientists, engineers, and clinicians with strong expertise in a broad range of disciplines. Traditionally, the National Institutes of Health and academic institutions support basic biomedical research, while industry supports commercial development of medicines and medical products. While scientists in academic and other basic science settings have made significant progress in furthering our understanding in biology, chemistry, and related disciplines, they often fail to make the critical link that allows this information to be useful in an industrial setting. Likewise, fiscal pressures that govern research efforts in industry make it increasingly difficult for companies to invest significant resources in exploratory projects and basic research that capitalize on translating the most exciting discoveries of basic science into marketable products. Because of this, companies may be compelled to launch expensive drug discovery and development programs based on intriguing but often poorly validated targets for novel therapeutic approaches.

Not surprisingly, CNS drug discovery has, historically, been designated as an extraordinarily risky endeavor. To gain further insight into the reasons for failure and success in CNS drug discovery, we focused on three target areas: schizophrenia, depression, and anxiety and examined the success rate for drugs that had entered at least the later stages of preclinical research. A total of 494 compounds (140 antipsychotic; 211 antidepressant; 143 anxiolytic) were initially classified based on their known molecular target(s) and then evaluated using three overall criteria: (1) type of preclinical validation, (2) whether or not preclinical studies predicted clinical efficacy, and (3) whether the compound was of greater efficacy than 'conventional treatment' (see Tables 1–3 for details). Of these 494 compounds, only 51 have been launched, although many others are in late phase clinical trials. Results from each therapeutic area will be summarized in turn.

For the treatment of schizophrenia, we found that preclinical models were highly effective at predicting whether or not a candidate molecule would have 'atypical' properties (ie produce fewer EPS than a conventional antipsychotic drug, such as haloperidol). On the other hand, the various preclinical models were only fair at predicting overall efficacy and ineffective at predicting efficacy greater than conventional treatment. Thus, some classes of compounds (eg σ 1-, D1-, and D4-selective compounds) were predicted by several preclinical animal models to be effective, but were subsequently found to be ineffective in humans. Finally, it was clear that 'multireceptor' compounds were uniformly more effective than 'single-target' compounds for treating schizophrenia and related disorders, at least for compounds that target monoamine receptors (Roth *et al*, 2004; Morphy *et al*, 2004; Morphy and

Table 1 Comparative Efficacy of Multireceptor and Single-Molecular Target Agents for Various Preclinical Antipsychotic Drug Models and Human Trial Outcomes

Molecular target	Prototypical agent	Catalepsy	cFOS (N Acc» D. striatum)	A10>A9 Depolarization	Blocks PPI inhibition due to PCP or Apo	CAR	Efficacy in small scale/phase II	Superior to conventional antipsychotic	Phase III	Weight gain
Multireceptor	Clozapine	None	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Multireceptor	Quetiapine	None	Yes	Yes	Yes	Yes	Yes	Yes (chronic)	Yes	Yes
5-HT _{2A} /D2	Risperidone	Less	Yes	No	Yes	Yes	Yes	Yes (chronic only)	Yes	Yes (<)
D2/D3 antagonist	Amisulpride	Less	Unknown	Yes	Yes	NA	Yes	No	Yes	Minimal
D2/D3 partial agonist	Aripirazole	No	Yes	NA	Yes	NA	Yes	Yes (chronic only)	Yes	Minimal
D4 selective	Soneprazole	No	Yes	No	Yes	No	No	No	NA	No
D3 selective	S 14297	No	No	No	No	No	NA	NA	NA (Kinney <i>et al</i> , 2003)	NA
D1 selective	SCH 39166	No	No	No	No (worsens)	Yes	No (worsened)	No	NA	NA
5-HT _{2A/2C} selective	SR-46349B	No	No	Yes	Yes	No	Yes	No	NA	No
σ selective	BMJ 14802	No	No	NA	Yes	Yes	No	No	No	NA
AMPAI	Org-24448	No	No	NA	NA	NA	Yes (added to clozapine)	No	No	NA
mGluR2/3	LY2140023	No	No	No	Yes	Yes	Yes	No	NA	No
Adrenergic-α2	Idozoxan	No	No	NA	No	No	No (single therapy; may enhance)	No	NA	NA
Glycine transporter inhibitors	NFPS	No	Yes	NA	Yes	Yes	No (single therapy; may enhance)	No	NA	NA
M1-muscarinic agonists	Xanomeline (nonselective)	No	Yes	Yes	Yes	Yes	Yes	No	NA	NA
NK-3	Osanant	No	NA	Yes	NA	NA	Yes	No	NA	No
NMDA-D-serine site	D-Serine	No	NA	NA	Yes	NA	Yes (when added)	NA	NA	NA
CB-1 antagonist	SR 141716A	No	Yes	No	No	No	No	No	NA	No (weight loss)
NT-1 antagonist	SR48692	No	No (increased prefrontal but not striatal)	Yes (acute)	No (agonists improve)	No (worsens)	No	No	NA	No

Oka *et al*, 2004; Merchant *et al*, 1996; Corrigan *et al*, 2004; Bristow *et al*, 1997; Audinot *et al*, 1998; Barnett *et al*, 1988; Sorensen *et al*, 1993; Gewirtz *et al*, 1994; Kinney *et al*, 2003; Roth *et al*, 2004; Meltzer *et al*, 2004; Kane *et al*, 1988.

A total of 140 compounds were evaluated and results summarized above. Of these eight have been launched (seven of eight are multireceptor compounds) and are, in general, superior to 10 mg haloperidol; all five currently in Phase III are multireceptor compounds. Only one single-target agent (a D2/D3-selective compound) has been tested beyond Phase II (amisulpride). Two single-agent compounds showed efficacy in large-scale Phase IIb trials: SR46349B (5-HT_{2A/2C} selective) and Osanant (NK-3 selective) but were not superior to conventional therapy (10 mg haloperidol).

Available preclinical models are good at predicting atypicality (efficacy in absence of EPS) but ineffective at predicting overall efficacy.

Table 2 Comparative Efficacy of Multireceptor and Single-Molecular Target Agents for Various Preclinical Antidepressant Drug Models and Human Trial Outcomes

Molecular target	Prototypical agent	FST	Tail suspension	Learned helplessness	BDNF	Phase II	Phase III	Superior to TCA/SSRI	Suicide risk
Many	ECT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
SERT/NET/Biogenic amine receptors	Desipramine (tricyclics)	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Biogenic amines/MAOA+B	Phenylzine (MAOI)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unknown
Biogenic amines MAOA	Moclobemide	Yes		Yes	Yes	Yes	Yes	No	Unknown
NET	Reboxetine	Yes	Yes	Unknown	Yes	Yes	Yes	No	Unknown
5-HT _{1A}	Buspirone	Yes	Yes	Yes	Yes (downstream)	Several failures	Several failures	No	
SERT	Fluoxetine	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Multireceptor (5-HT _{2A} /α ₂ /SERT/NET)	Mianserin		Yes	Yes	Yes	Yes	Yes	No	Unknown
NET/DAT	Bupropion	Yes	Yes	Unknown	No	Yes	Yes	No	Unknown
NET/SERT	Venlafaxine	Yes	Yes	No	Yes	Yes	Yes	Yes (SSRI only)	Yes
5-HT _{1B}	CP 94253	Yes	NA	Yes	NA	NA	NA	NA	NA
5-HT _{2A} antagonist	Nefazadone	Yes		Yes	NA	Yes	Yes	No	Unknown
5-HT _{2C} agonist	Org-12962	Yes	NA	NA	NA	Yes	No	Unknown	Unknown
α _{2A} /5-HT _{2A}	Mirtazepine	Yes	NA	NA	NA	Yes	Yes	No	Unknown
α _{2C}	MK-912	NA	NA	NA	NA	No (phase I only)	NA	NA	NA
β ₃ -agonist	SR-58611	Unknown	Unknown	Unknown	Unknown	Yes	Yes	Yes	Unknown
V1-antagonist	SR-149415	Yes	NA	NA	NA	No (phase I)	NA	NA	Unknown
CRF-1	SR125543	Yes	Yes	Yes	Unknown	Yes	NA	NA	NA
Melatonin-1A/5-HT _{2C}	Agomelatine	Yes	Unknown	Unknown	Unknown	Yes	Yes	Yes (CINP abstract)	Unknown
Glucocorticoid receptor	Mifepristone	No	Unknown	No	Unknown	Yes	Yes	Unknown; used with treatment resistant hence assumed superior	Unknown
σ ₁ -receptor	SA-4503	Yes	Yes	Unknown	Yes	Yes	NO	Unknown	Unknown
PDE-IV	Rolipram	Yes	Yes	Yes	Yes	Yes	Yes	No	Unknown
Sodium channel antagonist	Lamotrigine	Yes	Unknown	Unknown	Unknown	Yes	Yes	Unknown; used in maintenance phase of bipolar II = to Li.	Unknown
NK-1	L-759274	Yes	No	Yes (NK-1 k/o mice)	Yes	Yes	Yes (ineffective)	No	Unknown
NK-2	SR 48968	Yes	Unknown	Unknown	Unknown	Yes	Yes (preregistration)	No	Unknown
Melanocyte-inhibiting factor (MIF) analogue	Nemifitide	Yes	NA	NA	NA	Yes	NA	Unknown	Unknown
mGluR	MGS-0039	Yes	Yes	Unknown	Unknown	No	No	Unknown	Unknown
NMDA	Ketamine (could include memantine)	Yes	No (opposite)	Unknown	Inhibits	Yes—small scale rapid action	No	Yes (more rapid action)	Unknown
Unknown (Trace amine GPCR?)	SCT-11	Unknown	Unknown	Unknown	Unknown	Yes	No	Unknown	Unknown
Unknown	YKP-10A	Yes	Yes	Unknown	No	Yes	No	No	Unknown

Hudzik *et al*, 2003; Tatarczynska *et al*, 2004; Dingemans, 2003; Overstreet and Griebel, 2004; Ovalle *et al*, 2002; Matsuno *et al*, 1996; Saccomano *et al*, 1991; Zhang *et al*, 2002; Bourin *et al*, 2005; Zocchi *et al*, 2003. http://www.sanofi-aventis.com/Images/101_17242.pdf; Cooper *et al*, 1980; Yilmaz *et al*, 2002.

A total of 211 compounds evaluated; 30 launched (20 SSRI/SNRIs); ECT, nonselective MAOIs, and, possibly, ketamine, Agomelatine, and mifepristone are superior to TCAs clinically. SNRIs generally > SSRIs and equal to TCAs. Available preclinical models good/excellent at predicting clinical efficacy but are ineffective at predicting (a) speed of action and (b) overall efficacy. Novel antidepressants with potentially greater efficacy (NMDA antagonists, glucocorticoid antagonists) not predicted by preclinical tests to be effective.

Table 3 Comparative Efficacy of Agents for Various Preclinical Anxiolytic Drug Models and Human Trial Outcomes

Molecular target	Prototypical agent	Elevated plus maze	Fear-potentiated startle	Social interaction	Vogel paradigm	Phase II	Phase III	Nonsedating	Efficacy > diazepam
5-HT _{1A}	Buspirone	Yes	Yes	Yes	Yes	Yes	Many failures	Yes	No
5-HT _{1B}	AR-A2	Yes	No	Unknown	Yes	Yes	No	Yes	Unknown
5-HT _{2A}	Nefazadone	Yes	Unknown	Unknown	Unknown	Yes	Yes	No	No
5-HT _{2C/2A}	Deramcidane	Yes	Unknown	Yes	Yes	Yes	Failed	No	No
Peripheral benzodiazepine	AC-5216	Unknown	Unknown	Yes	Yes	Yes	No	Yes	Unknown
V1b-vasopressin	SR-149415	Yes	Yes	Yes	Yes	No (phase I)	No	Presumably	No (based on animal studies)
CCKB-cholecystokinin	GW-150013	No	No	Yes	No	Yes	No	Presumably	No (based on animal studies)
CRF-I	CP154,526	Mixed	Yes	Yes	Yes	Yes	No	Yes	No
GABA-A BZP nonselective (mainly $\alpha 1$ subtype)	Alprazolam	Yes	Yes	Yes	Yes	Yes	Yes	No	No
GABA-A BZP nonselective (mainly $\alpha 2/3$ subtype)	L-838417	Yes	Yes	Unknown	Yes	Yes	No	Yes	Unknown
mGluR2/3	Eglumetad	Yes	Yes	Yes	Yes	Yes	No	Yes	Unknown
SERT	Fluoxetine	Yes	Unknown	Unknown	Unknown	Yes	Yes	Yes	No
SERT/NET	Imipramine	Yes	Unknown	Unknown	Unknown	Yes	Yes	Yes	No
NK-1	NKP608	Yes	Unknown	Yes	Unknown	Yes	Yes	No	No (based on animal studies)

A total of 143 compounds evaluated; 13 launched: 2 = 5-HT_{1A}, 1 = 5-HT_{2A}, 1 = CRF modulator; rest BZP (Risbrough *et al*, 2003; Moret, 2003; Clark *et al*, 2004; Griebel *et al*, 1997a, 1997b, 2002; Kita *et al*, 2004; McKernan *et al*, 2000).

Preclinical models excellent at predicting *in vivo* anxiolytic actions and at predicting BZP-like side-effects. Many intriguing targets; no assays yet available which predict greater efficacy than diazepam in humans. Selected references.

Audinot V, Newman-Tancredi A, Gobert A, Rivet JM, Brocco M, Lejeune F, *et al*. (1998). A comparative *in vitro* and *in vivo* pharmacological characterization of the novel dopamine D3 receptor antagonists (+)-S 14297, nafadotride, GR 103,691 and U 99194. *J Pharmacol Exp Ther* **287**:187–197.

Barnett A, Iorio LC, McQuade R, Chipkin RE (1988). Pharmacological and behavioral effects of D1 dopamine antagonists. *Adv Exp Med Biol* **235**:137–144.

Bourin M, Masse F, Hascoet M (2005). Evidence for the activity of lamotrigine at 5-HT_{1A} receptors in the mouse forced swimming test. *J Psychiatry Neurosci* **30**:275–282.

Bristow LJ, Collinson N, Cook GP, Curtis N, Freedman SB, Kulagowski JJ, Leeson PD, Patel S, Ragan CI, Ridgill M, Saywell KL, Tricklebank MD (1997). L-745,870, a subtype selective dopamine D4 receptor antagonist, does not exhibit a neuroleptic-like profile in rodent behavioral tests. *J Pharmacol Exp Ther* **283**:1256–1263.

Clark MS, Vincow ES, Sexton TJ, Neumaier JF (2004). Increased expression of 5-HT_{1B} receptor in dorsal raphe nucleus decreases fear-potentiated startle in a stress dependent manner. *Brain Res* **1007**:86–97.

Cooper BR, Hester TJ, Maxwell RA (1980). Behavioral and biochemical effects of the antidepressant bupropion (Wellbutrin): evidence for selective blockade of dopamine uptake *in vivo*. *J Pharmacol Exp Ther* **215**:127–134.

Corigan MH, Gallen CC, Bonura ML, Merchant KM (2004). Effectiveness of the selective D4 antagonist sonepiprazole in schizophrenia: a placebo-controlled trial. *Biol Psychiatry* **55**:445–451.

Dingemans J (2003). Nemiflutide. *Innopharma. Curr Opin Investig Drugs* **4**:859–862.

Gewirtz GR, Gorman JM, Volavka J, Macaluso J, Gribkoff G, Taylor DP *et al* (1994). BMY 14802, a sigma receptor ligand for the treatment of schizophrenia. *Neuropsychopharmacology* **10**:37–40.

Griebel G, Perrault G, Sanger DJ (1997a). CCK receptor antagonists in animal models of anxiety: comparison between exploration tests, conflict procedures and a model based on defensive behaviours. *Behav Pharmacol* **8**:549–560.

Griebel G, Perrault G, Sanger DJ (1997b). A comparative study of the effects of selective and non-selective 5-HT₂ receptor subtype antagonists in rat and mouse models of anxiety. *Neuropharmacology* **36**:793–802.

Griebel G, Simiand J, Serradeil-Le Gal C, Wagnon J, Pascal M, Scatton B *et al* (2002). Anxiolytic- and antidepressant-like effects of the non-peptide vasopressin V1b receptor antagonist, SSR149415, suggest an innovative approach for the treatment of stress-related disorders. *Proc Natl Acad Sci USA* **99**:6370–6375.

Hudzik TJ, Yanek M, Porrey T, Evenden J, Paronis C, Mastrangelo M *et al* (2003). Behavioral pharmacology of AR-A000002, a novel, selective 5-hydroxytryptamine (1B) antagonist. *J Pharmacol Exp Ther* **304**:1072–1084.

Kane J, Honigfield G, Singer J, Meltzer HY, Group at CCS (1988). Clozapine for the treatment-resistant schizophrenic. *Arch Gen Psychiatry* **45**:789–796.

Kinney GG, Sur C, Burno M, Mallorga PJ, Williams JB, Figueroa DJ *et al* (2003). The glycine transporter type 1 inhibitor N-[3-(4'-fluorophenyl)-3-(4'-phenylphenoxy)propyl]sarcosine potentiates NMDA receptor-mediated responses *in vivo* and produces an antipsychotic profile in rodent behavior. *J Neurosci* **23**:7586–7591.

- Kita A, Kohayakawa H, Kinoshita T, Ochi Y, Nakamichi K, Kurumiya S *et al* (2004). Antianxiety and antidepressant-like effects of AC-5216, a novel mitochondrial benzodiazepine receptor ligand. *Br J Pharmacol* **142**: 1059–1072.
- Matsuno K, Kobayashi T, Tanaka MK, Mita S (1996). Sigma 1 receptor subtype is involved in the relief of behavioral despair in the mouse forced swimming test. *Eur J Pharmacol* **312**:267–271.
- McKernan RM, Rosahl TW, Reynolds DS, Sur C, Wafford KA, Atack JR *et al* (2000). Sedative but not anxiolytic properties of benzodiazepines are mediated by the GABA(A) receptor alpha1 subtype. *Nat Neurosci* **3**: 587–592.
- Meltzer HY, Arvanitis L, Bauer D, Rein W (2004). Placebo-controlled evaluation of four novel compounds for the treatment of schizophrenia and schizoaffective disorder. *Am J Psychiatry* **161**:975–984.
- Merchant KM, Gill GS, Harris DW, Huff RM, Eaton MJ, Lookingland K *et al* (1996). Pharmacological characterization of U-101387, a dopamine D4 receptor selective antagonist. *J Pharmacol Exp Ther* **279**:1392–1403.
- Moret C (2003). Depression: emerging research and treatment approaches. 16–17 January 2003, Paris, France. *IDrugs* **6**:183–186.
- Oka T, Hamamura T, Lee Y, Miyata S, Habara T, Endo S *et al* (2004). Atypical properties of several classes of antipsychotic drugs on the basis of differential induction of Fos-like immunoreactivity in the rat brain. *Life Sci* **76**:225–237.
- Ovalle S, Andreu F, Perez MP, Zamanillo D, Guitart X (2002). Effect of the novel sigma1 receptor ligand and putative atypical antipsychotic E-5842 on BDNF mRNA expression in the rat brain. *Neuroreport* **13**:2345–2348.
- Overstreet DH, Griebel G (2004). Antidepressant-like effects of CRF1 receptor antagonist SSR125543 in an animal model of depression. *Eur J Pharmacol* **497**:49–53.
- Risbrough VB, Brodtkin JD, Geyer MA (2003). GABA-A and 5-HT_{1A} receptor agonists block expression of fear-potentiated startle in mice. *Neuropsychopharmacology* **28**:654–663.
- Roth BL, Sheffler DJ, Kroeze WK (2004). Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. *Nat Rev Drug Discov* **3**:353–359.
- Saccomano NA, Vinick FJ, Koe BK, Nielsen JA, Whalen WM, Meltz M *et al* (1991). Calcium-independent phosphodiesterase inhibitors as putative antidepressants: [3-(bicycloalkoxy)-4-methoxyphenyl]-2-imidazolidinones. *J Med Chem* **34**:291–298.
- Sorensen SM, Kehne JH, Faday EM, Humphreys TM, Ketteler HJ, Sullivan C *et al* (1993). Characterization of the 5-HT₂ antagonist MDL 100907 as a putative atypical antipsychotic: behavioral, electrophysiological and neurochemical studies. *J Pharmacol Exp Ther* **266**:684–691.
- Tatarczynska E, Klodzinska A, Stachowicz K, Chojnacka-Wojcik E (2004). Effects of a selective 5-HT_{1B} receptor agonist and antagonists in animal models of anxiety and depression. *Behav Pharmacol* **15**:523–534.
- Yilmaz A, Schulz D, Aksoy A, Canbeyli R (2002). Prolonged effect of an anesthetic dose of ketamine on behavioral despair. *Pharmacol Biochem Behav* **71**:341–344.
- Zhang HT, Huang Y, Jin SL, Frith SA, Suvama N, Conti M *et al* (2002). Antidepressant-like profile and reduced sensitivity to rolipram in mice deficient in the PDE4D phosphodiesterase enzyme. *Neuropsychopharmacology* **27**:587–595.
- Zocchi A, Varmer G, Arban R, Griffante C, Zanetti L, Bettelini L *et al* (2003). Effects of antidepressant drugs and GR 205171, a neurokinin-1 (NK1) receptor antagonist, on the response in the forced swim test and on monoamine extracellular levels in the frontal cortex of the mouse. *Neurosci Lett* **345**:73–76.

Rankovic, 2005). Because it is difficult to ‘design-in’ the preferential ability of a drug to hit multiple identified molecular targets, we and others have suggested that novel chemical scaffolds and novel chemistries should be attempted to generate ‘multireceptorial compounds’.

In terms of the levels of preclinical validation, one of the most novel compounds—the NK-3 antagonist osanant, appears to have been minimally validated (Gueudet *et al*, 1999), despite showing efficacy in a phase IIb clinical trial (Meltzer *et al*, 2004). Recent phase II clinical studies demonstrating the efficacy of selective mGlu2/3 agonists for schizophrenia (Patil *et al*, 2007) illustrate a major example whereby preclinical models successfully predicted efficacy for compounds that act by a novel mechanism of action (Moghaddam and Adams, 1998). It is encouraging that mGlu2/3 receptor agonists have robust efficacy in several animal models that were originally developed based on actions of D2 and other monoamine receptor antagonists, despite their lack of appreciable activity at the monoamine receptors (Moghaddam and Adams, 1998; Chavez-Noriega *et al*, 2005).

Unfortunately, none of the available animal models reproducibly predicts the propensity of various antipsychotic drugs to induce weight gain and associated side effects, although this can be predicted based on a knowledge of *in vitro* receptor pharmacology (Kroeze *et al*, 2003). Finally, in terms of the domains of efficacy (eg improving cognition, diminishing suicidality, diminishing deficit symptoms), none of the commonly used animal models are highly predictive, although preclinical memory models may be useful for predicting the ability of selected agents to enhance cognition, and receptor-based studies might predict whether or not a compound may diminish suicidality. Thus, for instance, the M1-muscarinic agonist properties of N-desmethyl-clozapine (Sur *et al*, 2003; Davies *et al*, 2005) are predictive of the procognitive actions of clozapine. These findings imply that M1-agonists might be useful as ‘add-on medications’ for enhancing cognition.

For antidepressant drug development, several conclusions were evident. First, none of the newer therapeutics launched in the past decade has proven to be more effective than tricyclic antidepressants. As well, although SSRIs are better tolerated (Anderson, 2001) they may be associated with an increased risk of suicidality (Wong *et al*, 2004). Second, available preclinical models are only ‘adequate’ in predicting overall clinical efficacy and are inadequate at predicting efficacy greater than a standard comparator (eg fluoxetine or imipramine). Finally, compounds with complex modes of action that interact with multiple molecular targets appear to have greater efficacy in humans than single-target agents.

A close examination of preclinical validators reveals that older preclinical models of antidepressant drug action, such as the forced swim test, appeared to be at least as effective at predicting clinical efficacy as more recent innovations, including the reversal of learned helplessness and induction of BDNF gene transcription (see Table 2). Intriguingly, two drugs that have shown preliminary potential to have efficacy (agomelatine and mefipristone) would not have been predicted to have antidepressant actions based on the current dogma nor the prevailing animal

models. Indeed, agomelatine has recently been shown in a large-scale placebo-controlled trial to be effective and, perhaps, to have greater efficacy in individuals with severe depression (Kennedy and Emsley, 2006). Additionally, ketamine, an NMDA receptor antagonist, has been shown in multiple anecdotal and two randomized trials to have efficacy in depression (Kudoh *et al*, 2002; Berman *et al*, 2000; Zarate *et al*, 2006). Importantly, ketamine and other NMDA receptor antagonists do have activity in some animal models predictive of antidepressant activity, such as the forced swim test (Garcia *et al*, 2007; Maj *et al*, 1992; Trullas and Skolnick, 1990). However, until clinical evidence for ketamine efficacy began to emerge, these studies did not lead a focus on NMDA receptors as a target for antidepressant medications. Taken together, these results imply that continued research is needed in order to create new preclinical models that might be effective at predicting overall efficacy in humans.

For anxiolytic drug discovery, the outlook is only marginally different, although the preclinical models (in aggregate) appear to be highly effective at predicting human efficacy and side effect potential. Thus, mGluR2/3 agonists, for example, could become effective anxiolytics devoid of many of the side effects associated with the benzodiazepines (Grillon *et al*, 2003).

A major critique of current drug discovery approaches is that since the underlying causes of major mental illnesses remain incompletely understood, adequate treatments cannot be developed. It has thus been proposed that an enhanced understanding of the genetic basis of diseases such as schizophrenia will reveal validated molecular targets for drug discovery—even if the genes identified confer only a few percent to the overall risk of schizophrenia (Insel and Collins, 2003). Unfortunately, discovery of susceptibility genes for even the genetic basis for clearly inherited disorders often does not immediately lead to identification of a clear drug target. Recent success in discovery of mutations responsible for or involved in multiple CNS disorders, such as Huntington's disease, Parkinson's disease, and others, have been disappointing in their failure to provide direct insights into novel approaches for development of therapeutic agents. However, in other cases, clear drug targets may arise from understanding disease susceptibility genes and increased understanding may ultimately help guide patient selection for clinical studies, biomarker discovery, and eventual identification of novel targets that are involved in a pathway uncovered by genetic studies. For schizophrenia, DISC1 (disrupted in schizophrenia1; Millar *et al*, 2000) has emerged as a major risk factor for schizophrenia in cases of familial schizophrenia and bipolar disorder (Macgregor *et al*, 2004), although these findings have not been uniformly replicated in larger population-based studies (see Thomson *et al*, 2005; Zhang *et al*, 2005). In humans, variation in DISC1 is statistically associated with hippocampal structure and with overall cognition and memory functioning (Callicott *et al*, 2005; Hennah *et al*, 2005).

Recent studies indicate that the RNAi-mediated knock-down of DISC1 *in utero* induces a dysregulation of cortical development (Kamiya *et al*, 2005)—a result consistent with the neurodevelopmental hypothesis of schizophrenia (Harrison and Weinberger, 2005). This hypothesis posits a

neurodevelopmentally induced alteration in the micro-circuitry of the cerebral cortex with a prominent role for alterations in glutamatergic and GABAergic neuronal signaling (Lewis and Lieberman, 2000; Costa *et al*, 2002)—perhaps via epigenetic mechanisms (Tremolizzo *et al*, 2005; Veldic *et al*, 2005). The view that schizophrenia is a neurodevelopmental disorder is not uniformly accepted and schizophrenia does not have the characteristics of a classical developmental disorder. However, if schizophrenia and related disorders do have a neurodevelopmental component, due in part to both inherited genomic alterations in DISC1, dysbindin and COMT (Gornick *et al*, 2005), and epigenetic genomic alterations in reelin and GABAergic neuronal markers (Dong *et al*, 2005; Goldberger *et al*, 2005; Grayson *et al*, 2005), effective treatment strategies should target the underlying deficits. If the underlying defect is principally due to developmentally encoded deficits in microcircuitry, then obvious pharmacological strategies would be to ameliorate these deficits (see below for examples). On the other hand, if the deficits are due to abnormal migration of cortical neurons and subsequent dysregulation of cortical development, it may be impossible to ameliorate such deficits via simple pharmacological approaches. Finally, as has been shown for epigenetically induced alterations in reelin promoter hypermethylation, histone deacetylase inhibitors such as valproic acid (Phiel *et al*, 2001) can ameliorate hypermethylation and normalize cognitive deficits in some animal models of schizophrenia (Tremolizzo *et al*, 2005).

Recommendations

Encourage random small molecule-based screening and chemical optimization in academic settings. Historically, academic scientists have depended heavily on the drug discovery efforts carried out in industry to provide small molecules needed to dissect the functional roles of key proteins in biological systems. However, to remain viable, companies must focus on the most developed and validated approaches for drug discovery programs, so that small molecules having actions on the most novel but highly speculative new targets are not included in their efforts. Thus, industry scientists cannot be expected to provide all of the reagents required for developing basic understanding of biological systems that may ultimately lead to novel therapeutic approaches. In addition to advances in basic biology, we have realized tremendous advances in combinatorial chemistry, development of large libraries of small molecules, and other approaches to high throughput synthetic chemistry. These libraries are now widely available to the research community, and new high-throughput screening technologies have been developed that allow more widespread mining of the libraries. The combination of high throughput screening and synthetic chemistry provides an unprecedented opportunity for NIH-funded investigators to engage in discovery and development of small molecule probes of biological pathways. These probes could provide the tools needed to directly test the hypothesis that drug-like molecules can be developed that interact with a novel target of interest and have the effects that were predicted by molecular and genetic studies. Such advances could provide

a major step in discovery of novel therapeutic agents by helping to identify the most viable approaches for further investment in an industrial setting.

It has been proposed that initiatives like the NIH Molecular Library Screening Centers Network (MLSCN) will speed discovery for novel therapeutic approaches by providing validated molecular probes for preclinical research (Austin *et al*, 2004). As has acknowledged by proponents of the MLSCN (Austin *et al*, 2004; O'Connor and Roth, 2005), however, because of the enormous costs associated with drug discovery and development it is unlikely that new therapeutic agents will arise as a direct result of these screening efforts. One of the criticisms of this effort has been that even the development of 'molecular probes' will be impossible in an academic setting because HTS hits rarely provide useful information and the large costs associated with generating suitable 'leads' (currently estimated at \$3–5 million in the private sector) make this untenable except in an industry setting. However, this cost is greatly impacted by the drug discovery rather than basic science mission in the pharmaceutical industry and the strict focus on optimizing hits that can ultimately be developed into therapeutic agents. There are multiple examples of primary HTS hits providing novel insights into new areas of biology that stimulate subsequent drug discovery efforts. For instance, Varney *et al* (1999) discovered SIB1757, a primary HTS hit, as the first highly selective antagonist of the metabotropic glutamate receptor mGluR5. This revealed a novel allosteric mechanism for developing antagonists of this and other GPCRs and stimulated focused efforts in a number of pharmaceutical companies that yielded highly potent *in vivo* active antagonists of this receptor. More recently, we reported discovery of DFB as a novel allosteric potentiator of mGluR5 (O'Brien *et al*, 2003). DFB was a primary screening hit that represented the first highly selective activator of this receptor subtype and provided important proof of concept at the molecular level for a novel approach to activating this and other GPCRs. This discovery stimulated further efforts that have led to discovery of other series of mGluR5 potentiators, which have now been shown to have antipsychotic-like activity in animal models (Kinney *et al*, 2005). In a related program, PHCCC was identified as a novel allosteric potentiator of mGluR4 (Marino *et al*, 2003; Maj *et al*, 2003). This primary screening hit was used for demonstration that allosteric potentiation of this receptor regulates transmission at an identified synapse in the basal ganglia and has antiparkinsonian effects in rodent models (Marino *et al*, 2003).

Another recent example of major new insights offered by primary HTS hits includes the discovery AC42 as a novel 'ectopic' site agonist that has unprecedented selectivity for the M1 muscarinic receptor (Spalding *et al*, 2002). In each of these cases, these initial HTS hits were not viewed as drug leads but provided the first selective agents in their class and provided important proof-of-concept data at molecular, cellular and, in some instances, behavioral levels that have stimulated further research in both academic and industry settings.

In addition, while academic laboratories do not have the resources needed to drive full industry-level lead optimization efforts, modest medicinal chemistry in academic

laboratories can stimulate broader discovery efforts. For instance, we have now used medicinal chemistry to develop nM potency allosteric potentiators of mGluR5 from our initial hits and used these compounds to better understand the molecular mechanisms of action of these allosteric potentiators (Conn *et al*, 2005; Chen *et al*, 2007). Furthermore, based on our new understanding of allosteric regulation of GPCRs, we and our collaborators used synthetic chemistry around established mGluR5 antagonists to develop novel partial antagonists of this receptor (Rodriguez *et al*, 2005). These compounds are not viewed as drug leads, but provide the first demonstration of 'partial antagonists' of a GPCR. This is an activity that is clearly distinct from partial agonists at traditional orthosteric sites and provides molecular proof of concept a novel approach to GPCR modulation that may circumvent common problems with traditional antagonists, partial agonists, or inverse agonists.

In addition, we have used medicinal chemistry around known 5-HT receptor ligands to develop novel 5-HT_{2C} receptor agonists that have activity in rodent models of obsessive-compulsive disorder and obesity (Sard *et al*, 2005; and Sard *et al*, US patent submitted) and subhuman primate models of drug addiction (Rothman *et al*, 2005). In each of these examples, the basic science goals provide the ability to pursue compounds that may not receive attention in a drug discovery setting and allow proof-of-concept advances at costs considerably less than that required for development and characterization of drug leads or execution of full lead optimization efforts.

Encourage research into basic mechanisms of drug toxicities and side effect liabilities. Both industry and academic investigators are increasingly engaged in tackling the other critical issues inherent in modern drug discovery. A major example that deserves increasing attention is studies aimed at early predictions of drug toxicity and side effects. While this is clearly a major focus for many companies, it will be important for the biomedical community at large to engage more fully in this important endeavor. For instance, can we predict if a drug will have unforeseen toxicities or intolerable side effects? Rather than gaining answers to these questions at the end of a billion dollar program, the most talented basic and clinical scientists should develop biomarkers and screening assays that reliably predict toxicity. An excellent example of how this can be accomplished is the discovery that the 5-HT_{2B} serotonin receptor is the likely culprit responsible for the valvulopathy and pulmonary hypertension induced by the 'fen/phen' combination (Rothman *et al*, 2000; Launay *et al*, 2002). The 'fen/phen' case study is a highly pertinent example because it was (1) unexpected and (2) has resulted in the largest class-action suit against a pharmaceutical company to date (\$26 billion thus far). In this instance, we and others were not only able to identify the molecular target responsible for the side effects of fenfluramine, we were also able to accurately predict that medications that were 5-HT_{2B} agonists would have valvulopathy as an unexpected side effect (Rothman *et al*, 2000; Fitzgerald *et al*, 2000). Subsequently, we and others identified several approved medications as potent 5-HT_{2B} agonists (eg pergolide, cabergoline, dihydroergotamine; Newman-Tancredi *et al*, 2002; Setola *et al*, 2003) these

medications have subsequently been demonstrated to cause serious valvulopathy in humans (Roth, 2007). Pergolide was recently withdrawn from the market by the US FDA while cabergoline was given a black-box warning.

Another issue relates to the possibility that metabolites may have unexpected toxicities not likely to be identified using conventional preclinical toxicology models. A highly relevant example is that of 'fen/phen'-induced cardiac valvulopathy and pulmonary hypertension. In this case, it is now clear that norfenfluramine—the active metabolite of fenfluramine—is responsible for both valvular heart disease (Rothman *et al*, 2000; Fitzgerald *et al*, 2000) and pulmonary hypertension (Hong *et al*, 2004; Setola *et al*, 2003, 2005). Additionally, it is now clear that a minor metabolite of methysergide—methyergonovine—is the likely cause of methysergide-induced valvular heart disease (Setola *et al*, 2003; Roth, 2007).

From a more global perspective, we and others have recommended the screening of large libraries of medications and their metabolites at panels of 'druggable targets' in the genome and then deconvoluting this information to discover the molecular targets responsible for serious side effects (Armbruster and Roth, 2005; Fliri *et al*, 2005a,b; Setola and Roth, 2005). Recently, a group at Pfizer has provided an elegant proof of concept of this approach using both a chemical and informatics approach to provide structure-activity information for accurate side effect predictions (Fliri *et al*, 2005a,b). We have also used this approach to discover cyproheptidine and mirtazepine as candidate medications for Tysabri- and HIV-induced progressive multifocal leukoencephalopathy (Elphick *et al*, 2004; O'Connor and Roth, 2005).

Obviously, other approaches toward discovering and predicting toxicities should also be pursued using the combined resources of the public and private sectors. The C-Path Organization (<http://www.c-path.org/>), an outgrowth of the FDA's critical path initiative, is a pertinent example, which proposes accelerating the accumulation of information related to the pharmacogenomics of drug actions and toxicities. It is likely that an enhanced understanding of the pharmacogenomics of drug actions may lead to the discovery of novel candidate molecular targets for psychiatric drug actions. Thus, if certain subpopulations show altered responses to a particular medication, this could be due to polymorphisms in a molecular target responsible for a particular drug's action. Such a discovery could lead to a novel molecular target for psychiatric drug discovery. Although this is in theory a highly promising approach, we are unaware of any successes using this approach to discover novel candidate medications for psychiatric drug discovery.

More focus on target validation at every step in the drug discovery process. Often, major drug discovery programs are launched and proceed through the lead optimization, preclinical development, and early clinical development based on minimal target validation. This places too little focus on continued target validation throughout the drug discovery and early clinical development process. Instead, we should focus major effort on continually validating a target at every step in the process (see diagram). Industry scientists participate in every phase of

this process and many companies now demand increasing levels of validation as better tools are developed at each step of a program. While individual academic scientists cannot span all of these aspects of increasing levels of target validation, the areas in blue in this diagram are areas where we believe NIH funded scientists should be more aggressively involved in contributing to the drug discovery process, especially by focusing their talent on target validation (Figure 1).

The availability of screening centers in academic and other nonprofit institutions provides an unprecedented opportunity for academic scientists to provide the earliest possible validation at a molecular level by determining whether drug-like molecules can be developed that interact with a novel molecular target and whether this interaction has relevant actions *in vitro* and in some cases in animal models predictive of clinical efficacy. Obviously, a fundamental issue to be addressed regarding small molecule ligand discovery relates to having in place sufficient resources to follow-up on initial 'hits' from HTS campaigns to provide quality 'leads'. This includes not only teams of dedicated medicinal chemists but also appropriate resources for selectivity screening to verify the selectivity (or lack thereof) of the potential 'lead-like' compounds. It is well appreciated in both industrial and academic-based screening that follow-up chemistry and screening frequently requires a greater investment in money and personnel than that associated with identifying 'hits'. One of our formal recommendations (see below) relates to an opportunity for enhanced investment by the NIH for synthetic organic and medicinal chemistry programs. Currently, the NIGMS-funded Centers for Molecular Library Development and the pan-NIH-MLSCNs serve as model systems for how such programs might be initiated. In terms of selectivity screening in the public sector, programs such as the NIMH Psychoactive Drug Screening Program provides comprehensive selectivity screening similar to that provided by an increasing number of vendors such as Cerep and MDS Pharma, and many others that represent excellent models for this critical effort.

Figure 1 Major steps in the drug discovery and development process. Target validation should be a major focus at multiple steps where increasingly refined tools allow more rigorous validation of novel targets in more complex systems. The steps shaded in blue are steps where academic scientists can contribute at some level to drug discovery and development.

Another major focus should be on early proof-of-concept studies in man. In many cases, proof-of-concept studies can be achieved with compounds unsuited for large-scale use in humans because of bioavailability and pharmacokinetic considerations. Obviously, such studies should never be considered when pharmacokinetic shortcomings prevent confidence that the drug reaches the target tissue and occupies its molecular target. However, there are instances when this condition can be satisfied and meaningful proof-of-concept studies conducted well before optimization of a compound with all of the properties desired for maximal market penetration (ie high oral bioavailability, single daily dosing, etc). This is especially true when long-term chronic dosing is not required and proof-of-concept studies can be performed in relatively short-term clinical studies. Because of the inherent costs associated with such proof-of-concept studies, it is likely that most studies will be initiated in industry settings, although public-private collaborative efforts might be highly fruitful. A way in which this could be done is the TURNS (treatment units for research on neurocognition in schizophrenia) program which aims to provide proof-of-concept studies for potential cognition-enhancing agents for schizophrenia. If the therapeutic concept was proven, this would stimulate further optimization, discovery, and clinical development efforts by commercial entities.

A more pertinent example of how this can be done relates to the discovery by Golde and colleagues (Eriksen *et al*, 2003) that enantiomers of flubriprofen were identified as γ -secretase inhibitors. Indeed, the R-enantiomer was shown to inhibit γ -secretase while not targeting cyclooxygenase. The active enantiomer was subsequently patented (US Patent 6, 911, 466), licensed to Myriad Genetics for clinical trials and has now shown efficacy in a proof-of-concept phase 2 trial for Alzheimer's disease (http://www.myriad.com/alzheimers/phase2_ad.php).

Identification and validation of novel targets through bedside-to-bench research. In addition to a critical focus on bench-to-bedside translational research, we encourage renewed commitment of basic scientists to 'bedside-to-bench' research. Increased efforts should be focused on determining the mechanisms of action of agents with demonstrated clinical efficacy but no known molecular or cellular targets. As discussed above, drugs currently available for treatment of multiple psychiatric disorders began with the serendipitous discovery of clinical efficacy. In the past, this was followed by focused effort by multiple academic and industry laboratories to determine the molecular targets of these medications. Understanding these clinically validated molecular targets fueled the original discovery of the current medicines that represented significant improvements relative to the original drug in a class (Ayd, 1991).

There are multiple modern examples of drugs with established efficacy for CNS disorders that provide opportunities for the identification of (presumably) novel but prevalidated molecular and cellular targets (O'Connor and Roth, 2005). One very recent example of this approach is the discovery that the anxiolytic agent fenobam is a potent antagonist of the mGlu5 subtype of metabotropic glutamate

receptor (Porter *et al*, 2005). Fenobam was previously shown to have clinical efficacy as an antianxiety agent but had an unknown mechanism of action (Pecknold *et al*, 1982), a finding consistent with a growing body of literature showing that mGluR5 blockade is anxiolytic (Swanson *et al*, 2005).

Multiple additional examples exist for gaining insights into novel targets through investigation of clinically active compounds including various antiepilepsy medications used as mood stabilizers (eg valproic acid, lamotrigine, and carbamazepine; Quiroz *et al*, 2004) and modafinil, a nonstimulant drug for treatment of excessive daytime sleepiness and possible efficacy in treatment of ADHD (Pliszka, 2003). Parallel approaches should be employed in uncovering unknown mechanisms of action of known drugs, including phenotypic cell-based assays and molecular target-based approaches (O'Connor and Roth, 2005). One approach that has promise for these efforts is mining the receptorome, or broad screening of the effects of a clinically active compounds against a broad array of potential drug receptors (Armbruster and Roth, 2005). As previously mentioned, we and others have proposed that comprehensively screening the 'druggable genome' (Hopkins and Groom, 2002; <3000 molecular targets) using an array of approved medications, metabolites and candidate medications would likely lead to insights into many of the molecular targets responsible for the efficacies and side effects of drugs in humans (O'Connor and Roth, 2005; Fliri *et al*, 2005b).

New Opportunities for Breakthroughs in Psychiatric Drug Discovery

While there are no modern examples of novel approaches for the treatment of psychiatric disorders that offer the level of certainty that comes from refinement of an agent or mechanism that has been in wide clinical use with known efficacy, there are multiple examples of opportunities for fundamentally new approaches to treatment of CNS disorders that have been validated at some level in clinical studies or are soundly based on our understanding of the pathology of a disorder in humans. While extensive discussion or even listing of each of these novel approaches is beyond the scope of this review, there are several opportunities that have some level of clinical validation that may be especially promising. These include agonists or allosteric potentiators of mGluR2/3 metabotropic glutamate receptors (Swanson *et al*, 2005) or antagonists of mGluR5 (Porter *et al*, 2005) for treatment of anxiety disorders. Indeed, the approach of developing allosteric modulators of receptors is one likely to yield many novel agents for psychiatric drug discovery. Also, there are multiple new targets for treatment of negative symptoms or cognition-enhancing agents for schizophrenia that deserve focused attention, including M1 and/or M4 muscarinic receptor activators (Dean *et al*, 2003; Sur *et al*, 2003); subtype-selective nicotinic agonists (Martin *et al*, 2004), D1 dopamine receptor agonists (Goldman-Rakic *et al*, 2004); regulators of NMDA receptor function (Coyle and Tsai, 2004); and 5-HT6 receptor antagonists (Roth *et al*, 2003) to name but a few.

In addition, the growing evidence that action at multiple targets is required for full efficacy of many of the most successful drugs used for treatment of multiple CNS disorders (Frantz, 2005; Roth *et al*, 2004) makes it imperative that we focus on developing new approaches for rational design of multitarget compounds using novel chemistries and scaffolds. The rational design of multitarget drugs has recently been highlighted as an area of significant growth in medicinal chemistry and drug discovery (Morphy *et al*, 2004; Morphy and Rankovic, 2005; Frantz, 2005; Csermely *et al*, 2005).

As is the case with all small molecule-based drug discovery efforts, unexpected metabolites of the parent compound may display distinct multireceptorial profiles and differential receptor efficacies. A pertinent case in point is that of clozapine and *N*-desmethyl-clozapine, which display substantial differences in efficacies toward various biogenic amine receptors. Thus, for instance, *N*-desmethyl-clozapine is a potent partial agonist at M1-, M3-, and M5-muscarinic receptors while clozapine is generally considered to be an antagonist at these sites (Sur *et al*, 2003; Weiner *et al*, 2004; Davies *et al*, 2005). Additionally, *N*-desmethyl-clozapine has recently been demonstrated to be a partial D2- and D3-agonist, while clozapine is a weak inverse agonist (Burstein *et al*, 2005).

While progress in developing fundamentally new approaches to treatment of psychiatric disorders over the past three decades has been slow, evaluation of the current landscape of drug discovery in this arena is very encouraging. There has been an increasing number of translational and clinical studies over the past decade that are yielding promising results for therapeutic utility of some of the novel approaches that are being explored. These studies suggest that we may soon witness the benefit of our investments in postgenomic approaches. As we move forward in pursuing the high priority examples of novel but clinically validated approaches, it will be important to continue an emphasis on proof-of-concept studies with compounds with novel mechanisms of action. Also, we must continue to develop and validate animal models that predict enhanced efficacies as well as biomarkers for disease treatments and side effect liabilities.

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REFERENCES

- Anderson IM (2001). Meta-analytical studies on new antidepressants. *Br Med Bull* 57: 161–178.
- Armbruster BN, Roth BL (2005). Mining the receptorome. *J Biol Chem* 280: 5129–5132.
- Austin CP, Brady LS, Insel TR, Collins FS (2004). NIH molecular libraries initiative. *Science* 306: 1138–1139.
- Ayd Jr FJ (1991). Invited ACNP lecture. The early history of modern psychopharmacology. *Neuropsychopharmacology* 5: 71–84.
- Benkert O, Laakmann G, Ott L, Strauss A, Zimmer R (1977). Effect of zimelidine (H 102/09) in depressive patients. *Arzneimittelforschung* 27: 2421–2423.
- Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS *et al* (2000). Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* 47: 351–354.
- Burstein ES, Ma J, Wong S, Gao Y, Pham E, Knapp AE *et al* (2005). Intrinsic efficacy of antipsychotics at human d2, d3, and d4 dopamine receptors: identification of the clozapine metabolite *N*-desmethylozapine as a d2/d3 partial agonist. *J Pharmacol Exp Ther* 315: 1278–1287.
- Cade J (1949). Lithium salts in the treatment of psychotic excitement. *Med J Aust* 36: 349–352.
- Callicott JH, Straub RE, Pezawas L, Egan MF, Mattay VS, Hariri AR *et al* (2005). Variation in DISC1 affects hippocampal structure and function and increases risk for schizophrenia. *Proc Natl Acad Sci USA* 102: 8627–8632.
- Chavez-Noriega LE, Marino MJ, Schaffhauser H, Campbell UC, Conn PJ (2005). Novel potential therapeutics for schizophrenia: focus on the modulation of metabotropic glutamate receptor function. *Curr Neuropharmacol* 3: 9–34.
- Chen Y, Nong Y, Goudet C, Hemstapat K, de Paulis T, Pin J *et al* (2007). Activity of novel positive allosteric modulators of metabotropic glutamate receptor 5 requires binding to the same site as allosteric antagonists. *Mol Pharmacol* 71: 1389–1398.
- Conn PJ, Battaglia G, Marino MJ, Nicoletti F (2005). Metabotropic glutamate receptors in the basal ganglia motor circuit. *Nat Rev Neurosci* 6: 787–798.
- Costa E, Chen Y, Davis J, Dong E, Noh JS, Tremolizzo L *et al* (2002). REELIN and schizophrenia: a disease at the interface of the genome and the Epigenome. *Mol Interv* 2: 47–57.
- Coyle JT, Tsai G (2004). The NMDA receptor glycine modulatory site: a therapeutic target for improving cognition and reducing negative symptoms in schizophrenia. *Psychopharmacology (Berl)* 174: 32–38.
- Csermely P, Agoston V, Pongor S (2005). The efficiency of multi-target drugs: the network approach might help drug design. *Trends Pharmacol Sci* 26: 178–182.

- Davies MA, Compton-Toth BA, Hufeisen SJ, Meltzer HY, Roth BL (2005). The highly efficacious actions of *N*-desmethyldiclozapine at muscarinic receptors are unique and not a common property of either typical or atypical antipsychotic drugs: is M1 agonism a pre-requisite for mimicking clozapine's actions? *Psychopharmacology (Berl)* **178**: 451–460.
- Dean B, Bymaster FP, Scarr E (2003). Muscarinic receptors in schizophrenia. *Curr Mol Med* **3**: 419–426.
- Delay J, Deniker P, Harl J (1954). The treatment of excitement and agitation states by a method of medication derived from hibernotherapy. *Ann Med Psychol* **110**: 267–273.
- Dong E, Agis-Balboa RC, Simonini MV, Grayson DR, Costa E, Guidotti A (2005). Reelin and glutamic acid decarboxylase67 promoter remodeling in an epigenetic methionine-induced mouse model of schizophrenia. *Proc Natl Acad Sci USA* **102**: 12578–12583.
- Elphick GF, Querbes W, Jordan JA, Gee GV, Eash S, Manley K *et al* (2004). The human polyomavirus, JCV, uses serotonin receptors to infect cells. *Science* **306**: 1380–1383.
- Eriksen JL, Sagi SA, Smith TE, Weggen S, Das P, McLendon DC *et al* (2003). NSAIDs and enantiomers of flurbiprofen target gamma-secretase and lower Abeta 42 *in vivo*. *J Clin Invest* **112**: 440–449.
- Fitzgerald LW, Burn TC, Brown BS, Patterson JP, Corjay MH, Valentine PA *et al* (2000). Possible role of valvular serotonin 5-HT(2B) receptors in the cardiopathy associated with fenfluramine. *Mol Pharmacol* **57**: 75–81.
- Fliri AF, Logging WT, Thadeio PF, Volkmann RA (2005a). Biological spectra analysis: linking biological activity profiles to molecular structure. *Proc Natl Acad Sci USA* **102**: 261–266.
- Fliri AF, Logging WT, Thadeio PF, Volkmann RA (2005b). Biospectra analysis: model proteome characterizations for linking molecular structure and biological response. *J Med Chem* **48**: 6918–6925.
- Frantz S (2005). Drug discovery: playing dirty. *Nature* **437**: 942–943.
- Garcia LS, Comim CM, Valvassori SS, Reus GZ, Barbosa LM, Andreazza AC *et al* (2007). Acute administration of ketamine induces antidepressant-like effects in the forced swimming test and increases BDNF levels in the rat hippocampus. *Prog Neuropsychopharmacol Biol Psychiatry* **8**; e-pub ahead of print.
- Goldberger C, Gourion D, Leroy S, Schurhoff F, Bourdel MC, Leboyer M *et al* (2005). Population-based and family-based association study of 5'UTR polymorphism of the reelin gene and schizophrenia. *Am J Med Genet B Neuropsychiatr Genet* **137**: 51–55.
- Goldman-Rakic PS, Castner SA, Svensson TH, Siever LJ, Williams GV (2004). Targeting the dopamine D1 receptor in schizophrenia: insights for cognitive dysfunction. *Psychopharmacology (Berl)* **174**: 3–16.
- Gornick MC, Addington AM, Sporn A, Gogtay N, Greenstein D, Lenane M *et al* (2005). Dysbindin (DTNBP1, 6p22.3) is associated with childhood-onset psychosis and endophenotypes measured by the premorbid adjustment scale (PAS). *J Autism Dev Disord* **35**: 831–838.
- Grayson DR, Jia X, Chen Y, Sharma RP, Mitchell CP, Guidotti A *et al* (2005). Reelin promoter hypermethylation in schizophrenia. *Proc Natl Acad Sci USA* **102**: 9341–9346.
- Grillon C, Cordova J, Levine LR, Morgan III CA (2003). Anxiolytic effects of a novel group II metabotropic glutamate receptor agonist (LY354740) in the fear-potentiated startle paradigm in humans. *Psychopharmacology (Berl)* **168**: 446–454.
- Gueudet C, Santucci V, Soubrie P, Le Fur G (1999). Blockade of neurokinin3 receptors antagonizes drug-induced population response and depolarization block of midbrain dopamine neurons in guinea pigs. *Synapse* **33**: 71–79.
- Harrison PJ, Weinberger DR (2005). Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatry* **10**: 40–68.
- Hennah W, Tuulio-Henriksson A, Paunio T, Ekelund J, Varilo T, Partonen T *et al* (2005). A haplotype within the DISC1 gene is associated with visual memory functions in families with a high density of schizophrenia. *Mol Psychiatry* **10**: 1097–1103.
- Hong Z, Olschewski A, Reeve HL, Nelson DP, Hong F, Weir EK (2004). Nordexfenfluramine causes more severe pulmonary vasoconstriction than dexfenfluramine. *Am J Physiol Lung Cell Mol Physiol* **286**: 531–538.
- Hopkins AL, Groom CR (2002). The druggable genome. *Nat Rev Drug Discov* **1**: 727–730.
- Insel TR, Collins FS (2003). Psychiatry in the genomics era. *Am J Psychiatry* **160**: 616–620.
- Kamiya A, Kubo KI, Tomoda T, Takaki M, Youn R, Ozeki Y *et al* (2005). A schizophrenia-associated mutation of DISC1 perturbs cerebral cortex development. *Nat Cell Biol* **7**: 1167–1178.
- Kennedy SH, Emsley R (2006). Placebo-controlled trial of agomelatine in the treatment of major depressive disorder. *Eur Neuropsychopharmacol* **16**: 93–100.
- Kinney GG, O'Brien JA, Lemaire W, Burno M, Bickel DJ, Clements MK *et al* (2005). A novel selective allosteric modulator of metabotropic glutamate receptor subtype 5 (mGluR5) has an antipsychotic profile in rat behavioral models. *J Pharmacol Exp Ther* **313**: 199–206.
- Kroeze WK, Hufeisen SJ, Popadak BA, Renock SM, Steinberg S, Ernsberger P *et al* (2003). H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology* **28**: 519–526.
- Kudoh A, Takahira Y, Katagai H, Takazawa T (2002). Small-dose ketamine improves the postoperative state of depressed patients. *Anesth Analg* **95**: 114–118.
- Launay JM, Herve P, Peoc'h K, Tournois C, Callebort J, Nebigil CG *et al* (2002). Function of the serotonin 5-hydroxytryptamine 2B receptor in pulmonary hypertension. *Nat Med* **8**: 1129–1135.
- Lewis DA, Lieberman JA (2000). Catching up on schizophrenia. Natural history and neurobiology. *Neuron* **28**: 325–334.
- Macgregor S, Visscher PM, Knott SA, Thomson P, Porteous DJ, Millar JK *et al* (2004). A genome scan and follow-up study identify a bipolar disorder susceptibility locus on chromosome 1q42. *Mol Psychiatry* **9**: 1083–1090.
- Maj J, Rogoz Z, Skuza G, Sowinska H (1992). The effect of CGP 37849 and CGP 39551, competitive NMDA receptor antagonists, in the forced swimming test. *Pol J Pharmacol Pharm* **44**: 337–346.
- Maj M, Bruno V, Dragic Z, Yamamoto R, Battaglia G, Inderbitzin W *et al* (2003). (–)-PHCCC, a positive allosteric modulator of mGluR4: characterization, mechanism of action, and neuroprotection. *Neuropharmacology* **45**: 895–906.
- Marino MJ, Williams Jr DL, O'Brien JA, Valenti O, McDonald TP, Clements MK *et al* (2003). Allosteric modulation of the group III metabotropic glutamate receptor mGluR4: a novel approach to Parkinson's disease treatment. *Proc Natl Acad Sci USA* **100**: 13668–13673.
- Martin LF, Kem WR, Freedman R (2004). Alpha-7 nicotinic receptor agonists: potential new candidates for the treatment of schizophrenia. *Psychopharmacology (Berl)* **174**: 54–64.
- Meltzer HY, Alphas L, Green AI, Altamura AC, Anand R, Bertoldi A *et al* (2003). Clozapine treatment for suicidality in schizophrenia: international suicide prevention trial (InterSePT). *Arch Gen Psychiatry* **60**: 82–91.
- Meltzer HY, Arvanitis L, Bauer D, Rein W (2004). Placebo-controlled evaluation of four novel compounds for the treatment of schizophrenia and schizoaffective disorder. *Am J Psychiatry* **161**: 975–984.
- Millar JK, Wilson-Annan JC, Anderson S, Christie S, Taylor MS, Semple CA *et al* (2000). Disruption of two novel genes by a translocation co-segregating with schizophrenia. *Hum Mol Genet* **9**: 1415–1423.

- Moghaddam B, Adams BW (1998). Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. *Science* **281**: 1349–1352.
- Morphy R, Rankovic Z (2005). Designed multiple ligands. An emerging drug discovery paradigm. *J Med Chem* **48**: 6523–6543.
- Morphy R, Kay C, Rankovic Z (2004). From magic bullets to designed multiple ligands. *Drug Discov Today* **9**: 641–651.
- Newman-Tancredi A, Cussac D, Quentric Y, Touzard M, Verrielle L, Carpentier N *et al* (2002). Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor. III. Agonist and antagonist properties at serotonin, 5-HT(1) and 5-HT(2), receptor subtypes. *J Pharmacol Exp Ther* **303**: 815–822.
- O'Brien JA, Lemaire W, Chen T-B, Chang RSL, Jacobson MA, Ha SN *et al* (2003). A family of highly selective allosteric modulators of the metabotropic glutamate receptor subtype 5 (mGluR5). *Mol Pharmacol* **64**: 731–740.
- O'Connor K, Roth BL (2005). Teaching old drugs new tricks: a highly efficient approach for drug discovery and development in the public sector. *Nat Rev Drug Discov* **4**: 1005–1014.
- Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV *et al* (2007). Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized phase 2 clinical trial. *Nat Med* **13**: 1102–1107.
- Pecknold JC, McClure DJ, Appeltauer L, Wrzesinski L, Allan T (1982). Treatment of anxiety using fenobam (a nonbenzodiazepine) in a double-blind standard (diazepam) placebo-controlled study. *J Clin Psychopharmacol* **2**: 129–133.
- Phiel CJ, Zhang F, Huang EY, Guenther MG, Lazar MA, Klein PS (2001). Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen. *J Biol Chem* **276**: 36734–36741.
- Pliszka SR (2003). Non-stimulant treatment of attention-deficit/hyperactivity disorder. *CNS Spectr* **8**: 253–258.
- Porter RH, Jaeschke G, Spooren W, Ballard T, Buettelmann B, Kolczewski S *et al* (2005). Fenobam: a clinically validated non-benzodiazepine anxiolytic is a potent, selective and non-competitive mGlu5 receptor antagonist with inverse agonist activity. *J Pharmacol Exp Ther* **315**: 711–721.
- Quiroz JA, Singh J, Gould TD, Denicoff KD, Zarate CA, Manji HK (2004). Emerging experimental therapeutics for bipolar disorder: clues from the molecular pathophysiology. *Mol Psychiatry* **9**: 756–776.
- Rodriguez AL, Nong Y, Sekaran NK, Alagille D, Tamagnan G, Conn PJ (2005). A close structural analog of MPEP acts as a neutral allosteric site ligand on metabotropic glutamate receptor subtype 5 and blocks the effects of multiple allosteric modulators. *Mol Pharmacol* **68**: 1793–1802.
- Roth BL (2007). Drugs and valvular heart disease. *N Engl J Med* **356**: 6–9.
- Roth BL, Hanizavareh SM, Blum AE (2003). Serotonin receptors represent highly favorable molecular targets for cognitive enhancement in schizophrenia and other disorders. *Psychopharmacology (Berl)* **174**: 17–24.
- Roth BL, Sheffler DJ, Kroeze WK (2004). Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. *Nat Rev Drug Discov* **3**: 353–359.
- Rothman RB, Baumann MH, Savage JE, Rauser L, McBride A, Hufeisen SJ *et al* (2000). Evidence for possible involvement of 5-HT(2B) receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. *Circulation* **102**: 2836–2841.
- Rothman RB, Blough BE, Woolverton WL, Anderson KG, Negus SS, Mello NK *et al* (2005). Development of a rationally-designed, low abuse potential, biogenic amine releaser that suppresses cocaine self-administration. *J Pharmacol Exp Ther* **313**: 1361–1369.
- Sard H, Kumaran G, Morency C, Roth BL, Toth BA, He P *et al* (2005). SAR of psilocybin analogs: discovery of a selective 5-HT_{2C} agonist. *Bioorg Med Chem Lett* **15**: 4555–4559.
- Setola V, Dukat M, Glennon RA, Roth BL (2005). Molecular determinants for the interaction of the valvulopathic anorexigen norfenfluramine with the 5-HT_{2B} receptor. *Mol Pharmacol* **68**: 20–33.
- Setola V, Hufeisen SJ, Grande-Allen KJ, Vesely I, Glennon RA, Blough B *et al* (2003). 3,4-Methylenedioxymethamphetamine (MDMA, 'Ecstasy') induces fenfluramine-like proliferative actions on human cardiac valvular interstitial cells *in vitro*. *Mol Pharmacol* **63**: 1223–1229.
- Setola V, Roth BL (2005). Screening the receptorome reveals molecular targets responsible for drug-induced side effects: focus on 'fen-phen'. *Expert Opin Drug Metab Toxicol* **1**: 377–387.
- Spalding TA, Trotter C, Skjaerbaek N, Messier TL, Currier EA, Burstein ES *et al* (2002). Discovery of an ectopic activation site on the M(1) muscarinic receptor. *Mol Pharmacol* **61**: 1297–1302.
- Sur C, Mallorga PJ, Wittmann M, Jacobson MA, Pascarella D, Williams JB *et al* (2003). *N*-desmethyloclozapine, an allosteric agonist at muscarinic 1 receptor, potentiates *N*-methyl-D-aspartate receptor activity. *Proc Natl Acad Sci USA* **100**: 13674–13679.
- Swanson CJ, Bures M, Johnson MP, Linden AM, Monn JA, Schoepp DD (2005). Metabotropic glutamate receptors as novel targets for anxiety and stress disorders. *Nat Rev Drug Discov* **4**: 131–144.
- Thomson PA, Wray NR, Millar JK, Evans KL, Hellard SL, Condie A *et al* (2005). Association between the TRAX/DISC locus and both bipolar disorder and schizophrenia in the Scottish population. *Mol Psychiatry* **10**: 657–668.
- Tremolizzo L, Doueiri MS, Dong E, Grayson DR, Davis J, Pinna G *et al* (2005). Valproate corrects the schizophrenia-like epigenetic behavioral modifications induced by methionine in mice. *Biol Psychiatry* **57**: 500–509.
- Trullas R, Skolnick P (1990). Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. *Eur J Pharmacol* **185**: 1–10.
- Varney MA, Cosford ND, Jachec C, Rao SP, Sacca A, Lin FF *et al* (1999). SIB-1757 and SIB-1893: selective, noncompetitive antagonists of metabotropic glutamate receptor type 5. *J Pharmacol Exp Ther* **290**: 170–181.
- Veldic M, Guidotti A, Maloku E, Davis JM, Costa E (2005). In psychosis, cortical interneurons overexpress DNA-methyltransferase 1. *Proc Natl Acad Sci USA* **102**: 2152–2157.
- Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG *et al* (2001). The sequence of the human genome. *Science* **291**: 1304–1351.
- Weiner DM, Meltzer HY, Veinbergs I, Donohue EM, Spalding TA, Smith TT *et al* (2004). The role of M1 muscarinic receptor agonism of *N*-desmethyloclozapine in the unique clinical effects of clozapine. *Psychopharmacology (Berl)* **177**: 207–216.
- Wong IC, Besag FM, Santosh PJ, Murray ML (2004). Use of selective serotonin reuptake inhibitors in children and adolescents. *Drug Saf* **27**: 991–1000.
- Zarate CA, Singh JB, Carson PJ, Brutshe NE, Ameli R, Luckenbaugh DA (2006). A randomized trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* **63**: 856–864.
- Zhang X, Tochigi M, Ohashi J, Maeda K, Kato T, Okazaki Y *et al* (2005). Association study of the DISC1/TRAX locus with schizophrenia in a Japanese population. *Schizophr Res* **79**: 175–180.