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Translating Discoveries into Medicine: Psychiatric Drug Development in 2011

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INTRODUCTION

Recent reviews have described the crisis in central nervous system (CNS) drug development, especially for psychiatric disorders (Paul *et al*, 2010). As several pharmaceutical companies reduced their investments in psychiatric drug development, NIMH has asked: (1) why the retreat from one of the most important public health targets, and (2) how could we invest federal dollars to ensure that the public will have a next generation of treatments? We have heard many answers to the retreat question: abundance of generics, lack of novel validated targets, paucity of predictive animal models, absence of biomarkers, and regulatory challenges, to name a few. The business case for psychiatric drug development is not promising. CNS drugs cost more and take longer to reach the market than other types of drugs: only 8% of those that make it to clinical trials end up being approved and they tend to fail in late-stage clinical trials after a significant investment has been made. This commentary addresses the second question by summarizing the NIMH response to the first. Although we will not solve all of the challenges, our hope is that NIMH can catalyze new efforts to develop the next generation of more effective, safer medications for the group of disorders that now represents the largest source of medical disability in the developed world. Ultimately, our success will depend on creating personalized treatments for people with mental disorders, based on a deeper understanding of individual differences in biology and treatment response. In this study we will focus on the earlier step of developing the next generation of treatments.

ABUNDANCE OF GENERICS

Most of the blockbuster psychiatric medications have either become or will soon become available as generic drugs. Although this is oft-cited as a challenge for further development, what is less recognized is the failure of the current medications to reduce the prevalence or disability of any of the major mental disorders. Although current antidepressants and antipsychotics have been beneficial to industry, the extent of benefit for patients is less consistent, with too many patients left to settle for less than recovery from these highly disabling disorders. The need for a next generation of medications was emphasized by the large scale practical trials like CATIE, STAR*D, and STEP-BD, each of which revealed very modest effects with optimized use of the current generation of medications (Insel, 2007). The next generation of medications may be built on an understanding of pathophysiology rather than the 'me-too' approach that has characterized the past four decades of drug development.

TARGET PIPELINE

Human genomics and biological studies have revealed an unprecedented number of promising molecular targets for neuropsychiatric disorders, including G-protein-coupled receptors and transporters, intracellular and synaptic proteins, and microRNAs. High-throughput screening (HTS), structural biology, and targeted approaches (allosteric modulators, covalent drugs, agonist-biased signaling) have led to the ability to tackle more challenging targets such as evolutionarily conserved families of signaling molecules, cell phenotypes, and protein–protein interactions. The NIH Molecular Libraries Program (http://commonfund.nih.gov/molecularlibraries/) has implemented 600 HTS assays and generated more than 200 chemical probes. Although only about 20% of the targets have been specific to neuroscience, there is emerging interest in targeting molecules for schizophrenia and autism. To increase participation in target exploration and augment the pipeline of targets for neuroscience, the NIMH recently issued an initiative (http://grants.nih.gov/grants/guide/rfa-files/

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RFA-MH-11-040.html) to develop novel *in vitro* assays of neuronal or glial function.

In addition to molecular targets, NIMH research has revealed novel clinical targets for psychiatric drug discovery. The development and regulatory acceptance of therapeutics for cognitive impairment associated with schizophrenia (MATRICS, http://www.matrics.ucla.edu/ and CNTRICS, http://cntrics.ucdavis.edu/) has led to research focused on a number of novel compounds for this new indication (Wallace *et al*, 2011). Anhedonia in schizophrenia and depression, social deficits in autism, and suicidal ideation are additional examples of clinical targets for which drug discovery programs could address core deficits or domains of dysfunction. In this study the early term breakthrough may emerge from an astute clinical insight allowing the repurposing of an existing drug or biologic rather than the discovery of a new chemical entity.

Network and systems biology offers a novel way of approaching drug discovery by developing models that consider the physiological environment or protein targets within a pathway or circuit. As an example of one promising area, therapeutic approaches targeting epigenetic regulatory proteins could transform psychiatric treatments. A recent initiative (http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-11-030.html) at NIMH is exploring epigenetic modifications during brain development and in the etiology of disease.

Ironically, at the same time that many companies are leaving antidepressant drug development, new findings may be revolutionizing our approach to treating depression. Recent studies have identified several rapidly acting compounds for treatment-resistant depression (eg, NMDA receptor antagonists such as ketamine, scopolamine, and dextromethorphan). Even in the absence of a full understanding of the mechanism, these new findings suggest a paradigm change: shifting expectations of antidepressant effect onset from 4 weeks to 4 h. NIMH intends to establish a network of sites to identify and test promising interventions that produce antidepressant effects within 72 h of initial administration (the 'RAPID-network').

ANIMAL MODELS

Mental disorders may be uniquely human disorders. Nevertheless, the intensive study of mechanisms of animal cognition and behavior may yield fundamental principles relevant to human normal and abnormal behavior. However, we should not be surprised that drug effects in animals are not predictive of drug effects in humans. After all, drug effects differ across strains of mice as well as across species. The study of diversity is likely to be more informative than a search for animal models (Insel, 2007). Even more informative, human-induced pluripotent stem cell approaches can now be used to study human disease, even CNS disease. In addition to the 'disease in a dish' approach, which has recently been applied to schizophrenia (Brennand *et al*, 2011) and syndromic autism (Marchetto *et al*, 2010), stem cells offer the opportunity for predictive toxicology, personalized medicine, and, perhaps most important for psychiatry, the identification of biomarkers.

TRANSLATIONAL BIOMARKERS

The absence of biomarkers is a major barrier to progress in psychiatry. Neuroimaging, neurophysiological, and genomic technologies have the potential to serve as tools to test hypotheses that relate to normal biological processes, pathophysiology, and proof of mechanism in preclinical and clinical drug discovery. Although these tools are powerful, they have failed to end the 'quest for the test'. Many studies fail to replicate or seek statistical rather than useful clinical effects, and often they focus on comparisons with healthy subjects rather than addressing a contrast that is clinically relevant (bipolar *vs.* unipolar depression, for instance). The attempt to link biomarkers to diagnosis may be doomed by diagnostic categories that have no biological validity. Biomarkers will require a broader, coherent effort that rethinks diagnosis and standardizes the approach to clinical and biological assessments. A new diagnostic effort, the Research Domain Criteria (RDoC, http://www.nimh.nih.gov/research-funding/rdoc.shtml) is beginning to reorganize psychiatric diagnosis around biologically relevant domains (Insel *et al*, 2010). Standardized measures and protocols need to be implemented across sites along with common data acquisition and handling standards to enable broad sharing of data. Recently funded NIMH biomarkers studies are developing standardized methods to collect functional imaging, electrophysiological, and blood-based measures and promoting broad-based data sharing (eg, biomarkers for depression (EMBARC, http://www4.utsouthwestern.edu/embarc/) and risk factors for developmental disorders (Neurodevelopmental Genomics, http://projectreporter.nih.gov/project_info_description.cfm?aid=7943007&icde=7803579). Systematic application of standardized functional measures and strategies will determine the value of biomarker technologies for application in psychiatric drug development.

REGULATORY SCIENCE

Regulatory science will be the focus of the National Center for Accelerating Translational Science (NCATS), a new institute proposed at NIH, as well as a new NIH-FDA Leadership Council, which began meeting in 2010. One regulatory science area that needs to be addressed in the near term is combination therapies. It is amazing that there is so little evidence for the effectiveness or safety of combination treatments even though most psychiatric patients are on multiple medications. Multi-target therapies, add-on strategies, and/or combination therapies that include pharmacological and behavioral interventions will be critical strategies to address unmet clinical need. Targeting cellular function rather than single proteins is expected to introduce novel classes of multi-target drugs with fewer adverse effects and toxicity. However the regulatory

pathway for the co-development of innovative combination treatments may not be as clear for psychiatry as for infectious diseases and cancer (Woodcock *et al*, 2011).

CHANGING THE CULTURE — WHERE ARE WE GOING?

In order to develop a long-term strategy to de-risk promising compounds for further development by the private sector, a new paradigm is needed to rapidly profile novel compounds and to assess proof of clinical mechanism. Experimental medicine studies are needed to bridge between animal and human studies. Studies in healthy volunteers should include pharmacodynamic biomarkers to establish the link between the optimal dose of the compound and the molecular mechanism in addition to tolerability and safety. Experimental questions should be tested in small groups of patients to establish the link between molecular mechanism and clinical effect (pharmacology and risk/benefit assessment); these data would provide confidence in biological rationale and safety to inform go/no go decisions to advance a compound for further clinical development (Cohen, 2010). A network of clinical sites is needed with capabilities to apply standardized functional imaging, electrophysiological, and cognitive/behavioral technologies to address experimental medicine questions.

New models are needed to tackle the inefficiencies in drug development. Pre-competitive public–private partnerships (PPPs) exist for biomarkers and for methods development to support innovation in drug discovery. The Biomarkers Consortium (http://biomarkersconsortium.org/) focuses on validation of biomarkers for application in translational research and drug development; examples of neuroscience projects include proteomic approaches to validate a panel of markers using plasma and CSF samples from the Alzheimer's Disease Neuroimaging Initiative (http://www.adni-info.org/). The Innovative Medicines Initiative (http://www.imi.europa.eu/content/home) supports collaborative research projects and builds networks to enhance pharmaceutical innovation in Europe. One project, NEWMEDS (http://www.imi.europa.eu/content/novel-methods-leading-new-medications-depression-and-schizophrenia), focuses on development of animal models, standardized paradigms for fMRI and PET imaging, pharmacogenetic markers, and trial designs for developing new medications for depression and schizophrenia. A new, open access consortium model, Arch2POCM, offers a venue to extend partnerships between government, academia, and the private sector to identify compounds that explore proof of clinical mechanism (POCM) for selected diseases and targets (Strauss, 2011). Most recently, the NIH is exploring opportunities to partner with the private sector for repurposing of drugs that meet toxicity and safety criteria to deliver significant value at reduced cost and in dramatically shorter time frames for diseases with unmet medical need (Mullard, 2011). Successful PPPs will expedite pre-competitive collaboration between key stakeholders (not only government (NIH, FDA), academia, pharmaceutical, and biotechnology companies, but also disease foundations and advocacy groups) to advance novel targets and mechanisms into clinical development. Catalytic efforts are needed to fill the pipeline with the next generation of treatments for psychiatric disorders.

DISCLOSURE

Neither Dr Linda Brady nor Dr Thomas Insel has any conflict of interest to declare.

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