

Animal and Translational Models for CNS Drug Discovery

VOLUME 1

Psychiatric Disorders



EDITED BY Robert A. McArthur • Franco Borsini



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VOLUME I
Psychiatric Disorders

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This book is dedicated to that happy band of behavioral pharmacologists who over the generations have occasionally seen their compound progress into clinical development, and more rarely still seen it used to treat patients. New skills are being learned and new species creeping into the lab, including the ones “without tails.” These offer new opportunities and challenges, but equally so greater satisfaction working at the interface. May all your compounds be winners!

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What Do *You* Mean by “Translational Research”? An Enquiry Through Animal and Translational Models for CNS Drug Discovery: Psychiatric Disorders

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In the 50-odd years since the introduction of clinically effective medications for the treatment of behavioral disorders such as depression,¹ anxiety² or schizophrenia³ there has recently been growing unease with a seeming lack of substantive progress in the development of truly innovative and effective drugs for behavioral disorders; an unease indicated by escalating research and development expenditure associated with diminishing returns (e.g.,⁴ and discussed by Hunter⁵ in this book series). There are a number of reasons that may account for this lack of new drugs for CNS disorders (cf.,⁶), but according to the US Food and Drug Administration's (FDA) white paper on prospects for 21st century drug discovery and development,⁷ one of the main causes for failure in the clinic is the discrepancy between positive outcomes of candidate drugs in animal models and apparent lack of efficacy in humans, that is, the predictive validity of animal models. Consequently, there have been a number of initiatives from the US National Institutes of Health (NIH) (<http://nihroadmap.nih.gov/>) and The European Medicines Agency (EMA),⁸ to bring interested parties from Academia and Industry together to discuss, examine and suggest ways of improving animal models of behavioral disorders.⁹⁻¹⁴ The value of NIH-supported initiatives, even to the point of participating directly in drug discovery from screening to registration is not to be underestimated, as evidenced by the successful registration of buprenorphine (Subutex®) and buprenorphine/naloxone (Suboxone®) by Reckitt-Benckiser in collaboration with the National Institute on Drug Abuse (¹⁵see also¹⁶).ⁱ

Translational research and experimental medicine are closely related activities that have evolved in answer to the need of improving the attrition rate of novel drugs between the preclinical and clinical stage of development.^{5,19-22} In general, translational research defines the *process* through which information and insights flow from clinical observations to refine the development of animal models *as well as* the complementary flow of information and insights gained from animal models to the clinical

ⁱFor a comprehensive discussion of NIH-sponsored initiatives and collaborations and opportunities, please refer to Winsky and colleagues¹⁷ and Jones and colleagues¹⁸ for specifics on NIH-Academic-Industrial collaborations in schizophrenia.

setting, be it through improved diagnosis, disease management or treatment; including pharmacological treatment.²³ Experimental medicine, in terms of drug discovery, refers to studies in human volunteers to (1) obtain mechanistic and pharmacological information of compounds entering into development, (2) explore and define biological markers with which the state and progress of a disorder can be monitored, as well as the effects of pharmacological interventions on its progress and (3) establish models and procedures with which to obtain initial signals of efficacy test.^{5,15,22} Though claimed as an innovative paradigm shift, translational research nevertheless, is not a new concept, as pointed out by Millan in this book series.²⁴ The origins of psychopharmacology abound with numerous examples of how pharmaceutical or medicinal chemists interacted directly with their clinical colleagues to “test their white powder”, or clinicians who would knock at the chemists’ door for anything new. Kuhn and Domenjoz, for example, describes the initial “Phase II” trials of the novel “sleeping pill” forerunner of imipramine.^{25,26} Paul Janssen tells how the observation of the paranoid schizophrenia-like hallucinations experienced by cyclists who were consuming amphetamine to stay alert, led him to search for better amphetamine antagonists, one of which was haloperidol. This compound was subsequently given to a young lad in the midst of a psychotic episode by a local psychiatrist with good results.²⁷ Though largely overtaken in sales and prescription rates by 2nd generation atypical antipsychotics, Haloperidol (Haldol®) remains one of the standard drugs used in the treatment of schizophrenia.^{18,28,29}

Translational research is a two-way process which, nonetheless can lead to differences in emphasis and agenda. We have gathered a number of definitions from different sources listed in Table 1 below to help us determine what one of our authors asked us to do when he was contacted to contribute to this book project, “What do *you* mean by ‘translational research’?”

These definitions may emphasize the clinical, or top-down approach to translational research,^{20,30} or the bottom-up approach of “bench-to-bedside”.^{21,31} It is clear though, that translational research has a purpose of integrating basic and clinical research for the benefit of the patient in need. While we welcome this as a general definition of translational research, we acknowledge, as do others (e.g.,^{31,32}), that a more pragmatic, working definition is required. Consequently, we define translational research, in the context of drug discovery and research, as the partnership between preclinical and clinical research to align not only “... basic science discoveries into medications”,³¹ but also the information derived from the clinic during the development of those medications. The purpose of this reciprocal definition is to refine the model systems used to understand the disorder by identifying the right targets, interacting with those targets pharmacologically in both animals and humans and monitoring the responses in each throughout a compound’s development (cf.,^{5 and 15}). Central to this definition is the acknowledgement that the etiology of behavioral disorders and their description are too diffuse to attempt to model or simulate in their entirety. Consequently, emphasis must be placed on identifying specific symptoms or core features of the disorder to model, and to define biological as well as behavioral responses as indices of state, changes in state and response to pharmacological treatment. This process is made easier if, at the same time, greater effort is made to identify procedures used to measure these biological and behavioral responses that are consistent within and between species.^{23,24} Brain imaging is one technique that has cross-species consistency (e.g.,^{33,36}), as do various operant conditioning procedures.^{37,38}

Table 1 Selected definitions of translational research

Definition	Reference
Translational medicine may also refer to the wider spectrum of patient-oriented research that embraces innovations in technology and biomedical devices as well as the study of new therapies in clinical trials. It also includes epidemiological and health outcomes research and behavioral studies that can be brought to the bedside or ambulatory setting.	30
... connotes an attempt to bring information that has been confined to the laboratory into the realm of clinical medicine.	
To the extent that clinical studies could be designed to answer such questions (generated by information from the laboratory), they would represent types of translational clinical research.	20
... a two-way street where the drive to cure should be complemented by the pursuit to understand human diseases and their complexities.	21,136
1. Basic science studies which define the biological effects of therapeutics in humans	
2. Investigations in humans which define the biology of disease and provide the scientific foundation for development of new or improved therapies for human disease	
3. Non-human or non-clinical studies conducted with the intent to advance therapies to the clinic or to develop principles for application of therapeutics to human disease	
4. Any clinical trial of a therapy that was initiated based on #1–3 with any endpoint including toxicity and/or efficacy.	M. Sznol cited by ²¹
... research efforts intended to apply advances in basic science to the clinical research setting. For drug discovery and development, the term refers to research intended to progress basic science discoveries into medications.	31
By bringing together top-down and bottom-up approaches, there is potential for a convergence of unifying explanatory constructs relating aetiology to brain dysfunction and treatment.	37,137
... information gathered in animal studies can be translated into clinical relevance and vice versa, thus providing a conceptual basis for developing better drugs.	
... the application of scientific tools and method to drug discovery and development ... taking a pragmatic or operational rather than a definitional approach, a key to a successful translation of non-human research to human clinical trials lies in the choice of biomarkers.	32
... two-way communication between clinical and discovery scientists during the drug development process are likely to help in the development of more relevant, predictive preclinical models and biomarkers, and ultimately a better concordance between preclinical and clinical efficacy.	82

There are at least two aspects of translational research to be considered as a result of the definition proposed above. First is the concept of specific symptoms, or core features of the disorder to model. Attempts to simulate core disturbances in behavior formed the basis of early models of behavioral disorders. McKinney and Bunney, for example, describe how they sought to “translate” the clinically observed changes in human depressed behavior (secondary symptoms) with analogous changes in animals induced by environmental or pharmacological manipulations.³⁹

Whereas modelers have traditionally referred to diagnostic criteria such as DSM-IV⁴⁰ or ICD-10⁴¹ the consensus to be found in this book series and other sources is that these diagnostic criteria do not lend themselves easily to basic or applied research. The etiology of behavioral disorders is unclear, and there is considerable heterogeneity between patients with different disorders but similar symptoms. Nevertheless, attempts to model particular behavioral patterns have been and are being done. Thus, for example, the construct of anhedonia (the loss of ability to derive pleasure), or the construct of social withdrawal, may be diagnostic criteria for a number of behavioral disorders including depression, schizophrenia, as well as a number of other disorders (cf.,⁴²). There is considerable momentum to establish a dimension – rather than diagnostic-based classification or to “deconstruct” syndromes into “symptom-related clusters” that would help guide neurobiological research.^{ii 18,43,44} In order to define these “symptom-based clusters”, however, the symptoms have to be defined. Previously, these were identified as behavioral patterns, though lately they have been referred to variously as behavioral endophenotypes or exophenotypes (e.g.,^{45–49}). It is appropriate here to review the definitions of both. Exophenotype and endophenotypes have been defined by Gottesman and Schields⁵⁰ as:

John and Lewis (1966) introduced the useful distinction between exophenotype (external phenotype) and endophenotype (internal), with the latter only knowable after aid to the naked eye, e.g. a biochemical test or a microscopic examination of chromosome morphology (p. 19).ⁱⁱⁱ

Subsequently, endophenotypes have been more rigorously defined⁵¹ as:

1. *The endophenotype is associated with illness in the population.*
2. *The endophenotype is heritable.*
3. *The endophenotype is primarily state-independent (manifests in an individual whether or not illness is active).*
4. *Within families, endophenotype and illness co-segregate.*
5. *The endophenotype found in affected family members is found in non-affected family members at a higher rate than in the general population. (p. 639)*

ⁱⁱ For reviews of the initiatives deconstructing a complex disorder like schizophrenia, the reader is invited to consult the following 2 issues of *Schizophrenia Bulletin*, where these initiatives are thoroughly discussed: *Schizophr Bull*, 2007, 33:1 and *Schizophr Bull*, 2007, 33:4.

ⁱⁱⁱ See also Tannock *et al.*,⁶¹ for definitions of endophenotypes and biomarkers.

And that "... The number of genes involved in a phenotype is theorized to be directly related to both the complexity of the phenotype and the difficulty of genetic analysis" (*op cit.*, p. 637). On the other hand, exophenotypes have been defined by Holzman⁵² (and others) as:

... the external symptoms of a disorder that clinicians detect during an examination. An endophenotype, on the other hand, is a characteristic that requires special tools, tests, or instruments for detection. (p. 300)

It behooves the unwary researcher to be careful with terminology and thus not fall into the trap of pretending greater accuracy by changing the name of the phenomenon being studied. Finally, to quote Hyman's *caveat*,⁴³

The term "endophenotype" has become popular for describing putatively simpler or at least objectively measurable phenotypes, such as neuropsychological measures that might enhance diagnostic homogeneity. I find this term less than ideal, because it implies that the current diagnostic classification is basically correct, and that all that is lacking is objective markers for these disorders. If, however, the lumping and splitting of symptoms that gave rise to the current classification was in error, then the search for biological correlates of these disorders will not prove fruitful. (p. 729)

The second aspect to be considered in translational research is the concept of biomarkers. Biomarkers are crucial to translational research and serve as the interface between preclinical research, experimental medicine and clinical development. As with endophenotypes above, however, biomarkers also require some discussion. The FDA, NIH, and EMEA have been at the forefront in helping define and establish biomarkers, surrogate markers, and clinical endpoints⁵³⁻⁵⁷ (<http://ospp.od.nih.gov/biomarkers/>); an initiative now being carried out in partnership with private enterprise⁵⁸ (<http://ppp.od.nih.gov/pppinfo/examples.asp>). Lesko and Atkinson have provided summary definitions of various markers that are worth considering:⁵⁵

A synthesis of some proposed working definitions is as follows: (a) biological marker (biomarker) - a physical sign or laboratory measurement that occurs in association with a pathological process and that has putative diagnostic and/or prognostic utility; (b) surrogate endpoint - a biomarker that is intended to serve as a substitute for a clinically meaningful endpoint and is expected to predict the effect of a therapeutic intervention; and (c) clinical endpoint - a clinically meaningful measure of how a patient feels, functions, or survives. The hierarchical distinction between biomarkers and surrogate endpoints is intended to indicate that relatively few biomarkers will meet the stringent criteria that are needed for them to serve as reliable substitutes for clinical endpoints (p. 348).

An important characteristic of biomarkers is that they should also be capable of monitoring disease progression.⁵⁴ It is interesting more over that the establishment of biomarkers should also be subject to the same concepts of validity as defined by Willner initially for models of behavioral disorders, that is, face, construct and predictive validity.⁵⁹ Lesko and Atkinson further indicate that biomarkers must be evaluated and validated for (1) clinical relevance (face validity in being able to reflect

physiologic/pathologic processes), (2) sensitivity and specificity (construct validity that it is capable to measure changes through a given mechanism in a target population) and (3) must ultimately be validated in terms of clinical change, that is, predictive validity. Biomarkers also have other criteria that they need to fulfill such as: their accuracy, precision and reproducibility; an estimated rate of false positive and false negative probability; and practicality and simplicity of use. In addition, pharmacological isomorphism is used to establish a biomarker's predictive validity where response to a known clinically effective standard is ultimately required, especially if drugs of different mechanisms of action produce the same response in the biomarker. These criteria are very familiar to the animal modeler and highlight the shared interests and expertise that the preclinical researcher brings to the clinical arena. Biomarkers for behavioral disorders thus share many of the problems inherent to their animal models.⁶⁰ Nevertheless, it is among the most active pursuits in Pharma today (*cf.*,⁶¹⁻⁷⁰).

It is clear from the previous discussion that translational research demands the combined efforts of a number of participants, each of which contributes a particular expertise to achieve a common goal. Translational research cannot be done effectively using the “tried and true” process of compartmentalization prevalent up to the end of the last century, that is, the splitting of R from D, or maintaining the preclinical from clinical, academic from industrial divides. For the past decade Pharma has fostered cross-disciplinary collaboration with the creation of Project teams in which participants from preclinical, clinical and marketing sections of the Industry are brought together in relation to the maturity of the Project. The concept of “pitching the compound over the fence” is no longer tolerated, and preclinical participation even in mature Projects is expected. This creates a much more stimulating environment for all the participants, who not only learn from the experiences of others, but also maintain a sense of ownership even when their particular expertise is no longer required for a Project's core activities. Nevertheless, creation of and participation in Project teams is not always an easy task as group dynamics evolve. Team members are assigned to a Project by line managers, and can be removed depending on priorities. Some team members contribute more than their share, while others coast. The skills of the Project Leader must go beyond scientific expertise in order to forge an effective team and deliver a successful drug.

The use of animal models is an essential step in the drug discovery and indeed the translational research process. Use of appropriate models can minimize the number of drug candidates that later fail in human trials by accurately predicting the pharmacokinetic and dynamic (PK/PD) characteristics, efficacy and the toxicity of each compound. Selection of the appropriate models is critical to the process. Primary diseases such as those caused by infections, genetic disorders or cancers are less problematic to model using both *in vitro* and *in vivo* techniques. Similarly some aspects of degenerative diseases have also been successfully modeled. However, modeling of disorders with a strong behavioral component has been less successful. This is not to say that there are no models for various aspects of these disorders. Many models have been proposed, validated pharmacologically with standard, clinically effective drugs and extensively reviewed. Indeed, these models have become so standardized that their use to characterize mechanisms of action and lead novel compounds in CNS drug discovery projects is mandatory, and positive outcomes are required before these

compounds are considered for further development. However, it has become clear that positive outcome in these models is no guarantee that these new compounds will be efficacious medicines in humans. Refinements of existing models and development of new models relevant to drug discovery and clinical outcome are being pursued and documented (e.g.,⁷¹⁻⁷⁴). Advancements in genetic aspects of disease are also being aided through the development and use of genetically modified animals as model systems. However, even though these techniques are more precise in modeling aspects of a disease such as amyloid overexpression in Alzheimer's disease, the ability of procedures used to assess the changes in behavior, and relating them to altered human behavior remains uncertain.

Books on animal models of psychiatric and neurological diseases have tended to be compendia of so-called "standard" procedures developed over the years. Some of these books have formed part of classic reference texts for behavioral pharmacologists (e.g.,^{75,76}). Others – more pragmatic in their approach – describe the application of these models and are useful as "cookbook" manuals (e.g.,^{77,78}), while yet others have been very specific in their focus; for example, books entirely with models for a particular disorder, for example, depression or schizophrenia. It could be argued, however, that these books address a very circumscribed audience, and need not be necessarily so. Clinicians might and do claim that animal models are intellectually interesting, but of no relevance to their daily work of (1) demonstrating proof of concept, (2) showing efficacy or (3) treating their patients. Nevertheless, clinicians are constantly on the watch for potentially new pharmacological treatments with which to treat their patients, for example, new chemical entities that have reached their notice following extensive profiling in animal models. Academics develop a number of procedures or models to help them study neural substrates and disorders of behavior, and may use pharmacological compounds as tools to dissect behavior. The industrial scientist is charged with the application of these methods and models, establishing them in the lab at the request of the Project team and Leader. There is thus a shared interest in the development, use and ability of animal models to reflect the state of a disorder and predict changes in state following pharmacological manipulation. This shared interest has generated much collaboration between academics, clinicians and the industry (cf.,⁷⁹).

Paradoxically in view of shared interest, close ties and general agreement on the need for bidirectional communication, the integration of the perspective and experience of the participants in the drug discovery and development process is not always apparent and is a source of concern (e.g.,^{6,21,31,32,80-82}). Although we do not necessarily agree entirely with Horrobin's description of biomedical research scientists as latter day Castalians,⁸⁰ we suggest that there is a certain truth to the allusion that considerable segregation between the academic, clinician and industrial researcher exists (see also^{21,81}). There have been numerous attempts to break down these barriers, such as having parallel sessions at conferences, or disorder-specific workshops organized by leading academics, clinicians and industrial scientists (e.g., *op. cit.*,⁸³). With few exceptions, however, academics will talk to academics, clinicians to clinicians and industrial scientists will talk to either academics or clinicians; depending on at which stage their Project is. Willner's influential book,⁸⁴ *"Behavioral Models in Psychopharmacology: Theoretical, Industrial and Clinical Perspectives"* represents one of the first published

attempts that brings together academics, pharmaceutical researchers and clinicians to discuss the various aspects of the animal models of behavioral disorders. Yet even in Willner's book with alternating chapters expounding the academic, industrial and clinical perspective on a subject, the temptation is always to go to the “more interesting”, that is, directly relevant chapter and leave the others for later.

This three volume book series aims to bring objective and reasoned discussion of the relative utility of animal models to all participants in the process of discovery and development of new pharmaceuticals for the treatment of disorders with a strong behavioral component, that is, clearly psychiatric and reward deficits, but also neurodegenerative disorders in which changes in cognitive ability and mood are important characteristics. Participants include the applied research scientists in the Pharma industry as well as academics who carry out animal research, academic and industry clinicians involved in various aspects of clinical development, government officials and scientists setting funding priorities, and industrial, academic and clinical opinion leaders, who very clearly influence and help shape the decisions determining what therapeutic areas and molecular targets are to be pursued (or dropped) by Pharma. Rather than a catalog of existing animal models of behavioral disorders, the chapters of the book series seek to explore the role of these models within CNS drug discovery and development from the shared perspective of these participants in order to move beyond the concept of animal behavioral assays or “gut baths”,^{85,86} to stimulate the development of animal models to support present research of the genetic basis of behavioral disorders and to improve the ability to translate findings and concepts between animal research and clinical therapeutics.

As indicated, the aim and scope of this book series has been to examine the contribution of the animal models of behavioral disorders to the process of CNS drug discovery and development rather than a simple compendium of techniques and methods. This book goes beyond the traditional models book published in that it is more a considered review of *how* animal models of behavioral disorders are used rather than *what* they are. In order to achieve this goal, leading preclinical and clinical investigators from both Industry and Academia involved in translational research were identified and asked to participate in the Project. First, a single author was asked to write an introductory chapter explaining the role of animal and translational models for CNS drug discovery from their particular perspective. Each volume thus starts with an industry perspective from a senior Pharma research executive, which sets a framework. Considering the prominent role assumed by Governmental agencies such as the FDA or NIH in fostering translational research, NIH authors were asked to discuss animal and translational models from the perspective of the Government. A leading academic author was contacted to provide a general theoretical framework of how animal and translational models are evolving to provide the tools for the study of the neural substrates of behavior and how more efficient CNS drug discovery may be fostered. Finally, leading clinicians involved in the changing environment of clinical trial conductance and design were asked to discuss how issues in clinical trial design and conductance have affected the development and registration of CNS drugs in their area of specialty, and how changes are likely to affect future clinical trials.

Following these 4 introductory chapters, there are therapeutic area chapters in which a working party of at least 3 (industrial preclinical, academic and clinical) authors were identified and asked to write a consensual chapter that reflects the view

of the role of animal models in CNS translational research and drug development in their area of expertise. We deliberately created our chapter teams with participants who had not necessarily worked together before. This was done for three reasons. First, we were anxious to avoid establishing teams with participants who had already evolved a conceptual framework *a priori*. Second, we felt that by forcing people to “brainstorm” and develop new ideas and concepts would be more stimulating both for the participants and the readers. Thirdly, we wanted to simulate the conditions of the creation of an industrial Project team, where participants need not know each other initially or indeed may not even like each other, but who are all committed to achieving the goals set out by consensus. We sought to draw upon the experiences of industrial and academic preclinical and clinical investigators who are actively involved in CNS drug discovery and development, as well as translational research. These therapeutic chapter teams have contributed very exciting chapters reflecting the state of animal models used in drug discovery in their therapeutic areas, and their changing roles in translational research. For many, this has been a challenging and exhilarating experience, forcing a paradigm shift from how they have normally worked. For some teams, the experience has been a challenge for the same reason. One is used to write for one’s audience and usually on topics with which one is comfortable. For some authors, it was not easy to be asked to write with other equally strong personalities with different perspectives, and then to allow someone else to integrate this work into a consensual chapter. Indeed, some therapeutic area chapter teams were not able to establish an effective team. As a consequence, not all the therapeutic areas envisioned to be covered initially in this Project were possible. Nevertheless, as translational research becomes more established, what appears to be a novel and unusual way of working will become the norm for the benefit not only of science, but for the patient in need.

VOLUME OVERVIEW AND CHAPTER SYNOPSES

This volume comprises contributions by different authors on some psychiatric disorders, such as depression, bipolar disorders, anxiety, schizophrenia, attention deficit hyperactivity disorder (ADHD), autistic spectrum disorders (ASD), obsessive-compulsive disorders (OCD) and sleep disorders. A common theme that emerges from all of these chapters is the role played by stress, changes in the hypothalamic-pituitary-adrenal axis (HPA), and how the brain adapts to chronic stress through the process of allostasis (*cf.*,⁸⁷⁻⁸⁹ and discussed more in detail by Koob in Volume 3, Reward Deficit Disorders of this book series⁹⁰). Response to chronic stress and vulnerability to stress mediated by neurodevelopmental insults are key risk factors inherent in psychiatric disorders. As discussed above, dissatisfaction with DSM-IV or ICD-10 is leading to the “deconstruction” of syndromes and the classification of behavioral disorders in terms of clusters of symptoms, or phenotypes,⁴³ each of which are amenable to investigation. This shift away from viewing behavioral disorders as discrete syndromes has very much produced a conceptual change of viewing animal models from the traditional and unrealistic “of” to “for”.^{17,19,24,91} This is not only an important semantic change of emphasis, but one that (1) limits the expectations from positive results in one or more procedures or models to global changes in a heterogeneous patient population,^{19,92}

(2) aligns academic, industrial and clinical uses of models to study the neurobiology of behavioral disorders,^{18,61} and how new chemical entities and biological interact at a systems level to modulate those behaviors (e.g.,^{5,17,24,93–97}).

Millan describes the issues regarding discovery and development of pharmacotherapy from an industrial point of view. While the development and implementation of animal models for aspects of abnormal behavior is crucial, this is not the only area in which animal models intervene in the drug discovery process. He discusses the importance of pharmacokinetic/pharmacodynamic approaches in defining the relationship drug exposure/drug effect, concluding that it is very difficult to define “therapeutic” doses of psychotropic drugs early in their pharmacological characterization. Correct PK/PD assessment in humans is crucial to determine whether the compound is present at the right receptors at a concentration sufficient to have the desired effect (see also^{5,91,97–99} for further discussion on this theme). The author also points to the fact that there is a dearth of information on experiments addressing the consequences of stopping treatment, drug switching, drug combinations, comorbidity, and those with respect to age and gender. In addition to allostatic responses to chronic stress, Millan introduces the concept of epigenetics (*cf.*,^{100,101}), which is later taken up by Jones *et al.*¹⁸ and by Doran and colleagues.⁹⁶ Millan discusses epigenetic mechanisms, such as histone acetylation and methylation, meiotic imprinting, and how these can modify gene expression and could have behavioral consequences across generations. Brain imaging is far and beyond the most effective translational technique that is being used extensively in early development. This is, however, a very expensive technique, a factor that must be kept in mind. Notwithstanding the problems of adapting imaging techniques to animals, we can expect to see further developments in the future. Millan points to the fact that, in addition to animal models, complementary procedures (biochemical, electrophysiological, etc.) are necessary to validate models, targets and drugs, and points out that the true “predictive validity” of models really has not been put to the full test until a clinically effective drug; working through a novel mechanism is described. Finally, Millan introduces the importance of complementary non-pharmacological therapy in the treatment of behavioral disorders. These therapies, which include cognitive behavioral therapy, exercise, light exposure, phytotherapy, dietary supplements and even aromas are discussed by most authors in this Volume^{18,61,97,102,103}, as well as other chapters in the book series (e.g.,^{95,104–106}).

Winsky *et al.* This chapter details the initiatives that the NIH has instituted to promote drug discovery and development, and model development for psychiatric disorders described previously above. Workshops are sponsored by the NIH that are tasked with identifying areas that allow for bidirectional translational work and to develop biologically based models to study psychopathology and to assess novel therapeutics. The NIH is also at the forefront of sponsoring initiatives such as the MATRICS and TURNS initiatives that aim to identify treatments of core features of a behavioral disorder such as cognition in schizophrenia and to provide the infrastructure of clinical development of such compounds (see also¹⁸ for further discussion regarding these initiatives). The identification of endophenotypes and biomarkers is an important area of concern for the NIH. They are also concerned with genetic studies to identify genetic risk factors for complex disorders to facilitate new molecular target discovery for prevention, diagnosis and treatment. Development of novel models relies upon