CHAPTER 2

Drug Discovery and Development Initiatives at the National Institute of Mental Health: From Cell-Based Systems to Proof of Concept

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The mission of the National Institute of Mental Health (NIMH) is to reduce the burden of mental illness and behavioral disorders through research. Toward this goal, the NIMH promotes the development of novel models as an integral part of a larger effort aimed at understanding the neurobiological mechanisms responsible for both normal and disrupted cognitive and emotional control and toward the development of new mechanism of action therapeutics. This chapter presents an overview of NIMH efforts to stimulate treatment discovery and development through support of basic research, targeted drug discovery programs, translational research support, and facilitation of communication between public, private, and government agencies.

THE NEED FOR NEW TREATMENTS FOR MENTAL DISORDERS

Neuropsychiatric disorders have devastating impact for individuals and communities and are among five of the top ten causes of disability worldwide.[1] Available medications and non-pharmaceutical treatments are effective in treating specific symptoms for subsets of affected individuals. However, a significant proportion of individuals with mental disorders do not demonstrate considerable life improvement with available treatments. In addition, serious side effects limit the use of some otherwise effective medications. Finally, specific domains of function, such as cognitive deficits in schizophrenia, are only poorly treated by available psychotherapeutics.

Tremendous advances have been made in the past few decades toward understanding the neurobiology of cognition and emotional regulation. However, these basic science discoveries have not yielded parallel advances in the treatment of mental disorders. Indeed, most of the classes of drugs currently used to treat neuropsychiatric disorders were identified well before much of our current knowledge of brain biology was established.[2,3] Drugs more recently marketed for the treatment of psychosis, mood, and anxiety disorders represent predominantly variations of existing compounds that presumably act through similar mechanisms.[4] Many factors contribute to the absence of novel mechanism of action drugs for treating mental disorders including the staggering cost of bringing drugs to market, and the high attrition rate of candidate therapeutics during development and clinical testing. The inability of preclinical screens to predict potential clinical efficacy accurately and adverse effects contributes to the high rate of failure of new compounds in clinical trials.[5]

MODELS IN DRUG DISCOVERY OF NEUROPSYCHIATRIC DISORDERS

Mental disorders are diagnosed and treatment effectiveness in patients is assessed through behavioral measures, usually as self-reports. While the DSM and ICD-10 diagnostic manuals produce reliable diagnoses,[i] they do not weigh the relative disability imparted by specific clinical features and the symptom profile of some individuals may qualify them for multiple diagnoses.[6] As a result, it is accepted that individuals with the same diagnosis may have different underlying pathology within the brain resulting from different causes.[7] While promising avenues are under investigation, the development of a reliable bioassay for diagnostic purposes is at this point only a goal. Thus, it is not surprising that preclinical screens for the potential effectiveness of new candidate therapeutics rely on assessment of drug effects in behavioral models that are intended to measure changes in function within core domains such as cognitive and emotional processes associated with disorders. It is also not surprising that the match between the preclinical models and measures and clinical diagnoses is generally poor. Since potentially effective drugs may not produce behavioral effects against a normal background, much of the preclinical screening is performed against a genetic and/or environmental (e.g., stressor) manipulation meant to mimic some component of underlying pathology in an animal. The failure of a screen to predict efficacy may thus be due to the use of a manipulation that does not adequately model the neuropathology of a disorder, or only does so for a small percentage of patients. While the target behavioral effects of a new compound in preclinical screens may represent the best estimate of efficacy available, it is difficult to assess if the measures tap into key deficit areas of function for mental disorders. Finally, the predictive validity of many preclinical screens is based on the degree to which the models detect drugs of known clinical efficacy. This requirement may inadvertently limit the ability to detect truly novel mechanism of action compounds.

Models typically employ syndromal or parallel measures approaches. Syndromal models attempt to emulate, through some manipulation, an array of deficits with characteristics indicative of diagnostic criteria for a specific mental disorder. It is presently not possible to assess whether any syndrome model is truly analogous to a mental disorder. Such verification must wait for the availability of reliable and specific non-verbal assessment tools (biomarkers) that are similarly affected in both humans and models. However, the use of a battery of measures to examine the effect of a presumed contributor to the pathology of a disorder, such as a gene defect, may help to identify the aspects of the disorder most affected by the perturbation.

The parallel measures approach involves investigation of a key area of deficit that may be present in more than one mental disorder. Typically, these measures are objective and well-defined behavioral or physiological indices that may be validated as disrupted in both animal models as well as in patients. For example, sensory gating deficits have been demonstrated in both schizophrenic patients and in animal

[i] Please refer to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision (DSM-IV-TR), or The International Statistical Classification of Diseases and Related Health Problems 10th Revision, published by the American Psychiatric Association and the World Health Organization, respectively, for current diagnostic criteria manuals in use.

models emulating the dopaminergic or glutamatergic dysregulation of this disorder.[8] The advantage of this approach is that it is amenable to neurobiological investigation and the application of knowledge of underlying brain processes and regulatory systems may suggest new avenues for therapeutic target development. Depending on how well linked the measure is to a key area of deficit in a disorder, this parallel measure approach may provide a reasonable model for screening novel mechanism of action drugs. An example of how this approach is being applied toward measuring cognitive function and response to novel drug treatments for schizophrenia is presented later in this chapter.

NIMH SUPPORT FOR DISCOVERY SCIENCE AND BASIC NEUROSCIENCE RESEARCH

The NIMH supports a wide breadth of research spanning from basic molecular neuroscience and behavioral science through clinical trials testing the effectiveness of therapeutics for treating mental disorders. Support of basic neuroscience is critical for placing newly identified brain changes associated with mental disorders and treatment targets within a functional context. Discovery science and neuroscience research are supported predominantly through the funding of investigator-initiated grants. Funding decisions are based on the merit of proposed work as well as relevance to the goals of the NIMH.

The NIMH engages in periodic review of the portfolio of basic research support in order to identify potential new opportunities for expanding basic knowledge and increasing the potential impact of basic research findings toward treatment development (Breaking Ground, Breaking Through: The Strategic Plan for Mood Disorders Research, Setting Priorities for Basic Brain and Behavioral Research at NIMH, http://www.nimh.nih.gov/strategic/stplan_mooddisorders.cfm). These reviews provide guidance and recommendations of areas for research advancement relevant to mental disorders. For example, the NIMH National Advisory Council workgroup review of the basic behavioral and neuroscience grant support concluded that the NIMH had a strong and impressive portfolio but suggested that more emphasis could be placed in support of research spanning across levels of analysis including the support for refined animal models. NIMH also conducts workshops, aimed at identifying areas of specific need or interest and developing strategies to address them.[9]

ROLE OF NIMH IN DRUG DISCOVERY AND MODEL DEVELOPMENT

In addition to its traditional role of evaluating the efficacy and effectiveness of currently available medications, the NIMH has launched a broad network of programs and initiatives aimed at increasing the likelihood and speed of developing novel treatments for mental disorders. This new effort resulted from the recognized public health need for a new generation of innovative therapeutics for the most prevalent disorders and a first generation of medications for orphan diseases, including developmental disorders. In addition to new NIMH initiatives, the Institute is highly invested in larger scale National Institutes of Health (NIH) efforts related to both the NIH Roadmap for

Biomedical Research and NIH Blueprint for Neuroscience Research, (http://neuroscienceblueprint.n ih.gov/). The following section outlines the breadth of NIMH programs and initiatives spanning from drug and target discovery through first in human studies. A description of ongoing and recently completed large clinical trials supported by NIMH can be found at the NIMH: Clinical Trials (http://www.nimh.nih.gov/studies/index.cfm).

GRANT SUPPORT FOR DRUG DISCOVERY AND MECHANISM OF ACTION STUDIES

Basic research pertinent to drug discovery and model development is supported within defined programmatic areas. These programs house most of the NIMH funded basic research aimed at developing and characterizing both novel ligands and approved drug treatments across levels of analyses from design, synthesis, and molecular characterization through identification of effects within relevant signaling pathways and cells, identification of mechanism of behavioral action in intact systems, to first in human studies. These efforts are further supported through specific funding initiatives identified below. A complete listing of programs is available at the NIMH website (http://www.nimh.nih.gov/researchfunding/index.cfm).

NIMH Resource Support for Drug Discovery

The NIMH has identified several opportunities for linking molecular neuroscience with efforts to facilitate both drug and tool discovery relevant to mental disorders. In order to address the needs of a diverse set of researchers interested in advancing the study of novel compounds toward these goals, the NIMH has established contract services for drug screening, synthesis, and preclinical toxicology studies (http://www.nimh.nih.gov/research-funding/grants/biological-and-technical-resources-for-research.shtml).

The *NIMH Psychoactive Drug Screening Program* is a resource program that provides screening of novel psychoactive compounds for pharmacological and functional activity at cloned human or rodent CNS receptors, channels, and transporters. The contract also provides assays for predicting bioavailability and cardiovascular toxicity and supports a Ki database (http://pdsp.med.unc.edu/pdsp.php) of affinity constants for ligand binding.

The *NIMH Chemical Synthesis and Drug Supply Program* synthesizes and distributes novel research chemicals, psychoactive drugs, and compounds unavailable to the scientific community from commercial sources. The program also supports radiosynthesis and Good Manufacturing Practice (GMP) synthesis of promising candidate compounds for use in clinical studies.

The *NIMH Toxicological Evaluation of Novel Ligands Program* provides toxicology and safety assessment of promising, target-selective compounds for use as imaging ligands in human studies, and limited assessment of novel psychoactive agents for clinical research and as potential therapeutics. Toxicology and safety data generated by the program can be used to support an Investigational New Drug (IND) application

to the Food and Drug Administration (FDA), and for Radioactive Drug Research Committee (RDRC) evaluation of a compound for human studies.

NIH Resource Support for Drug Discovery

The goal of the *Molecular Libraries and Imaging Roadmap* (http://nihroadmap.nih.gov/molecularlibraries) initiative is to establish a national high throughput screening (HTS) resource in the academic environment to improve the understanding of biology and disease mechanisms. At the core of this initiative is the Molecular Libraries Screening Centers Network (MLSCN, http://www.mli.nih.gov). The MLSCN optimizes and performs HTS for the identification of small biologically active molecules. While the focus of the MLSCN is not explicitly geared toward any disease, many of the assays would detect current treatments for mental disorders through their effects on, for example, G-protein coupled receptors (GPCRs), transporters, ion channels, protein kinases, and other enzymes. Compounds screened by the MLSCN are maintained within the Small Molecule Repository (http://mlsmr.glpg.com/) that was established in 2004 and currently has a set of approximately 300,000 compounds of specified purity, quantity, and solubility. Data generated by the MLSCN centers including assay descriptions, chemical structures, and results for individual compounds is stored in a publicly accessible database maintained by the National Library of Medicine (PubChem, http://pubchem.ncbi.nlm.nih.gov/). Investigators may access the MLSCN resources through the submission of assays for optimization and HTS development, by submitting compounds into the Small Molecule Repository for screening, and through PubChem. For more information on this effort, see recent review.[10]

NIH-RAID (Rapid Access to Interventional Development) is an NIH Roadmap Pilot program intended to reduce some of the common barriers between laboratory discoveries and clinical trails of new therapeutic entities (http://nihroadmap.nih.gov/raid/). The goal of the NIH-RAID Pilot is to make available, on a competitive basis, certain critical resources needed for the development of new small molecule therapeutic agents. Potentially available services by the NIH-RAID program include production, bulk supply, GMP manufacturing, formulation, development of an assay suitable for pharmacokinetic testing, and animal toxicology. The NIH-RAID Pilot is not a grant program. The funds to support individual projects are provided by Roadmap funds and individual Institutes. NIH-RAID projects of interest to the NIMH involve the development of novel small molecule therapeutics for mental disorders.

NIMH Initiatives Supporting Drug Discovery and Target Identification

The NIMH complements support of investigator-initiated grants in the area of treatment research through specific initiatives developed to stimulate and facilitate drug discovery and development efforts. These initiatives are intended to encourage investigators interested in developing new therapeutics or novel ways to test candidate compounds, including new assays or model systems to evaluate potential efficacy and utility in the treatment of mental disorders. The initiatives span the breadth of the drug development process, from target identification and ligand discovery, to preclinical development and clinical testing, through effectiveness trials.

Preclinical CNS Drug Discovery

To maximize the potential for translating basic molecular science into treatment and tool discoveries, the NIMH created this initiative specifically to encourage the submission of applications aimed at drug discovery and early preclinical testing of compounds with therapeutic potential (http://grants.nih.gov/grants/guide/pa-files/PAR-07–048.html). The initiative encourages studies aimed at design, synthesis, and preclinical testing of compounds, development of novel delivery systems, and cell-based assays for screening of candidate compounds for efficacy and/or toxicity. The announcement also encourages the development of novel assays using model organisms or behavioral systems for preliminary screening or further evaluation of candidate compounds, including *in vivo* models that emulate critical features of specific CNS disorders. Model development must be directed toward assessing potential efficacy rather than elucidating disease mechanisms. Applications submitted in response to this announcement are directed to a Drug Discovery Special Emphasis Review Panel convened by the Center for Scientific Review.

PET and SPECT Ligand Imaging

This initiative encourages applications aimed at developing novel radioligands for positron emission tomography (PET) or single photon emission computed tomography (SPECT) imaging in human brain, and that incorporate pilot or clinical feasibility evaluation in preclinical studies, model development, or clinical studies. The long-term goal of this initiative is to facilitate the broad application of neuroimaging probes in pathophysiological studies, drug discovery/development research, and in biomarker development/qualification studies as quantifiable indicators of disease progression and treatment efficacy (http://grants.nih.gov/grants/guide/pa-files/PA-06–461.html).

Small Business Innovation Research (SBIR)

Small businesses play an increasingly important role in drug discovery and development (http://www.nimh.nih.gov/research-funding/small-business/index.shtml). The NIMH supports small business involvement in drug discovery through the publication of several targeted initiatives that support the development of novel pharmacologic treatments for mental disorders (http://grants.nih.gov/grants/guide/pa-files/PA-06-027.html), including novel screening assays from molecular/cellular screens to whole animal tests, the commercial development of novel radioligands for PET and SPECT imaging in human brain (http://grants.nih.gov/grants/guide/pa-files/PA-06-017.html), the development of biomarkers, and high throughput tools for brain research at any level of analysis from molecules through behavior (http://www.nimh.nih.gov/research-funding/small-business/index.shtml).

Developmental Psychopharmacology

Developmental psychopharmacology solicits applications to examine the neurobiological impact of psychotherapeutic medications upon the immature brain. Investigations in model organisms that examine molecular, genetic, neurochemical, physiological, and behavioral effects of early drug administration in both juvenile and adolescent animals are encouraged (http://grants.nih.gov/grants/guide/pa-files/PA-07-084.html).

Neurodevelopmental and Neuroendocrine Signaling in Adolescence: Relevance to Mental Health

This program encourages submission of applications aimed at the identification of neurodevelopmental and neuroendocrine mechanisms that impact emotional and cognitive development and emerging psychopathology during adolescence, using animal models and human studies (http://grants1.nih.gov/grants/guide/pa-files/PA-07-208.html).

Women's Mental Health and Sex/Gender Differences Research

This program invites applications targeting the development of models to examine sex differences and the impact of hormonal transitions across the lifespan of females on brain physiology and function, including, for example, neural plasticity, cognition, and mood (http://grants.nih.gov/grants/guide/pa-files/PA-07-164.html).

Women's Mental Health in Pregnancy and the Postpartum Period

Women's mental health in pregnancy and the postpartum period encourages the development of appropriate models of the peripartum period combining genetic and environmental influences on postpartum hormonal status, emotionality, and/or maternal behavior, which will be essential for understanding the neurobiology of perinatal mood disorders (http://grants.nih.gov/grants/guide/pa-files/PA-07-081.html).

Functional Links Between the Immune System, Brain Function and Behavior

This program targets the development and refinement of animal models of immune signaling in brain, including models examining the effects of pre- and post-natal infection on brain development and behavior, models of the effects of acute and chronic immune challenge on brain function and behavior, and models of the role of the blood–brain barrier in neuroimmune responses (http://grants.nih.gov/grants/guide/pa-files/PA-07-088.html).

NIMH Initiatives for Drug Development: Preclinical, First in Human, and Clinical Studies

The NIMH participates in several large grant and cooperative agreement mechanisms aimed at fostering partnerships between NIMH, academia, and industry to advance the development and testing of fundamentally new, rationally designed medications, and treatments for mental disorders. These initiatives provide a vehicle for industry and academic scientists to pool intellectual and material resources for the translation of basic science findings into the conceptualization, discovery, and evaluation of new chemical entities in preclinical, first in human, and proof of concept studies in the treatment of mental disorders. Below are descriptions of translational programs, active in 2007, which have been an effective means for NIMH to assist the academic and private sector efforts to fill the drug discovery pipeline with novel mechanism of action compounds for the treatment of mental disorders.

National Cooperative Drug Discovery Group Program

The goal of the National Cooperative Drug Discovery Group (NCDDG) program (http://grants.nih.gov/grants/guide/pa-files/PAR-07-159.html) is to accelerate innovative

drug discovery, the development of pharmacologic tools for basic and clinical research on mental disorders, drug or alcohol addiction, and the development and validation of models for evaluating novel therapeutics for mental disorders through encouraging scientific collaborations between academia and the private sector. The NIMH supports NCDDG studies of molecular targets in two or more of the following areas:

1. ligand discovery for therapeutics development and as research tools (e.g., imaging probes) for novel molecular targets implicated in mental illnesses;
2. preclinical testing of novel compounds in disease-based models;
3. development and validation of novel, disease-based genetic models combined with environmental or behavioral manipulations for evaluating therapeutic compounds;
4. initial Good Laboratory Practice (GLP) toxicology, safety pharmacology, and pharmacokinetics to support IND application to the FDA to begin human clinical testing; and/or
5. limited Phase I studies.

The program also supports the goal of developing and evaluating new cellular, circuit, genetic, or pathophysiology based models for validation of novel targets for mental disorders.

Cooperative Drug Development Group

As with the NCDDG, grants funded under the Cooperative Drug Development Group (CDDG) program are intended to foster long-term partnerships between NIMH, academia, and industry aimed at advancing the development and testing of new medications and treatments for serious mental disorders (http://grants1.nih.gov/grants/guide/pa-files/PAR-05-010.html). However, in contrast with the NCDDG, which is aimed at more preclinical discovery, the principal aim of the CDDG program has been the testing in humans of novel mechanism therapeutics, with testing of new IND-ready pharmacological agents or approved agents in clinical populations as a mandatory element. As such, the grants funded under the CDDG program help fill the gap between preclinical drug discovery efforts and clinical effectiveness trials networks also supported by the NIMH.

Centers for Intervention Development and Applied Research

The Centers for Intervention Development and Applied Research (CIDAR) program encourages interdisciplinary teams of leading basic, applied, and clinical investigators to engage in a focused research program targeting a specific problem in the diagnosis or treatment of mental illness. The program focuses on research to (1) define predictors and understand the mechanism of treatment response in major mental disorders; (2) create and refine biomarkers to assess the presence and/or extent of mental illness; and/or (3) hasten the development of novel treatments for mental disorders. The goal of CIDAR is to support the translation of basic and clinical research into innovations in clinical assessment and therapeutics (this program is currently not accepting new applications).

FACILITATING THE DEVELOPMENT AND EVALUATION OF PRECLINICAL MODELS FOR THERAPEUTIC DISCOVERY

Many of the programs and initiatives described above incorporate within them requests for the development of novel models capable of reliably detecting clinical efficacy of new mechanism of action compounds. Not included in this list are previous targeted and time-limited funding initiatives. For example, a specific request for applications was issued in 2003 to request proposals aimed at developing new models relevant to bipolar disorder, based on the recognized need in this difficult to study area. It is too early to assess the success of this specific request. In general, the success of such initiatives is likely to depend on the state of both clinical and basic research at the time of the request and the ability to translate information into relevant neurobiological questions. Through support of a strong portfolio of basic neuroscience research and efforts aimed at increasing the communication between clinical and basic researchers, the NIMH is well poised to translate novel clinical neuroscience findings toward the development of novel models.

Workshops Addressing Barriers in Treatment Development

The NIMH has conducted several workshops and workgroups to evaluate the status of preclinical models as used for understanding psychopathology and for novel treatment development.[9] These workgroups customarily task groups of clinical and basic researchers to identify areas of opportunity with maximal traction for expanding bidirectional translational work toward the development of novel, biologically based models for understanding psychopathology, and for assessing novel therapeutics. Common themes expressed during these workshops include the need to develop parallel measures in model systems that emulate core deficits in mental disorders, the value of identifying appropriate quantifiable behavioral and physiological cross-species measures to assess key neurobiological deficits, the need to expand basic neurobiological studies of circuits contributing to pathology, and complementary efforts to determine how and when specific susceptibility factors contribute to the etiology of specific disorders and the expression of symptoms.

IDENTIFICATION OF KEY MEASURES OF CLINICAL EFFICACY: THE EXAMPLE OF COGNITIVE DEFICITS IN SCHIZOPHRENIA

Assessment of the usefulness of new models and screens for testing potential therapeutics is typically based on the ability of the new model to identify medications having efficacy for treating disorders (predictive validity). However, this approach is not available in drug discovery for new indications where effective treatments are not yet available. For example, while currently available models may sufficiently identify treatments for psychotic symptoms of schizophrenia, other areas of deficit that significantly impact function are only beginning to be modeled for treatment development.

Cognitive deficits are core and enduring features of schizophrenia and the extent of cognitive deficits is considered a key predictor of outcome and quality of life for patients with schizophrenia. Unfortunately, existing antipsychotic medications are

relatively ineffective in improving cognitive function, strongly indicating the need for new mechanism of action drugs targeting these deficits. The programs elaborated below are examples of collaborative efforts focusing on this problem and involving broad participation of NIMH, FDA, academia, and the pharmaceutical/biotechnology sector. This model approach could be applied to identify clinical targets in other disease areas where broad input is needed, such as social cognition in autism, impulse control in ADHD or bipolar disorder, or anhedonia and sleep disturbances in mood disorders.

Measurement and Treatment Research to Improve Cognition in Schizophrenia

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) program was designed by the NIMH to support the development of pharmacological agents for improving the neurocognitive impairments that are a core feature of schizophrenia (http://www.matrics.ucla.edu/). The goals of the NIMH MATRICS program were to catalyze regulatory acceptance of cognition in schizophrenia as a target for drug registration, promote development of novel compounds to enhance cognition in schizophrenia, leverage economic research power of industry to focus on important but neglected clinical targets, and identify lead compounds that support proof of concept trials for cognitive enhancement in schizophrenia. A series of conferences were held as part of the MATRICS process to assess what is known about cognitive deficits in schizophrenia, develop a consensus on the promising targets for intervention and the most promising models (animal and human) for use in drug development for this indication, identify a core battery of cognitive assessment tests, and identify the most appropriate clinical trials design. These conferences included participants from NIMH, the FDA, academia, and industry. The major outcome of these conferences was the identification of key domains of cognitive function that are disrupted in schizophrenia and the development of a consensus test battery to assess those domains for use in clinical trials of procognitive medications for schizophrenia. For a recent review of the program and targets for cognitive enhancement in schizophrenia, see[11–14].

NIMH Workshops on Developing Assessment Tools for Cognitive Functioning

NIMH has recently supported a new series of workshops as a continuation of MATRICS. The goal of these workshops is to develop measures for use in clinical trials further. The current clinical tests used to assess cognition in schizophrenic patients and the effects of therapeutics on ameliorating cognitive deficits were developed before basic research in cognitive neuroscience identified specific neural circuits and systems potentially involved in cognitive processes. Cognitive neuroscientists have developed animal models and testing paradigms that tap into the basic neural mechanisms believed to underlie cognition; however, these paradigms have not, for the most part, been used in the drug development process and have not been translated to the clinical setting. The workshops are intended to help develop tests that are more specific measures of brain functions related to cognitive function in schizophrenia and to assure that these measures are validated for use in clinical trials.

Treatment Units for Research on Neurocognition and Schizophrenia

The Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) initiative is another component of the NIMH effort to stimulate academic and industry sponsored research focused on cognitive deficits in schizophrenia. It follows completion of MATRICS described above (http://www.turns.ucla.edu/). The TURNS program is an NIMH-supported network that provides an infrastructure for clinical studies of pharmacological agents for enhancing neurocognition in patients with schizophrenia. The TURNS clinical research network evaluates the safety, efficacy, pharmacokinetics, and pharmacodynamics of new agents for the treatment of cognitive deficits of schizophrenia. The TURNS program also aims to further characterize and define key aspects of cognition in schizophrenia as potential treatment targets.[ii]

FUTURE OPPORTUNITIES FOR MODEL DISCOVERY

The NIMH has adapted a broad strategy of support ranging from basic neuroscience through clinical research toward the goal of improving outcomes for individuals with mental disorders. This includes the recognized need to identify model systems and measures that more closely predict clinical benefit or adverse effects of new drug entities for the treatment of mental disorders. Below are some areas of promise and opportunity for facilitating this effort.

Development of Biomarkers for Mental Disorders

As previously discussed, the greatest impediment in the development of reliable animal models for drug discovery relevant to psychiatric disorders is the inherent discontinuity between models and the use of imprecise diagnostic methods that are not based on the neurobiology of the disorders. The development of endophenotypes or biomarkers that reliably identify individuals with specific deficits is expected to be a major advance for both clinical research and treatment development. The biomarkers may arise from efforts to develop well-defined psychometric measures, neuroimaging, genetics, proteomics, and other approaches supported through NIMH. In addition, the Foundation for NIH, a non-profit organization that complements NIH efforts, recently announced support for an extension of the NIMH-supported STAR*D depression trials to identify biomarkers associated with effective treatment response (Whole Genome Association in Major Depressive Disorder: Identifying Genomic Biomarkers for Treatment Response; WGA), through the Biomarkers Consortium (http://www.fnih.org/news/news_events_Oct.shtml).[iii]

[ii] Please refer to Jones *et al.*, Developing new drugs for schizophrenia: From animals to the clinic, in this volume for further discussion on modeling cognitive disorders in schizophrenia as well as the MATRICS and TURNS initiatives.

[iii] For more information about the Biomarkers Consortium, see http://www.fnih.org/Biomarkers%20Consortium/Biomarkers_home.shtml.

Modeling Genetic, Developmental, and Environmental Risk Factors

Additional large efforts to identify genes associated with mental disorders are being supported by NIH and other agencies. For example, through the Autism Consortium, NIH is supporting studies aimed at identifying genes associated with autism spectrum disorders (http://www.nimh.nih.gov/press/autismconsortiumgrants.cfm). NIH funds whole genome association studies to identify genetic factors influencing risk for complex diseases in order to facilitate discovery of new molecular targets for prevention, diagnosis, and treatment through the Genetic Association Information Network (GAIN, http://www.fnih.org/GAIN/GAIN_home.shtml) and genotyping and other genomic research methodologies to identify the major susceptibility and etiologic factors for complex diseases of significant public health impact through the Genes and Environment Initiative (GEI, http://www.genome.gov/19518663). These efforts are complimentary to private efforts. For example, the Broad Institute of MIT and Harvard University recently announced the application of a sizable gift fund from the Stanley Medical foundation primarily to identify and characterize risk genes for psychiatric diseases through linkage and association studies in the human population, with additional efforts to develop animal and cellular models to investigate the function of candidate genes and pathways, to develop sophisticated imaging techniques for elucidating brain-based phenotypes in clinical disease, and to design high throughput chemical screens for identifying molecules that modulate important cellular targets related to neural function (see http://www.broad.mit.edu/psych/).

Functional genomics approaches are beginning to identify risk factors in humans that may offer valuable insights into the molecular, cellular, and systems-level pathogenesis of mental disorders and potentially new targets for therapeutic development. Translational strategies such as a convergent functional genomics approach used by Le-Niculescu and colleagues[15] to identify schizophrenia candidate genes by integration of brain gene expression data from pharmacogenetic mouse models with human genetic linkage and postmortem brain data hold promise for identifying risk alleles in other mental disorders. As results of genetic studies in clinical populations begin to identify potential risk factors, it will be important to follow up these results with functional studies in basic neurobiological systems to identify how identified genes impact brain function. In addition, as we discover risk genes in humans we may, by the creation of transgenic mice, expressing one or more human risk alleles, begin to understand how disease-associated gene alterations impact brain signaling within circuits contributing to the core symptoms of mental disorders and use this information to develop at least partial animals models of pathology. Understanding where, when, and how these genes affect normal brain function will likely lead to new model systems, perhaps even cell-based models, that may be applied toward the development and testing of new potential therapeutics in an efficient manner.

Genetic analysis of behavioral domains is another example of a promising approach to develop models of genetic, developmental, and environmental risk factors for psychiatric disorders. The behavioral domain approach of Kas and colleagues[16] focuses on understanding the genetics of naturally occurring behaviors such as social interaction, appetitive motivation, activity, and cognitive function that cut across DSM-IV diagnostic boundaries of mental disorders. The approach depends on conserved gene function, the

presence of functional polymorphism(s) in the gene or set of genes across species, and is critically dependent on the choice of an analogous phenotype in both humans and the model species. The combined use of genetically tractable model organisms and behavioral measures of disease domains will be crucial to understanding the mechanisms by which gene–environment, genotype–phenotype relationships, and gene-by-sex interactions influence susceptibility to mental disorders.

MODELING KEY DEFICITS IN MENTAL DISORDERS

Mental disorders are heterogeneous, with significant differences in the patterns of emotional, cognitive, and physiological symptoms that may be present in affected individuals as well as age of onset and precipitating factors. Focused efforts aimed at identifying core deficits of these disorders, such as the MATRICS and TURNS initiatives described above, serve as a model for programs aimed at exploring new opportunities for targeting endophenotypes or key symptoms as therapeutic targets.These initiatives encourage greater collaboration between clinical researchers and basic scientists toward identification of areas for targeting treatment development and assessment of efficacy.

APPLICATION OF DATA-MINING TECHNOLOGY IN MODEL EVALUATION AND DRUG DISCOVERY

While novel pharmacological treatments have not yet been approved for treating mental disorders, several new mechanism of action compounds are in the pipeline for potential drug discovery for major mental disorders targeting, for example, NMDA, GABA, and peptide systems.[12,17] Early trials of novel compounds will present an opportunity to evaluate the predictive validity of existing preclinical models for their potential to identify new mechanism of action drugs. Informatics efforts linking results of preclinical tests with clinical effectiveness for promising new treatments in trials could illuminate which currently used models best predict efficacy, and could also elaborate the clinical characteristics or patient populations with the greatest treatment response. Success of this type of endeavor would require increased communication and sharing of preclinical data between industry, academia, and government motivated by the understanding that such data could ultimately reduce the time and cost of bringing new drugs to market. Furthermore, as efforts such as the NIH Molecular Libraries continue to collect data on the chemical structure and functional activity of a broad range of small molecules, they are creating a large searchable database (PubChem) that links structure to functional assay analyses. These databases may suggest not only new lead structures for drug development but may also identify structures conferring potential adverse effects. For example, recent evaluation of drugs inducing valvular heart dysfunction revealed common binding of a diverse series of drugs with this effect on serotonin 5-HT_{2B} receptors suggesting that activity of a new chemical entity at this receptor might be a strong indicator of an adverse effect on heart function.[18]

CONCLUSIONS

The NIMH encourages the development and refinement of preclinical models through investigator-initiated research support and by targeted efforts addressing the need for novel mechanism of action treatments. The potential for success in developing new models that reliably predict clinical efficacy or adverse effects relies ultimately on improvements in both clinical evaluation and the application of basic science toward translational boundaries. Communication between clinicians and clinical and basic neuroscientists is essential for this synthesis. Support for basic science is critical for understanding the underlying biological mechanisms and functional significance of newly identified clinical indicators (e.g., genetic, neuroimaging) of risk, pathology, or treatment response. As pathways are identified and linked, new molecular and cellular targets for treatment development are likely to emerge from this translational discovery science. These discoveries will need to be adapted into cellular, circuit-based, physiological, and/or behavioral models to allow screening and efficacy testing of candidate therapeutic compounds. Similarly, the identification of core deficits in psychiatric disorders with significant negative impact on the health and functioning of patients, such as the recognition of cognitive deficits as a treatment development target in schizophrenia, also has potential to improve the predictive validity of preclinical models. Efforts to increase the concordance between the measures of the clinical condition and the models will likely improve the utility of models for identifying truly novel medications.

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