IMPROVING AND ACCELERATING THERAPEUTIC DEVELOPMENT FOR NERVOUS SYSTEM DISORDERS

WORKSHOP SUMMARY

Forum on Neuroscience and
Nervous System Disorders

Board on Health Sciences Policy

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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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This workshop summary has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published workshop summary as sound as possible and to ensure that the workshop summary meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this workshop summary:

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Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the workshop summary before its release. The review of this workshop summary was overseen by **Eric B. Larson,** Group Health Research Institute. Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this workshop summary was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this workshop summary rests entirely with the rapporteurs and the institution.

Contents

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Introduction and Overview[1]

Although there is a high burden associated with nervous system disorders, development of new therapeutics remains stagnant. During the past decade, fewer new drugs for nervous system disorders have garnered approval in comparison to other therapeutic areas. Current data suggest that drug development, from the start of a discovery program to regulatory approval, can take an average of 12 to 15 years (Wegener and Rujescu, 2013). This familiar statistic prompts an equally familiar question: Can this time line be shortened? Nervous system drugs, on average, have longer regulatory approval and mean clinical trial times (Tufts CSDD, 2012). In addition, there is an increased probability of clinical trial failures at later stages in the drug development pipeline, even though resource investments are high for these drugs (Bunnage, 2011). The science is challenging and the prospects for success are discouraging to the point that drug companies are moving away from neuroscience research programs (Abbott, 2011; Miller, 2010).

There are several challenges to the current drug development pipeline for nervous system disorders. The fundamental etiology and pathophysiology of many nervous system disorders are unknown and the brain is inaccessible to study, making it difficult to develop accurate models. Patient heterogeneity is high, disease pathology can occur years to dec-

[1]The planning committee's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and are not necessarily endorsed or verified by the Institute of Medicine, and they should not be construed as reflecting any group consensus.

ades before becoming clinically apparent, and diagnostic and treatment biomarkers are lacking (Hyman, 2012; Insel, 2012a). In addition, the lack of validated targets, limitations related to the predictive validity of animal models—the extent to which the model predicts clinical efficacy—and regulatory barriers can also impede translation and drug development for nervous system disorders (Riordan and Cutler, 2010).

CHALLENGES WITH THE UTILITY AND TRANSLATION OF ANIMAL MODELS

This workshop builds on a previous Institute of Medicine (IOM) workshop, Improving the Utility and Translation of Animal Models for Nervous System Disorders, held in 2012 by the Forum on Neuroscience and Nervous System Disorders (IOM, 2013). That workshop focused on strategies to maximize the translation of effective therapies for nervous system disorders from animal models to clinical practice. Richard Hodes, director of the National Institute on Aging and a co-chair of the workshop planning committee, summarized the following key points highlighted during the workshop:

- Animal models can provide critical insight on specific disease mechanisms or targets of interest.
- Many participants noted that animal models typically do not fully mimic or recapitulate nervous system disorders.
- Animal models and clinical research can inform each other through bidirectional translation; failures may be due to a mismatch between endpoints used in clinical trials and preclinical animal studies.
- Reproducibility of animal studies might benefit from standardization, improved experimental design, and appropriate statistical analysis.
- Improved translation might result from establishment of realistic expectations about the predictive validity of animal models.

Hodes noted that many have lost confidence in the ability of animal models to predict efficacy and that the models may, in fact, be screening out potentially effective compounds. Consequently, workshop participants posed several questions: Under what circumstances would it be worthwhile and ethical to go directly into clinical trials after establishing

safety? Should research continue to emphasize animal models or should more emphasis be placed on cellular models and/or Phase 0 trials?[2] Are there alternative strategies to accelerate therapeutic development by combining animal models with new and emerging tools, technologies, and techniques? These questions set the stage, said Hodes, for the current workshop.

WORKSHOP OBJECTIVES

To explore these concepts, the IOM Forum on Neuroscience and Nervous System Disorders convened a workshop to examine opportunities to accelerate early phases of drug development for nervous system drug discovery (see Box 1-1). Workshop participants discussed challenges in neuroscience research for enabling faster entry of potential treatments into first-in-human trials,[3] explored how new and emerging tools and technologies may improve the efficiency of research, and considered mechanisms to facilitate a more effective and efficient development pipeline.

ORGANIZATION OF THE REPORT

The following report summarizes the presentations from expert speakers and discussions among workshop participants. Chapter 2 provides an overview of the drug discovery and development pathway along with a review of the regulatory process for investigational new drug (IND) applications. Key challenges for improving and accelerating drug development are also highlighted in this chapter. The ensuing chapters review opportunities to improve target identification (Chapter 3) and validation (Chapter 4). Chapter 5 examines several opportunities for improving discovery research through novel approaches and infrastructural changes. Finally, perspectives on potential next steps identified by workshop session chairs are summarized in Chapter 6.

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[2]An exploratory investigational new drug study, or Phase 0 study, is conducted very early in Phase I and involves microdosing in a very limited number of human participants (FDA, 2005b).

[3]A first-in-human trial can refer to (1) the first clinical trial in which humans, usually healthy volunteers, are given a new drug, or (2) cellular and molecular studies of human cells and tissues during the early phases of drug discovery (FDA, 2005a).

BOX 1-1
Statement of Task

- Examine opportunities and challenges in neuroscience research for facilitating faster entry of potential treatments into first-in-human trials.
  - Identify avenues for moving directly from cellular models to human trials minimizing the need for animal models to test efficacy.
  - Discuss the potential benefits and risks of such an approach.
- Consider regulatory mechanisms, including those supported by the Food and Drug Administration's Advancing Regulatory Science Initiative, which may facilitate faster entry of potential treatments into first-in-human trials.
  - Identify potential metrics for determining readiness for first-in-human trials.
- Explore the potential usefulness of new neuroscience technologies and techniques that would hasten the translation of research and facilitate the jump from cellular models to first-in-human trials (e.g., induced pluripotent stem cells, in vitro neuronal circuits, connectomics, brain imaging, etc.).
  - Explore the usefulness of alternative tools for validation (e.g., surrogate models).
- Consider mechanisms for integration and proliferation of new technologies and techniques to the broader neuroscience research community.

TOPICS HIGHLIGHTED DURING PRESENTATIONS AND DISCUSSIONS[4]

Throughout the workshop, participants discussed a number of central themes. Discussions primarily focused on opportunities to improve early drug development with a focus toward preclinical trials. Many participants noted that discussions regarding how to accelerate to first-in-human trials would be premature before considering improvements at earlier stages in the drug development process. These themes, listed on the next page, are expanded on in the succeeding chapters.

[4]The following list highlights recurring topics and is provided here as part of the factual summary of the workshop. Items on this list should not be construed as reflecting any consensus of the workshop participants or any endorsement by the Institute of Medicine or the Forum on Neuroscience and Nervous System Disorders.

Challenges

- **Limitations of current practices:** After reviewing the current drug development pipeline, many participants noted the need for improved translational science—the application of fundamental research to therapeutic development—from discovery through clinical trials. As noted earlier, some pharmaceutical companies are moving away from nervous system drug development due to high failure rates following large financial investments. Several participants noted that there is a certain amount of uncertainty and risk associated with the current development process. These same participants suggested that developing mechanisms by which tolerance of risk could be increased might be a more productive approach moving forward. Potential mechanisms include identifying regulatory constraints and developing partnerships to share resource investments. Specific barriers include

    - ***Biological mechanisms of disease:*** Many participants reiterated that due to unknown pathophysiology of many nervous system disorders and the complexity of human behavior, developing validated and targeted therapies is challenging. Several participants noted that failures along the drug development pipeline might be related to this lack of understanding of underlying mechanisms of disease. For example, a few participants noted that the underlying cause of Alzheimer's disease is unclear due to several unknown factors, including the role of β-amyloid.
    - ***Animal models:*** A number of participants noted that animal models are often valuable at capturing a particular aspect of disease or specific target of interest, but rarely recapitulate an entire disorder or disease. Several participants asked: How much of the problem is due to poor animal models compared to researchers prematurely rushing forward with answers from models without systemically validating the data?
    - ***Phenotyping:*** Several participants noted that the current model of drug development does not facilitate translation of discovery research directly into clinical trials for new therapeutics. One speaker highlighted that the field has lost track of clinical phenotyping and endotyping even though failures

of clinical trials are almost always predictable due to the known heterogeneity of the population affected by nervous system disorders.

- ***Resources:*** Several participants discussed resource constraints in the field and how organizations such as the National Institutes of Health and venture capital companies are critical in supporting the early discovery process since pharmaceutical companies may now be less likely to take on that task.
- ***Target identification:*** A large number of participants suggested that better target identification could significantly improve drug development. The need for target identification strategies based on human data via patient stratification, rather than animal models, was discussed. One participant discussed a novel approach to target identification in schizophrenia by translating genes of interest into molecular mechanisms of illness through RNA sequencing.
- ***Target validation:*** In addition to target identification, many participants noted the importance of target validation. Several suggested that rapid target *invalidation* is equally important. A few participants noted that target engagement is critical and measuring exposure pharmacodynamically is important. In addition, many participants highlighted the need for a greater number of validated biomarkers and translational endpoints to determine clinical efficacy.

Opportunities

- **New tools, technologies, and approaches:** Many participants noted that emerging tools and technologies (e.g., induced pluripotent stem cells [iPSCs], humanized animal models, computational neuroscience) may be important to further understand mechanisms of diseases, and help to identify and validate drug targets. For example, iPSCs may be better than animal models for target identification. Humanized animal models may help improve understanding of nervous system disorders and identify mechanisms of disease by engrafting human tissue stem cells into mice, a few participants noted. Computational neuroscience in conjunction with neuroimaging might aid in understanding underlying neurobiological mechanisms of diseases. However,

several participants cautioned that these novel assays do not fully mimic or recapitulate human diseases and disorders. These same participants therefore suggested that earlier human trials in the drug discovery pathway remain critical and validating targets using multiple models could provide more accurate information about the target than using a single model.

- **Humans as the starting point:** Several participants noted that an initial focus on human phenotypes rather than animal models might better inform the drug discovery process. Some participants suggested going directly into the patient population to validate targets. However, several participants noted that it might be faster to go into a control populations rather than patients because controls are easier to recruit. A few participants proposed reversing the pipeline and using humans for target identification and then animal models for target validation while others suggested that both identification and validation could be accomplished in humans.
- **Patient stratification:** Several participants discussed the need for improved patient stratification for improved target identification, due to the high heterogeneity of patients with a nervous system disorder. Through clinical phenotyping and identification of common genetic variants, small clinical trials of homogeneous populations could be useful, such as those with rare diseases, to establish proof of concept and further understand disease pathogenesis (Fishman, 2013; Leaf, 2013).
- **Combination therapies:** Because of heterogeneity and complexity of pathophysiology, several participants expressed the view that a single drug is not likely to be as effective for any given disorder compared to combination therapies. Rather than taking a singular approach, many participants suggested that starting drug development assuming that multiple drugs in combination will be needed to help patients, a multipronged approach, could potentially improve and accelerate drug development.
- **Increasing and sharing standards for preclinical studies:** Many participants stated that the current drug development paradigm might need to change, particularly for preclinical studies. It was noted that it might be beneficial for preclinical studies to have rigorous standards, similar to clinical trials, to ensure sound research design and credible statistical analyses. This, in turn, could improve the reproducibility of preclinical studies, which is

a major challenge for the field, according to many participants. Several participants also agreed that the publication of negative studies is important along with the development of a mechanism to share preclinical experimental design and results in an accessible repository similar to www.clinicaltrials.gov (e.g., "www.preclinicaltrials.gov").

- **Regulatory pathways:** Many participants expressed lack of familiarity with current regulatory processes and sought clarification from speakers. Requirements for obtaining approval of an IND application include safety pharmacology, extensive toxicity testing, and testing for absorption, distribution, metabolism, and excretion. Although a number of participants indicated a need for more specific application guidelines, Food and Drug Administration speakers emphasized that, in order to maintain flexibility in their approaches, applications are handled on a case-by-case basis. Several participants noted the value of pre-IND meetings to discuss specific questions prior to submission of applications.
- **Precompetitive space:** Participants discussed opportunities for the scientific community (academia, industry, and government) to come together in the precompetitive space to discuss challenges and opportunities to move the field forward as a whole. Many participants noted that no one group will be able to solve the challenges associated with developing therapeutics. Many participants discussed the importance of "de-risking" research throughout the drug discovery process. By sharing risk across sectors, resources could be saved, attracting companies to reinvest in nervous system disorder drug discovery.
- **Public–private partnerships:** Many participants noted that, as discovery research advances and becomes increasingly resource intensive and challenging, researchers could gain confidence and increase the probability of success through greater collaboration. Several speakers described the establishment of new preclinical public–private partnerships, especially for target validation.

2

Drug Development Challenges

Key Points

- Drug development is a lengthy, complex, and costly process, entrenched with a high degree of uncertainty that a drug will actually succeed.
- The unknown pathophysiology for many nervous system disorders makes target identification challenging.
- Animal models often cannot recapitulate an entire disorder or disease.
- Challenges related to heterogeneity of the patient population might be alleviated with increased clinical phenotyping and endotyping.
- Greater emphasis on human data might lead to improved target identification and validation.
- There is a lack of validated diagnostic and therapeutic biomarkers to objectively detect and measure biological states.
- Unfamiliarity with current regulatory processes for investigational new drug (IND) applications can be resolved through pre-IND meetings.

NOTE: The items in this list were addressed by individual speakers and participants and were identified and summarized for this report by the rapporteurs, not the workshop participants. This list is not meant to reflect a consensus among workshop participants.

David Michelson, vice president of clinical neuroscience and ophthalmology at Merck Research Laboratories, opened the workshop by underscoring drug discovery challenges for nervous system disorders. The years- to decades-long process can be complex, and there is nearly

always a moment of uncertainty that a drug will succeed to the next phase of development. This long development pipeline faces increasing costs and additional challenges, including the lack of predictive validity of current animal models, insufficient knowledge regarding underlying mechanisms of disease, patient heterogeneity, lack of targets and biomarkers, a high rate of failed clinical trials, and regulatory challenges. To better understand how these challenges create bottlenecks in the development pipeline, William Potter, senior advisor in the Office of the Director of the National Institute of Mental Health, began with an overview of current practices.

DRUG DISCOVERY AND DEVELOPMENT PATHWAY

Potter described the process of drug discovery and development beginning with target identification and validation (see Figure 2-1). A target can be a protein, DNA, or RNA that causes or contributes to disease. Its validation consists of demonstrating that modulating the target has a therapeutic effect. Assay development follows target validation and is an objective method for screening putative compounds to determine interaction and/or modification of the target. After an assay is established, the next step is to find compounds that actively engage the target. From a pool of potential compounds, a few select leads that demonstrate a relationship between chemical structure and target-based activity in a biochemical or cell-based assay are generated.

The process of moving from target identification to lead generation is often done entirely without animal studies, said Potter. Potential compounds, for example, can be generated through binding/functional, biochemical, and cellular or cytotoxicity assays. High-throughput screening through a large compound library can identify multiple compounds. Progressing to a lead compound(s) can involve complex cellular assays, toxicological surrogate assays, biopharmacological surrogates, and surrogates for absorption, distribution, metabolism, and excretion (ADME).

Potter noted that animal models are often used first to narrow the number of lead compounds to one or two candidates that can proceed into clinical trials. The lead compound(s) is tested in animals for its pharmacological and toxicological properties. Animal tests for efficacy—as opposed to safety—are, in most cases, not required prior to first-in-human testing,

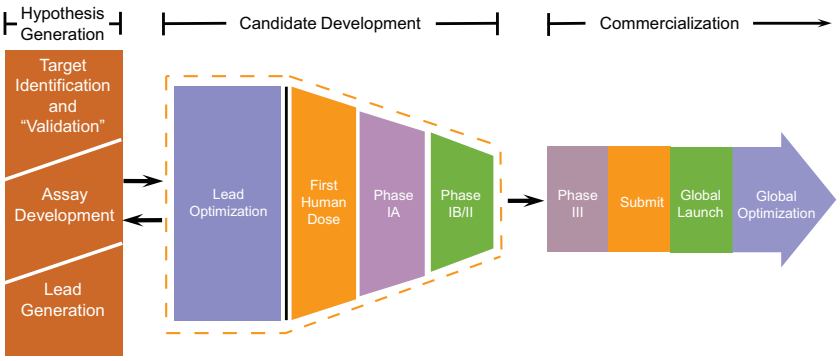

FIGURE 2-1 Overall drug discovery and development process.
SOURCE: Potter presentation, April 8, 2013.

a point repeatedly stressed by several workshop participants. After a lead compound is generated, it undergoes further testing to optimize physicochemical and pharmacological properties, especially potency and selectivity. Optimization is an elaborate process that can be costly and time-intensive. Despite the resources (e.g., time, personnel, and finances) devoted to generating lead compounds, Potter observed that many fail during optimization.

Once optimization is complete, first-in-human testing can begin with a Phase Ia clinical trial in which a single dose of the drug is given to healthy volunteers. This is followed by Phase Ib trials, which consist of multiple escalating doses to establish safety, steady-state pharmacokinetics, and maximum tolerated dose. There is increasing use of Phase Ib trials to provide evidence of efficacy in order to establish proof of concept (POC).[1] Potter noted that a typical POC clinical trial is a small controlled study conducted at fewer than 4 sites with less than 100 subjects/patients. If the drug succeeds at POC, clinical trials then proceed to larger Phase II and Phase III trials, which consist of randomized, usually placebo-controlled arms, to ensure safety and efficacy (see Table 2-1).

[1]POC refers to the minimum number of experiments/studies that provide critical data—efficacy, receptor occupancy, safety, and tolerability—to support either going forward to larger clinical trials or "killing" a compound, said Potter.

TABLE 2-1 Stages of Drug Development

Stage	Method	Purpose
Preclinical	Animal, in vitro, and laboratory studies	Testing toxicity, efficacy, pharmacokinetics, and pharmacodynamics
Investigational New Drug Application		
Phase I	Healthy human volunteers (~20–100)	Testing the safety of a single dose (Phase Ia) and multiple doses (Phase Ib) of a drug; also includes pharmacokinetics and maximum tolerated dose
Phase II	Patients (~100–300)	Assessing safety and efficacy
Phase III	Patients (hundreds to thousands; typically 1,000–2,000)	Assessing safety and efficacy
New Drug Application		
Phase IV	Varies	Postmarketing surveillance

SOURCE: Potter presentation, April 8, 2013.

After successful completion of Phase III and submission of a new drug application (NDA) to the U.S. Food and Drug Administration (FDA), a drug becomes eligible for marketing. Even with marketing approval, a drug continues to be studied through postmarketing surveillance to ensure safety.

CURRENT DRUG DEVELOPMENT CHALLENGES

Christopher Austin, director of the National Center for Advancing Translational Science (NCATS), highlighted underlying challenges behind translational failures that need to be addressed to improve the drug development pipeline for nervous system disorders (Wegener and Rujescu, 2013) (see Box 2-1).

BOX 2-1
Drug Development Challenges for Nervous System Disorders

- Insufficient knowledge of underlying biological mechanisms of diseases
- Translational failures using animal models
- Lack of detailed clinical phenotyping and endotyping due to high heterogeneity of patient populations
- Lack of valid biomarkers and surrogate endpoints
- Inability to replicate preclinical studies
- Inadequate collaboration among academic researchers, industry, and government
- Innovation gaps leading to an inability to address the unmet need

NOTE: The items in this list were addressed by individual speakers and participants and were identified and summarized for this report by the rapporteurs, not the workshop participants. This list is not meant to reflect a consensus among workshop participants.

Unknown Biological Mechanisms and Biomarkers of Diseases

One prominent challenge is that mechanisms behind nervous system disorders are poorly understood. Austin stated that if mechanisms of nervous system disorders were better understood, then more effective interventions could be developed; however, clinical observations made during drug development and conventional neuropharmacology should not be omitted as mechanisms for understanding these disorders. Several participants also noted that having a better understanding of the specific neural pathways involved in disease etiology may help researchers develop more comprehensive assays using emerging tools and technologies. This, in turn, may lead to the development of more targeted therapeutics. In addition, identifying biomarkers is essential, not only to provide proof of mechanism but also to refine targets, provide POC, and evaluate whether an early intervention focused on a single target can prevent or forestall disease (IOM, 2011, p. 34). According to Fleming and Powers, biomarkers are indirect measures of clinically meaningful endpoints, which are direct measurements of how patients feel, function, and survive (Temple, 1995). Although they may provide valuable information regarding effects on biological activity during an intervention, biomarkers can be unreliable predictors of clinical efficacy. Extensive

clinical trials in patient populations are needed to validate biomarkers as true surrogate endpoints, outcome measures that are used as a substitute for a clinically meaningful endpoint (Fleming and Powers, 2012).

According to Reisa Sperling, director of the Center for Alzheimer's Research and Treatment and professor of neurology at Harvard Medical School, and Paul Aisen, director of the Alzheimer's Disease Cooperative Study and professor in the department of neurosciences at the University of California, San Diego (UCSD), Alzheimer's disease (AD) is a prominent example of how a greater understanding of mechanism and improved biomarkers might accelerate drug development. Both speakers commented that AD begins years, perhaps decades, prior to the onset of symptoms, but the absence of objective biomarkers continues to be a challenge. The best opportunity to intervene may be prior to symptoms, but earlier interventions decrease the likelihood of detecting clinical signals of the disease (Rowe et al., 2010). Aisen commented that the central hypothesis for AD, specifically, the amyloid hypothesis, might not be valid. Although compelling genetic data exist to support the role of β-amyloid and converging data indicate that the presence of β-amyloid increases risk of cognitive decline in prodromal and preclinical AD, there are still many unknowns, Sperling said. One unknown is whether β-amyloid itself is sufficient to cause AD, because there might be other factors necessary to initiate the disease process. Another unknown is what species of β-amyloid should be targeted, such as β-amyloid$_{42}$ or oligomeric β-amyloid, or other cleavage products of amyloid precursor protein (APP). Weighing against the β-amyloid hypothesis are disappointing results from multiple anti-β-amyloid clinical trials in mild to moderate dementia, said Sperling.

If the underlying biological mechanisms of a disease are unknown, how can researchers identify targets and eventually develop drugs? How do you develop biomarkers for diseases and disorders that are difficult to define? Starting at the molecular level is important, said Austin; however, it is not a stepwise process (A to B to C) to clinical trials.

Translational Failures Using Animal Models

Many participants discussed the inability of animal models to accurately predict efficacy as a challenge to drug development. Although animal models work reasonably well to prioritize reagents for a clinically validated target, they are not as useful to prioritize reagents aimed at

novel targets, opined Chas Bountra, head of the Structural Genomics Consortium and professor of translational medicine at the University of Oxford. In addition, animal models can be poor predictors of clinical efficacy and therapeutic index. This is most likely due to animal models' inability to fully mimic diseases, as demonstrated by a groundbreaking study of the failure of mouse models in human inflammatory diseases (Seok et al., 2013). Potential mismatch of preclinical and clinical endpoints could be another reason for translational failures, although corresponding preclinical and clinical endpoints may not be sufficient enough to predict clinical efficacy (IOM, 2013). Austin noted that there are many examples of a lack of drug efficacy in clinical trials after successful animal studies (i.e., failure of efficacy) as well as the presence of human toxicity not previously shown in animal studies (i.e., failure of toxicity). Some of these failures relate back to the lack of understanding of mechanisms for disease; how can successful animal models be created based on unknown mechanisms?

Two speakers noted that the limitations of existing animal models have resulted in translational failure. Lawrence Goldstein, director of the UCSD Stem Cell Program and distinguished professor in the department of neurosciences at the UCSD School of Medicine, highlighted several challenges related to existing animal models of AD, including the inability to develop all the symptoms of AD; overexpression of proteins linked to disease (e.g., APP) at levels high enough to produce abnormal phenotypes; transgenic mouse models that fail to fully recapitulate AD pathology (Duff and Suleman, 2004); lack of sporadic AD models, which account for 95 percent of cases (Young and Goldstein, 2012); and inability of drugs found efficacious in animal models to translate to clinical trials. Wayne Drevets, scientific vice president and disease area leader in mood disorders at Janssen Pharmaceutical Companies of Johnson & Johnson, echoed similar comments for depression (Banasr et al., 2011; Manji et al., 2001; Savitz et al., 2013), one of which is the lack of animal models for spontaneously recurring mood disorders (e.g., bipolar disorder). To summarize, Bountra noted that animal models do not always accurately predict dose, tolerability, efficacy, and research priority.

Lack of Clinical Phenotyping and Patient Stratification

Austin stated that the field has lost track of detailed clinical phenotyping, which has advanced other fields. It is important that the

field improve phenotyping of nervous system disorders, he noted. Failed clinical trials are almost predictable simply due to patient heterogeneity. From an investment standpoint, stated Kiran Reddy, principal at Third Rock Ventures, the heterogeneity of patient populations necessitates larger, more complex, and thus more expensive clinical trials. Patient populations with depression and bipolar disorder, for example, are highly heterogeneous, and segregating patients based on phenotypes may serve as a useful method of patient stratification when conducting clinical trials. Without new ways to stratify patients, physicians cannot always predict dose responses or the speed of response, noted Bountra. When planning clinical trials, it will be important to consider patient groups in which the mechanism of disease is most likely to be homogeneous. Patient stratification could produce better clinical trial outcomes and additional information about potential therapeutic targets. Austin also pointed out that a simple relationship between genotype and phenotype mechanisms does not exist. Investigators often mistakenly think that after the genes or polymorphisms are identified, the clinical effect will be understood. This is often not the case, and more research is needed to identify the relationship between phenotype and genotype mechanisms, Austin stated.

Inability to Rely on Published Data

Reproducibility remains a critical issue for translation. The ability to rely on published data and process those data from one lab to another is critical for the successful translation of discovery research, noted speakers Austin and Hodes. Investigators have finally reached the point at which success cannot be achieved independently; Austin made an analogy to the field having reached the first step in any 12-step rehabilitation program: acknowledging that an issue exists. A participant pointed out two systemic lapses that may need to be addressed regarding the current 95 percent confidence interval: (1) only top-tier journals have statistical editors to assess whether or not a p value is credible; and (2) funding agencies also require a p value of 0.05 or less for potential grantees; however, there is no assessment for statistical credibility. The field would likely benefit from publicly available data on everything from compound activity to patient registries to natural history, said Austin. In addition, explicit reporting of experimental results could increase reproducibility. Consistent with discussions from the 2012 Institute of Medi-

cine animal models workshop, the scientific validity and reproducibility of preclinical data are important when making decisions regarding when to go into clinical trials (IOM, 2013).

Inadequate Collaboration Among Academia, Industry, and Government

Bountra said that organizational challenges are formidable in the drug development process. The greatest challenge is that the majority of the field is working competitively on the same few molecular targets. Bountra noted that many academic laboratories are interested in researching disease networks and biological pathways, but have limited access to reagents, such as inhibitors and antibodies. Because most drug testing fails in Phase IIa and because the negative results are usually not shared, the field is potentially wasting resources (e.g., time and money), said Bountra. As mentioned previously, there is a shift in focus of research and development groups; industry is successful at processes that require scale and infrastructure (e.g., high-throughput screening, lead optimization, and manufacturing), noted Bountra, whereas academia continues to be a source of new knowledge in biomedical research needed for early drug discovery (Bunnage, 2011).

Pipeline Challenges

Reddy expressed the view that there are several pipeline problems plaguing large pharmaceutical companies. During the past 15 years, companies have steadily increased expenditures on research, but the number of new drug approvals has dipped (see Figure 2-2). Adrian Ivinson, director of the Harvard NeuroDiscovery Center at Harvard University, noted that during this timeframe, only a small handful of nervous system drugs were approved, despite a growing market coupled with unmet need.

At a recent life sciences conference, venture capitalists were surveyed about which therapeutic areas in the life sciences offered the most promising investment opportunities, said Reddy. Oncology and immunology were seen as the best areas of opportunity by 30 and 17 percent of respondents, respectively. Nervous system disorders fell significantly behind, with only 8 percent of investors viewing the field favorably.

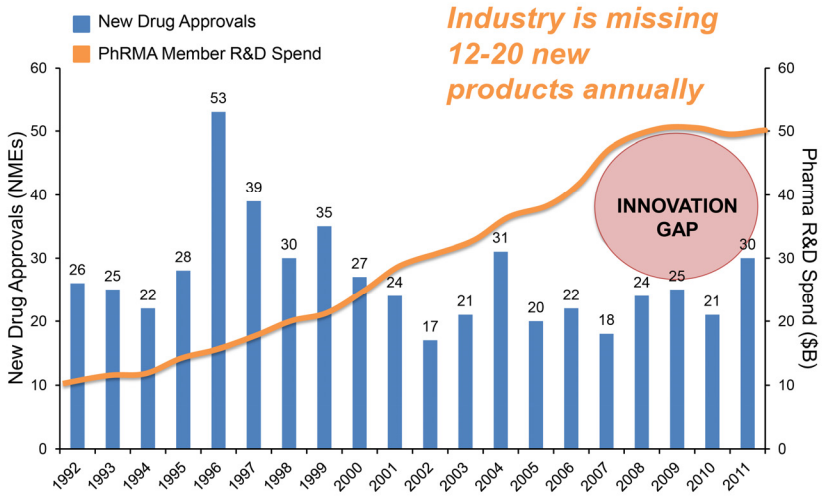

FIGURE 2-2 Opportunity for venture capital firms to fill the innovation gap.
NOTE: NME = new molecular entity; P*h*RMA = Pharmaceutical Research and Manufacturers of America; R&D = research and development.
SOURCE: Reddy presentation, April 9, 2013.

Kazumi Shiosaki, managing director at MPM Capital, noted that when her organization looks to invest in a particular drug, it uses a checklist of questions to gauge the risk of investment, including

- Has the drug target been identified (versus a drug identified in a phenotypic screen)?
- Has the target been validated as a way to arrest the disease?
- Are the biochemical interactions of the drug candidate known?
- Is there information about dose dependence in animal models?
- Has safety of administration on a chronic basis been shown?
- Can the drug cross the blood–brain barrier?
- Do toxicology studies show it is a safe drug?
- Is there a sufficient therapeutic window?
- Are drug purity and stability acceptable?
- Is there good protection of intellectual property?

Multiple challenges can impact the drug development pipeline, originating with the lack of understanding of underlying biological mechanisms of nervous system disorders. Lawrence Goldstein suggested that the field identify key bottlenecks in the pathway and become better at

tolerating a certain amount of uncertainty and risk to improve therapeutic development.

THE REGULATORY PROCESS

Several speakers from FDA relayed their individual perspectives on the regulatory process. Speakers emphasized that IND applications are reviewed on a case-by-case basis and that researchers can use pre-IND meetings as a resource to answer technical questions prior to submission. To begin the conversation, Imran Khan, pharmacologist and toxicologist in the Office of New Drugs, Center for Drug Evaluation and Research of FDA, provided an overview of the review process for IND applications; common inadequacies that could put applications on clinical hold, an FDA-ordered delay or suspension of clinical trials[3]; and how issues can be mitigated.

To initiate clinical trials, IND regulations[4] state that the drug's sponsor first must submit adequate evidence from pharmacological and toxicological studies in laboratory animals or in vitro studies that supports the conclusion that the proposed clinical trial is reasonably safe. The application would need to contain evidence of the drug's chemistry, manufacturing, and controls (CMC) (details of product manufacturing, product stability, and shelf-life), and preclinical studies of pharmacology, pharmacokinetics (PK), and ADME. Results from acute, sub-chronic, and chronic toxicity tests, including reproductive and developmental toxicity and special toxicity testing related to the drug's mode of administration or conditions of use, would be included. The data requirements for drugs can vary according to their clinical experience or history: new molecular entities (NMEs) never tested in humans, NMEs with prior human experience, and marketed drugs for which the sponsor seeks a new indication.

In the case of an NME never tested in humans, pharmacological studies require inclusion of in vitro receptor binding screens and in vitro pharmacodynamic (functional) assays. However, Khan noted that animal efficacy models are not necessary at this stage. Under safety pharmacology, a core battery of studies is required to assess the effects of the drug on vital organs, such as those within the cardiovascular, respiratory, and central nervous systems. PK must be conducted in the same animal spe-

[3]See http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm082022.pdf.

[4]21 C.F.R. 312.22 and 21 C.F.R. 312.23.

cies used for toxicity testing. Also required are tissue distribution and in vitro metabolism data in microsomes and/or hepatocytes from humans and animals. Toxicological studies are required to be conducted in two species, a rodent and a non-rodent—usually dog, monkey, or guinea pig—of similar or longer duration than the proposed human exposure. The genotoxic potential[5] of the drug is required to be studied in a battery of in vitro and in vivo assays for determining mutations and chromosomal damage. Impurities with genotoxic potential may also need to be assessed for genetic toxicity.

In the case of an NME with previous human experience, Khan stated that some of the studies outlined above may not be required. For example, new safety pharmacological data are not needed if adequately documented safety data with previous human experience are included. However, the intended duration of drug administration must be supported with comparable or longer repeat-dose toxicity studies. Furthermore, genotoxicity, fertility, and reproductive studies may also be required. For example, studies of fertility in early embryonic development and ADME in fetal development must be completed prior to Phase III, and pre- and post-natal development studies completed prior to submission of the NDA.

In the case of an already-approved drug for which a new indication is sought, most of the non-clinical studies are not required, said Khan, as long as the following are true: the proposed dose and duration are consistent with those of the approved product; the intended route of administration must be the same as the marketed product; the patient population must be similar to that for which the product has been already approved; and the predicted PK/ADME are sufficiently similar to the marketed product.

Khan noted that biologics are regulated differently from small molecules in the following ways:

- Biologics may not need to be tested for genotoxicity.
- Biologics may not need to be tested in two species, because sometimes only one species is pharmacologically relevant.
- Biologics may not need to be tested for antidrug antibodies, especially if no toxicity is observed at an adequately high dose.
- The criteria for an adequately high dose may be different.

[5]The drug's ability to cause genetic damage.

- The assessment of pharmacodynamic effects in toxicity studies may be helpful.
- Acute-dose toxicity studies may not be adequate to support a single-dose clinical trial if a long half-life of elimination in humans is anticipated.

Clinical Holds

Khan noted that many common reasons can lead to a clinical hold of an IND application. Non-clinical studies that are irrelevant or inadequate are two possible reasons. Inadequate studies might lack sufficient documentation, test too few animals, not assess standard parameters or not provide data, study inadequate doses, use a route of administration other than that proposed for the humans without justification, and have had an insufficient duration. Another common reason for a clinical hold is that a no-effect dose for serious toxicity was or could be determined. Serious toxicity with no or an inadequate strategy for monitoring the toxicity in humans could warrant a clinical hold as well. In addition, problems with CMC that require non-clinical safety testing (e.g., impurities associated with genotoxicity) and a novel excipient[6] in the clinical formulation that has not been adequately tested in animals are problematic. Lastly, if the clinical investigator has an inadequate brochure, then that could lead to a clinical hold, said Khan.

In some cases, a clinical hold may be avoided, said Khan. For example, a sponsor can revise the clinical protocol to limit the dose to provide a sufficient safety margin (e.g., one-tenth of the plasma C_{max} at the no observed adverse effect level [NOAEL] for convulsions in animals). The sponsor can also limit the duration of dosing, ascend doses slowly with careful monitoring, or limit the drug's duration if the toxicity occurs after prolonged administration. In other cases, the sponsor can submit scientific justification to support the original clinical protocol. For example, for inadequate high-dose selection in a pivotal toxicity study, the sponsor can provide data to document that the toxicity is not relevant to humans. Khan emphasized that when protocols depart from standard testing requirements, justification is necessary.

[6]An inactive ingredient that is formulated with a therapeutic (e.g., solvents, fillers, and flavors) (FDA, 2005b).

Guidance and Clarification for IND Applications

Following Khan's overview, Eric Bastings, deputy director of the Division of Neurology Products in the Center for Drug Evaluation and Research (CDER) at FDA, and Ni Khin, medical team leader in the same division, joined Khan to field questions from participants related to the regulatory process. When asked to explain the animal rule for IND applications, Bastings explained that animal studies are needed only when human efficacy trials are neither feasible nor ethical. In some cases, a risk–benefit analysis is needed for protocols in which animal efficacy models may be needed. Bastings added that, typically, animal models are not required for INDs to be tested in clinical trials. Bastings and Khin stressed the importance of case-by-case decision making regarding regulatory requirements and reiterated the importance of a pre-IND meeting for discussion of the elements of a successful IND.

Several participants inquired about the regulatory process for therapeutics that could potentially treat serious or life-threatening disorders. Bastings noted two programs designed to expedite FDA's review process in these cases. The first is known as Fast Track, which applies to drugs intended for serious diseases or that fill an unmet need. The unmet need criterion is defined as providing therapy where none exists or providing therapy that may be potentially superior to existing therapies (FDA, 2013b). The process for receiving a Fast Track designation is expedited in the following ways: more frequent meetings with FDA, more frequent written correspondence, and a rolling review process, which allows a sponsor to submit portions of its NDA before the rest of its submission. Normally, FDA requires that the entire package be submitted together.

The second FDA program to expedite regulatory review is through a "breakthrough therapy designation." Breakthrough therapies must meet two criteria: be intended for serious or life-threatening conditions, and demonstrate preliminary clinical evidence that the drug may have substantial improvement over available therapy (FDA, 2013a). Breakthrough therapies can take advantage of all the features of the Fast Track designation plus more intensive guidance from FDA on an efficient drug development program. These additional features include holding meetings throughout the different drug development processes, ensuring that the design of clinical trials is as efficient as possible, and assigning a cross-disciplinary project lead for the FDA review team to facilitate review.

Many participants noted that there is complexity and a lack of clarity in the IND application process. Khin directed participants to the FDA website to find guidance on the process; however, Khin noted that the guidance is non-binding. A participant stated that there has been a transition from traditional efficacy studies using animals to select efficacy studies when there are sufficient safety data and a plausible mechanism. The field is developing tools to better understand the molecular level of a disease and move toward a patient-stratified approach with the goal of developing compounds with less toxicity. The participant concluded with an open question about whether the IND application process would be different for these cases.

Strategies to Improve Communication and Reduce Regulatory Delays

Robert Conley, regulatory leader of Biomedicines at Eli Lilly and Company, offered several thoughts on how to improve communication and reduce regulatory delays. Conley first observed that startups and small drug companies seem to be afraid of communicating with FDA. One way to reduce fear and improve understanding is to meet with FDA at pre-IND meetings. These meetings can help to explain the basis for regulatory requirements.

Next, Conley observed that increased harmonization of requirements among FDA divisions might lead to a better understanding of requirements by applicants and, therefore, higher rates of and faster times to acceptance. Problems with conflicting or divergent requirements occur most frequently with drugs for which a new indication is sought. For example, the safety pharmacology requirements might differ between nervous system drugs and cardiovascular drugs, making it necessary for the sponsor to conduct an unexpected new round of pharmacological testing. The time and expense might be too great for a fledgling sponsor. If an impasse is reached between FDA and a sponsor, then it is important to learn from the experience, said Conley.

Conley's third observation was to point to the cultural disconnect between FDA and the National Institutes of Health as a potential reason for delays in the approval process. Academics sometimes approach FDA as though they are the "experts" and, because of extensive peer review, believe less oversight is needed. Laws, regulations, and guidance drive

FDA culture; it is not driven by the standards of merit that typically apply to the academic community.

Finally, Conley suggested that academic and industry colleagues come to any FDA meeting with a "Plan B" in order to encourage resolution of differences and decrease delays. Conley asserted that academics and industry tend to argue too vehemently for their own points without understanding the constraints under which FDA operates.

The current drug development pipeline is multifaceted and complex, composed of great risk that a drug will not be successful even after many resources have been invested. Nervous system disorder drugs in particular face a number of challenges that complicate drug development even further. Although regulatory processes are not intended to hinder drug development, many investigators are unclear of the specific requirements for INDs and request comprehensive guidance. Opportunities to improve and accelerate drug development for nervous system disorders through emerging new tools and technologies, novel methodological approaches, and infrastructural changes is explored in subsequent chapters.

3

Target Identification

Key Points

- Stem cell technologies can be used to model "human" disease pathology at the cellular level and may be a faster alternative to animal models.
- Humanized animal models are a tool to improve understanding of nervous system disorders and identification of mechanisms of disease.
- Greater understanding of the genetic underpinnings of nervous system disorders may facilitate target identification.
- Imaging technologies might be helpful to understand underlying neurobiological mechanisms of diseases.
- Patient stratification through clinical phenotyping and identifying common genetic variants is important for target identification.

NOTE: The items in this list were addressed by individual speakers and participants and were identified and summarized for this report by the rapporteurs, not workshop participants. This list is not meant to reflect a consensus among workshop participants.

Target identification is a critical step in the drug development pipeline. Speakers and participants discussed ways to improve this starting point and thereby accelerate therapeutic development through the use of stem cells, humanized animal models, increased knowledge of genetics, and imaging.

STEM CELLS

Stem cells, which are undifferentiated cells that can divide for indefinite periods of time and differentiate into specialized cells, may serve as a faster tool for the discovery of novel targets. Embryonic stem cells are cells that are derived from embryos that can develop into any cell and tissue throughout the body, whereas somatic (also referred to as adult) stem cells are cells that naturally exist in the body, responsible for maintaining and repairing tissue (NIH, 2002). Induced pluripotent stem cells (iPSCs) are somatic stem cells artificially reprogrammed with transcription factors to express pluripotent properties of embryonic stem cells—meaning they have the potential to differentiate into mature cells of all types. Because embryonic stem cells and iPSCs exhibit inherited traits and disorders, researchers can use them to better understand the underlying mechanisms of diseases and create disease models more representative of the actual disease than animal models (Rubin, 2008). Particularly for target identification, comparing patient-derived iPSCs to normal cells may offer researchers the ability to detect when physiological deviations occur at the cellular level (Grskovic et al., 2011; Yang et al., 2011). This, in turn, could improve identification of drug targets. Speakers provided examples of this for Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS), in addition to the use of stem cells to create humanized animal models.

Induced Pluripotent Stem Cells

iPSCs provide a valuable tool for studying diseases and understanding pathways needed to develop potential therapeutics, said Lawrence Goldstein, director of the University of California, San Diego (UCSD), Stem Cell Program and distinguished professor in the department of neurosciences at the UCSD School of Medicine. When differentiated into neurons and other nervous system cells, iPSCs can potentially overcome the translational limitations of animal models. iPSCs enable analysis of human-specific phenotypes that cannot be modeled in animals (Young and Goldstein, 2012). Lawrence Goldstein highlighted several benefits of using iPSCs; they

- can be produced in unlimited quantities because of their capacity for self-renewal;

- carry uniquely human biochemistry;
- are euploid (contain the normal number of chromosomes) and are genetically stable;
- capture the range of human genomic variation;
- can be studied electrophysiologically;
- are useful for basic science, disease modeling, and drug screening; and
- can be manipulated, a beneficial attribute for mechanistic studies.

Although there are benefits to using iPSCs, a few participants noted that iPSCs may be simply another step in drug development rather than a means to truly accelerate the process to first-in-human trials. Particularly, several participants indicated that there could be significant benefit from defining the iPSC phenotypes that would be most suitable for study of human nervous system disorders. A participant noted that cellular readouts may be difficult to obtain for neuropsychiatric disorders, and, as a result, researchers might turn to physiological and imaging readouts to subset patient populations. A few participants noted that although there will be an influx of useful genetic data pouring into the field, researchers are, at times, unaware of specific disease phenotypes—making drawing conclusions from data challenging. As mentioned in Chapter 2, understanding phenotypes, in several participants' opinions who spoke, is necessary to improve drug discovery.

Alzheimer's Disease

Lawrence Goldstein and colleagues recently demonstrated that iPSCs could be successfully reprogrammed from human fibroblasts for the purpose of modeling AD (Israel et al., 2012). This was accomplished with fibroblasts from two patients with familial AD, two with sporadic AD, and two normal controls. The iPSC cultures differentiated into neural precursor cells and then neurons, which were harvested by cell-sorting technology. The cultures consisted of 90 percent neurons, many of which formed synapses and displayed normal neuronal electrophysiological activity. The neuron cultures from patients with familial AD and one with sporadic AD displayed higher levels of three proteins implicated in AD pathophysiology: β-amyloid, phosphorylated tau, and glycogen synthase kinase 3 (GSK3β). These findings model the biochemical phenotypes of AD. However, the cultures did not contain glial cells. In addi-

tion, the cultures contained more than one neurotransmitter type with a mix of γ-aminobutyric acid (GABA), glutamate, and some peptidergic neurons. Given differences in relative susceptibility of neuronal populations in AD, the ability to obtain cultures with one neurotransmitter phenotype containing glia is needed to control for variability, noted Lawrence Goldstein. He and his colleagues are working to overcome these limitations.

Lawrence Goldstein's laboratory is also using iPSCs to study the role of sortilin 1 (SORL1), a trafficking factor, which is a susceptibility gene for late-onset AD (Lee et al., 2008). SORL1 protein levels control the rate at which amyloid precursor protein (APP) is processed. Risk variants of SORL1 are hypothesized to have decreased expression, which is thought to lead to an increase in β-amyloid production. Recently, Lawrence Goldstein's laboratory found that, as neuronal stem cells were differentiating into neurons, cells with the risk variant of SORL1 did not respond to brain-derived neurotrophic factor (BDNF), which normally generates higher expression of SORL1. On the other hand, cells with a protective variant of SORL1 demonstrate strikingly increased expression in response to BDNF. If these findings are accurate, Lawrence Goldstein and colleagues suggest that increased SORL1 may lead to reduced β-amyloid. Consequently, drugs that increase SORL1 may be desirable for AD, and patients participating in clinical trials could benefit from stratification for risk vs. protective variant SORL1 genotypes.

Adrian Ivinson, director of the Harvard NeuroDiscovery Center at Harvard University, discussed a similar approach in which his laboratory tested its library of compounds against cells from 50–200 patient-derived, induced pluripotent stem neuronal cell lines. It is a departure from the standard convention of testing thousands of compounds against one assay designed to model the disease process. The risk of this widely practiced approach is that the assay may not be a good representation of the disease. In the case of AD, for example, one cell line could be from a patient with the inherited form of the disease, while another could be from a patient with the sporadic or late-onset form of disease, while yet another could be from a patient who has positron emission tomography (PET)-amyloid-positive imaging, but is asymptomatic. The goal is to build patient heterogeneity into the drug discovery process and hopefully find a pattern of hits that are active in some portion of patient-derived cell lines. Ivinson said this patient-stratified approach might be one method to accelerate drug discovery.

Amyotrophic Lateral Sclerosis

Stem cells could also speed go/no-go decisions by using them to interrogate potential drugs, said Kevin Eggan, associate professor at the Harvard Stem Cell Institute. Eggan observed that pluripotent stem cells allow hypotheses from animals to be tested in human neurons, in many forms of the disease, and in "human-specific" biology. ALS is a neuromuscular condition characterized by spreading loss of spinal motor neurons, which results in fatal paralysis. Early in the disease, motor neurons are selectively vulnerable to degeneration and death. Genetic progress has been made in recent years, with about 25 percent of ALS now explained by mutations in about a dozen different genes, including superoxide dismutase 1 (SOD1) and chromosome 9 open reading frame 72 (C9orf72), said Eggan. The genes encode proteins that are involved in many different aspects of neurobiology and cell biology. Researchers are trying to understand how mutations in these genes induce motor neuron degeneration and why motor neurons are selectively sensitive to the effects of mutation when other cells are not.

The answers to these questions have been slow in coming largely because of a lack of animal models. Most investigators rely on one particular mouse model, the SOD1 mouse, which offers a good phenocopy of ALS by virtue of displaying rapid motor neuron degeneration. But drugs in several clinical trials (e.g., minocycline) have failed despite showing success in the SOD1 mouse (Couzin, 2007). The lack of translation might be due to differences between mice and humans, or differences between SOD1 mutations and other forms of ALS.

Eggan said that a new and faster alternative to animal studies has emerged—the use of human stem cells. One approach is to reprogram skin fibroblasts into iPSCs, followed by directed differentiation into motor neurons. The latter is accomplished by treating iPSCs with an agonist of the sonic hedgehog signaling pathway and retinoic acid, and then by plating on laminin (Dimos et al., 2008). A second approach is by lineage conversion, starting with skin fibroblasts and, using transcription factors that are expressed in neurons, transdifferentiating the fibroblasts into motor neurons. Stem cells made by either method function normally, said Eggan.

Eggan's current research examines motor neurons from differentiated iPSCs derived originally from ALS patients. Eggan and colleagues are trying to determine whether motor neuron degeneration is caused by de-

fects in cells interacting with the motor neuron (i.e., astrocytes and microglia), or whether the degeneration is caused by defects intrinsic to the motor neuron. The researchers found that patients had a defective prostanoid DP1 receptor. Eggan and colleagues then turned to animal models to determine the validity of this finding. After knocking out the DP1 gene, they found that ALS animals with one or two copies knocked out lived longer than those with the defective gene, said Eggan.

In closing, Eggan said there is a torrent of released genetic data that might support the use of iPSCs. Genetic information might help determine the location of variants that are causative for disease, although it will not provide much information on how the molecular biology of patients is changing. In his opinion, many of the genetic variants may be near neuronal genes in regulatory regions, which are not well conserved between humans and mice. Because of this, understanding how regulatory regions change the expression of nearby genes by using human iPSCs or human embryonic stem cell–derived neurons might lead to greater success compared to conventional animal models. In the end, Eggan advocated for a measured approach and suggested that rather than overinvesting in one hypothesis or target, a broad-based platform of investment that raises all areas could be beneficial to accelerate the development of therapeutics.

Humanized Animal Models

The use of humanized animal models may be another helpful technique in identifying molecular targets by examining the function of normal or genetically diseased human-tissue stem cells in mice. By genetically characterizing specific mouse strains with known genetic backgrounds, researchers might further understand the disease and identify associated traits (Schughart et al., 2012). Beginning in the 1980s, Irving Weissman, director of the Institute of Stem Cell Biology and Regenerative Medicine at Stanford University, and colleagues transplanted human fetal liver hematopoietic cells, thymus, and lymph node into a severe combined immunodeficiency (SCID) mouse (McCune et al., 1988). The fetal cells subsequently differentiated in the mouse host into functionally mature cells, leading to the use of humanized mouse models in disease research.

Weissman and colleagues isolated central nervous system stem cells from human neural fetal tissue using antibodies to early cell surface markers (Uchida et al., 2000). In vitro, the stem cells differentiate into

neurons and glia. When transplanted into the lateral ventricles of immunodeficient mice, the stem cells displayed engraftment, migration, and differentiation into neurons, astrocytes, and oligodendrocytes. The cells migrated throughout the brain to the cerebral cortex, corpus callosum, and cerebellum, as well as to sites of neurogenesis, where the cells continued to proliferate up to 7 months after the transplant. Weissman noted that the success of this experiment gave rise to clinical trials to replace tissues lost in two different conditions—hypomyelinating disease and spinal cord injury.

Weissman concluded with optimism that human nervous system stem cells hold promise for neurodegenerative diseases that exhibit widespread cell loss. He noted that stem cells themselves are a therapeutic entity and must be researched in vivo. Only stem cell transplants, in his view, have the potential to repopulate large swaths of tissue lost to disease-induced neuronal degeneration. Weissman hopes to work toward developing a true human neuronal mouse using iPSC-derived human neural stem cells to potentially validate his work and understand the disease pathogenesis to help develop therapeutics.

GENETICS

Using genetics as a tool to better understand variations in patient populations compared to healthy populations may facilitate the identification of novel therapeutic targets for nervous system disorders. Through DNA sequencing, researchers have the ability to locate molecular sites associated with specific diseases. More specifically, examining changes to gene expressions that contribute to or alter disease pathology may help pinpoint potential targets (Altar et al., 2009; Orth et al., 2004). Many speakers highlighted the usefulness of understanding genetics when selecting animal models and understanding overlap among diseases and molecular mechanisms of individual diseases.

Evolutionary Considerations

New analytic and genetic techniques exist that allow for the examination of species differences in the development and interpretation of disease models. Daniel Geschwind, Gordon and Virginia MacDonald Distinguished Professor in the school of medicine at the University of

California, Los Angeles, discussed how therapeutic development for nervous system disorders might be better served by considering evolutionary differences between species and humans when using animal models. Developing disease-altering medicines for nervous system disorders using animal (mouse) models has not been as successful as predicted, and although there are many reasons for this, evolutionary differences are seldom explored or highlighted (Bolker, 2012).

Mice and humans diverged at least 70 million years ago from when they shared a common ancestor. Genes in the brain show different patterns of expression in mice and humans, said Geschwind. Not only are there more neurons in humans, but there is also greater complexity of evolutionary regions, especially in the temporal and frontal lobes. The temporal lobe is involved in auditory and visual processing, language comprehension, memory, and emotion. The frontal lobe is responsible for high-level cognition, including multitasking, social cognition, and planning and manipulating of abstract representations (Konopka et al., 2012). In a study of FOXP2, a transcription factor implicated in human speech and language dysfunction, a change of two amino acid sequences leads to significant functional deficits, largely due to FOXP2's regulatory role (Konopka et al., 2009). In general, when considering genes, it is important to understand connectivity, interactions, regulation, and network dynamics, said Geschwind.

In a recent study, Geschwind and colleagues used high-throughput DNA screening methods, "next-generation DNA sequencing," and microarrays to compare the transcriptome of the telencephalon in the human, chimpanzee, and macaque (Konopka et al., 2012). They found a dramatic increase in transcriptional complexity specific to the human frontal lobe. Only one-quarter of frontal pole modules[1] were preserved in humans, whereas caudate nucleus modules were highly conserved across species. Non-conserved modules were likely to have hub genes (central genes within a module) under positive selection.[2] This applied to the CLOCK gene, a circadian rhythm gene that is implicated in bipolar disorder, and, in a separate study, this also applied to the presenilin gene implicated in AD (Miller, 2010). Geschwind and colleagues concluded in their study that genes within modules associated with higher connectivity—hub genes—are more likely to be disease genes.

[1]Sets of genes co-regulated to respond to different conditions (Segal et al., 2003, p. 166).

[2]Process in which beneficial/adaptive genetic variants increase throughout a population.

Case Study for Drug Discovery

David Goldstein, director of the Center for Human Genome Variation at Duke University, provided an overview of the first discovery project of the National Institute of Neurological Disorders and Stroke–funded consortium known as Epi4K to study the genetics of epileptic encephalopathies. The initiative is a "center without walls" for studying 4,000 cases of highly selected and well-characterized epilepsy (Epi4k Consortium, 2012). David Goldstein and colleagues' project was to search for de novo mutations[3] in two types of epileptic encephalopathies, infantile spasms (IS) and Lennox-Gastaut syndrome (LGS). IS is found in 1 in 3,000 live births, with onset between 4 and 12 months of life and characterized by chaotic interictal and electroencephalogram patterns of hypsarrhythmia. LGS has onset between 1 and 8 years and is characterized by mixed seizure types and intellectual disabilities. David Goldstein and colleagues hypothesized that a significant number of IS and LGS cases of unknown etiology are likely due to dominant de novo mutations. The approach was to conduct whole-exon sequencing on 300 family trios consisting of a child with IS or LGS and their unaffected parents, using samples collected by the Epilepsy Phenome/Genome Project.[4]

David Goldstein and colleagues found there was 1 de novo mutation in 92 children, 2 in 45 children, and 3 in 25 children. But not all of these mutations were in genes that caused or contributed to the disease. Consequently, David Goldstein and colleagues performed new statistical techniques to find causative mutations. The group found that genes intolerant to functional variation were more likely to carry mutations that cause or contribute to disease. Altogether, the analysis produced 25 epileptic encephalopathy genes, of which 11 were also implicated in other nervous system disorders.

David Goldstein noted that recent studies have shown the existence of genetic overlap across neuropsychiatric disorders (Serretti and Fabbri, 2013). The implication is that drugs found beneficial in one disorder might be beneficial in another. David Goldstein and colleagues also found that the de novo mutations playing an causative role could be grouped into functional categories. For example, six de novo mutations were found in GABA receptor subunits. Another group of mutations impinge on the epidermal growth factor (EGF)/extracellular signal-

[3]De novo mutations are genetic mutations that neither parent possessed or transmitted.
[4]See http://www.epgp.org.

regulated kinases (ERK) signaling pathway. Even though mutations were likely to differ among patients, it seemed likely that patients could be stratified by functional groups. The functional characterization of the de novo mutations is an essential part of the interpretation of the data. It then may be possible to match patients having certain mutations with a specific type of antiepileptic drug that targets the affected functional pathway.

Case Study of Identifying New Targets

Daniel Weinberger, director and chief executive officer of the Lieber Institute for Brain Development at Johns Hopkins University, described a new approach, or roadmap, to target identification in schizophrenia, which involves translating genes of interest into molecular mechanisms of illness. The key feature of this roadmap is a reliance on RNA sequencing in the brain after a gene has been identified. Studying the transcriptome has the potential to shed light on non-coding variations that affect gene function, specifically associated with illness state and genetic risk. Molecular mechanisms of association can be studied in cellular and animal models once these variations are understood. Weinberger provided two examples illustrating this roapmap: a metabotropic glutamate receptor and a novel potassium channel.

The metabotropic glutamate receptor 3 (GRM3) "regulates synaptic glutamate via a presynativ mechanism and by regulating the expression of the glial glutamate transporter, which inactivates synaptic glutamate" (Tan et al., 2007). Gene variation in GRM3 has been found to be associated with schizophrenia in patient samples studied by the Psychiatric Genomics Consortium[5] and by Weinberger's laboratory (Egan et al., 2004). Several single-nucleotide polymorphisms (SNPs) found thus far are located in non-coding regions, prompting study of RNA transcripts. Weinberger and colleagues discovered an alternatively spliced form of GRM3, termed GRM3Δ4, which yields a truncated receptor protein (Sartorius et al., 2006). Weinberger and colleagues sought to quantify mRNA expression levels of GRM3 and GRM3Δ4 in regions of the brain most affected by schizophrenia, the dorsolateral prefrontal cortex and hippocampus. They found increased expression of GRM3Δ4 in the prefrontal cortex of schizophrenia postmortem brains

[5]See https://pgc.unc.edu.

relative to controls (Sartorius et al., 2008). The fact that increased mRNA expression is associated with both disease state and genetic risk has propelled Weinberger and his colleagues to further study molecular mechanisms of association. This is a work in progress and all the RNA sequence data from thousands of brains will be available to other researchers through the Lieber Institute's website.[6]

In a separate study, Weinberger and colleagues found a new schizophrenia susceptibility gene, an isoform of the gene KCNH2, that encodes a novel hERG potassium channel protein (KCNH2-3.1) (Huffaker et al., 2009). The 3.1 isoform, which turns out to be primate- and brain-specific, is encoded in close proximity to risk-associated SNPs. In a cell model system, the isoform lacks a domain necessary for slow channel deactivation and repolarization, leaving neurons to fire in rapid trains of activity (Huffaker et al., 2009). The isoform exhibits increased expression in schizophrenia and is associated with risk genotype. Weinberger and colleagues showed that schizophrenic patients with the genotype for the novel isoform *KCNH2* were five times more likely to complete a clinical trial with the antipsychotic drug clozapine (Apud et al., 2012). Patients without the genotype were more likely to discontinue clozapine. The isoform, in short, modulates treatment response.

Finally, Weinberger's laboratory has created a mouse model that overexpresses the novel hERG potassium channel, as previously discussed. The mouse demonstrates executive cognitive deficits, episodic memory defects, and electrophysiological channel characteristics seen in cellular models of schizophrenia. It also has a deficit in hippocampal long-term potentiation, but the deficit does not emerge until animals reach young adulthood—an important feature of a developmental model of schizophrenia. When the novel gene is repressed during adult life, the cognitive deficits in the animals are reversed. With an eye toward drug development, Weinberger and colleagues have identified several molecules that show selectivity for this brain-specific novel potassium channel.

A better understanding of the genetic underpinnings of nervous system disorders has the potential to facilitate drug development through improved target identification.

[6]See http://www.libd.org.

IMAGING TECHNIQUES

Imaging technologies are another tool that may improve and accelerate therapeutic development. While functional imaging—used to characterize physiological changes in the body—can serve as an objective biomarker, molecular imaging—which attempts to illustrate biological processes at the cellular level—can be used to identify new targets (Rudin and Weissleder, 2003; Willmann et al., 2008). Through imaging of transgenic animals, researchers might be better equipped to determine molecular targets that correlate with nervous system disorders.

Translational Tools for Drug Development for Mood Disorders

Wayne Drevets, scientific vice president and disease area leader in mood disorders at Janssen Pharmaceutical Companies of Johnson & Johnson, discussed several translational tools and models relevant to therapeutic development in mood disorders. Drevets is currently studying mood disorders with bioimaging modalities due to the limited number of animal models that fully recapitulate the behavioral and biological abnormalities of mood disorders. His focus is on the medial prefrontal network, which includes the medial prefrontal cortex (mPFC) and anatomically related limbic, striatal, thalamic, and basal forebrain structures. The limbic structure of greatest interest is the subgenual anterior cingulate cortex (subACC). Targeting the subACC with deep-brain stimulation causes striking remission of symptoms in treatment-refractory depression (Mayberg et al., 2005).

By imaging the mPFC, Drevets and colleagues (1997) found lower metabolic activity and decreased cortical volume in patients with bipolar and unipolar depression. Similarly, the subACC exhibited reduced metabolism and cortical volume in both types of depression (Drevets et al., 2008). Patients taking lithium or valproate, both of which have neurotrophic effects in experimental animals, had larger subACC volume. In a prospective study, lithium was found to increase gray-matter volume in the prefrontral cortex (PFC) and subACC (Moore et al., 2009).

The PFC and subACC regions are significant in the prognosis of mood disorders, Drevets said. Nineteen of 23 studies showed that higher pre-treatment ACC activity, measured with a variety of imaging techniques, predicted better response to antidepressant treatment

(Pizzagalli, 2011). People with more severe gray-matter reductions in the PFC and ACC tend to display a greater severity of major depressive disorder (Salvadore et al., 2011).

The subACC also serves as a potential region to study biomarkers of treatment response (Pizzagalli, 2011). A pattern shift in metabolic activity is associated with reversal of negative emotional processing bias in depressed patients. The pattern shift is evident upon administration of several antidepressant drugs, including selective serotonin reuptake inhibitors (SSRIs) and drugs with novel antidepressant action, said Drevets.

Ketamine, when given to animals, acts as a rapid antidepressant and reverses loss of dendritic spines in mPFC and loss of synaptic function (Duman and Aghajanian, 2012; Duman et al., 2012). Previous human and animal studies have found that depression is associated with dendritic atrophy, synapse loss, and reduction in glia and GABA-ergic interneurons in limbic-mPFC circuits, noted Drevets. Ketamine is thought to produce a beneficial effect by disinhibition of fast-spiking inhibitory interneurons. This increases glutamate release and leads to induction of synaptogenesis and dendritic spine outgrowth (Duman et al., 2012). According to Drevets, the success with ketamine and its mechanism of action has led to the identification of new targets for rapid antidepressant action with a new class of drugs that is less toxic than ketamine. Drevets and his colleagues are working on increasing studies conducted on people with depression rather than using old behavioral assays in animal models.

Identifying Molecular Targets in Traumatic Brain Injury

Ramon Diaz-Arrastia, professor of neurology at the Uniformed Services University of the Health Sciences, spoke about the use of imaging to identify new molecular targets in traumatic brain injury (TBI). TBI is responsible for 1.7 million emergency department visits each year. Eighty percent of cases are mild, 10 percent are moderate, and 10 percent are severe. Two percent of the U.S. population, or 5.3 million people, live with disabilities resulting from TBI, making it the most common cause of death or disability in people under age 45 (Thurman et al., 1999).

TBI is an umbrella category for many subtypes of traumatic injury, including epidural hematoma, subdural hematoma, parenchymal contusi-

on, diffuse axonal injury, and traumatic subarachnoid hemorrhage. Most patients tend to have mixed pathologies, said Diaz-Arrastia. In general, computed tomography (CT) scans underestimate the extent of injury, whereas magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) provide better resolution. A recent prospective study of whole-brain volume as a biomarker found that patients experienced substantial global atrophy, displaying a mean volume loss of 4.5 percent by an average of 8 months post-TBI (Warner et al., 2010). Atrophy continues to occur months after the injury, but the greatest atrophy occurs in the acute/early subacute time period.

Atrophy is not uniform after diffuse traumatic axonal injury. Subcortical structures that are vulnerable to TBI-induced atrophy include the hippocampus, amygdala, and thalamus. In the cortex, the most vulnerable regions are the precuneus, posterior cingulate, superior parietal cortex, and superior frontal cortex (Warner et al., 2010). These cortical regions overlap somewhat with regions of cortical atrophy in AD (Perrin et al., 2009). Atrophy detected with MRI can be used as a surrogate biomarker of neuroprotective efficacy. There is a strong relationship between atrophy and function: The greater the atrophy, the greater the extent of disability (Warner et al., 2010).

Several new classes of drugs are being tested against emerging targets in TBI, noted Diaz-Arrastia. One promising target is vascular injury. Consequently, researchers are interested in drugs that promote angiogenesis or growth of new blood vessels. Several U.S. Food and Drug Administration–approved drugs related to blood flow—erythropoietin, sildenafil, and statins—are being "repurposed" for TBI, said Diaz-Arrastia. Enriched endothelial progenitor cells are also under study to help revasculize the site of injury (Hristov et al., 2003). Another target is Nogo, a myelin-based protein that inhibits neurite outgrowth. Anti-Nogo monoclonal antibodies have witnessed some measure of success in animal models of TBI and spinal cord injury (Freund et al., 2007; Marklund et al., 2007). Bone marrow–derived mesenchymal stem cells are also under study, noted Diaz-Arrastia.

Diaz-Arrastia concluded with the observation that stem cells are more likely to work in TBI and spinal cord injury as opposed to AD and Parkinson's diseases. The patients are generally younger, their brains are better equipped to regenerate, and an underlying neurodegerative disease process is not continuing to contribute to further pathology. In summary, imaging modalities show promise to identify new molecular targets in

the brain following TBI and have the potential to serve as biomarkers to help in the drug discovery process, said Diaz-Arrastia.

Top-Down Approaches

Beginning with imaging studies in humans and then validating findings in animal models, a top-down approach could improve and accelerate therapeutic development, said Scott Small, professor of neurology at Columbia University Medical Center. Small provided evidence for this approach using an example of neuroimaging to map human hippocampal pathology in vivo. The hippocampus is abnormal in several nervous system disorders, including AD. Small and colleagues sought to find out if different patterns of vulnerability were associated with different disorders that affect the hippocampus. If this could be demonstrated, Small noted it might be helpful for identifying biomarkers and underlying mechanisms of nervous system disorders. Small and colleagues conducted neuroimaging studies in humans to further understand hippocampal patterns for AD and schizophrenia, followed by validation studies in animals.

In a series of experiments, Small and colleagues sought to distinguish cognitive dysfunction in AD versus normal aging using functional MRI (fMRI). They found hypometabolism in the entorhinal cortex, but not in the dentate gyrus, whereas the opposite was true in normal aging. The results were first established in humans and later confirmed in monkeys and transgenic mice carrying an Alzheimer-related transgene (Moreno et al., 2007; Small et al., 2002, 2004). Hippocampal imaging thus has the potential to serve as a biomarker for drug discovery distinguishing AD from normal aging, noted Small.

Having established the dentate gyrus as a site affected by normal aging, Small and coauthors examined whether any interventions could restore function. The researchers took fMRI measurements of the dentate gyrus before and after several weeks of exercise in healthy mice and humans. Results were similar across both species: Exercise was correlated with increased cerebral blood volume (CBV) in the dentate gyrus, but not in other regions of the hippocampus (Pereira et al., 2007). In humans, increases in CBV are correlated with improved cognitive testing. Neurogenesis may underlie the improvement, given that the dentate gyrus is one of few regions of the brain known to display neurogenesis, according to the authors.

Small and colleagues sought to determine if abnormalities in hippocampal subregions were exhibited in patients with schizophrenia. Patients with prodromal psychosis, who are at risk for schizophrenia, exhibited hypermetabolism in the CA1 subregion of the hippocampus (Schobel et al., 2009). In a subsequent study, Small and colleagues used fMRI and structural MRI to map the hippocampus of prodromal schizophrenia (Schobel et al., 2013). After 3–4 years, the hypermetabolism seen in sub-region CA1 spread to the subiculum, another subregion of the hippocampus, resulting in atrophy. The atrophy, which was presumably caused by hypermetabolism, became apparent during the emergence of psychosis. In an effort to identify the underlying mechanisms, Small and coworkers turned to a mouse model of psychosis. Ketamine administration in this model was found to mimic the hippocampal pattern of hypermetabolism seen in schizophrenia. The investigators hypothesized that hypermetabolism was generated by increased activity of the neurotransmitter glutamate. A glutamate antagonist and direct measurements of extracellular glutamate revealed that glutamate was behind the abnormalities, hypermetabolism, and subsequent loss of hippocampal volume (Schobel et al., 2013). The investigators proposed that lowering glutamate might be an effective pharmacological strategy during early stages of schizophrenia to reduce hippocampal hypermetabolism, protect hippocampal volume, and halt disease progression.

Imaging is a tool that can be used in several facets of drug development for nervous system disorders. Particularly for target identification, researchers are able to visually map areas of the brain that are associated with specific disorders, which in turn may help to objectively determine potential targets.

4

Target Validation

Key Points

- Establishing pharmacologically relevant exposure levels and engagement are two key steps in target validation.
- There is a need for better biomarkers to objectively measure biological states and therapeutic effects.
- In addition to target validation, several participants highlighted the importance of rapid target invalidation.
- Understanding and examining the specific metrics of target validation and qualification may be useful for portfolio assessment.
- Going directly into first-in-human trials might be feasible for highly validated targets.

NOTE: The items in this list were addressed by individual speakers and participants and were identified and summarized for this report by the rapporteurs, not the workshop participants. This list is not meant to reflect a consensus among workshop participants.

Target validation ensures that engagement of the target has potential therapeutic benefit; like target identification, this is a critical step in drug development. If a target cannot be validated, then it will not proceed in the drug development process. Early validation of targets along with improved biomarkers were two opportunities discussed by Samuel Gandy, professor in the departments of neurology and psychiatry and associate director of Mount Sinai's Alzheimer's Disease Research Center, and Reisa Sperling, director of the Center for Alzheimer's Research and

Treatment and professor of neurology at Harvard Medical School. In addition, Kalpana Merchant, chief scientific officer of Tailored Therapeutics–Neuroscience at Eli Lilly and Company, offered a portfolio assessment tool outlining specific metrics for target validation and qualification, which could help assess confidence in a drug throughout the development process.

EARLY VALIDATION OF TARGETS

Gandy discussed how early validation of targets can accelerate therapeutic development using examples from Alzheimer's disease (AD) and traumatic encephalopathy[1] (acute and chronic). One pathological feature shared by these conditions is abnormal extracellular deposits of β-amyloid$_{42}$.[2] In the case of AD, the accumulation of β-amyloid$_{42}$ or its assembly form, oligomeric β-amyloid, begins as early as 15 years prior to symptoms (Rowe et al., 2010).

Gandy evaluated β-amyloid$_{42}$ and oligomeric β-amyloid against a list of criteria for an ideal drug target to determine whether or not they were strong targets for therapeutic development (see Box 4-1). Gandy noted that β-amyloid$_{42}$ fulfills most of the criteria, with three exceptions: (1) there is ambiguous evidence regarding proven function in pathophysiology of diseases; (2) it is uniformly distributed throughout the body, which can lead to peripheral side effects when modulated; and (3) a biomarker for monitoring therapeutic efficacy or target modulation is not entirely perfected. However, Gandy noted that even though there is much interest in oligomeric β-amyloid because some experts believe it may be the toxin associated with many degenerative diseases, it is not a well-established drug target, and there are currently limited biomarkers for this peptide (Reitz, 2012).

Gandy suggested that the current paradigm of drug development might require change, and that change might best occur via the development of novel approaches such as timing of the intervention; novel systems for screening drugs; novel approaches to known targets; and development of novel biological antagonists against aggregated proteins.

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[1]Diffuse disease of the brain that alters brain function or structure (e.g., trauma, tumor, infectious agents, etc.) (NINDS, 2010).

[2]β-amyloid$_{42}$ is a fragment of the amyloid precursor protein with 42 amino acids. There are other β-amyloids that range from 37 to 49 amino acids.

BOX 4-1
Properties of an Ideal Drug Target

- Disease modifying and/or proven function in the pathophysiology
- Highly selective to reduce adverse events
- If needed, a three-dimensional structure for the target is available
- Target has favorable "biochemical and/or cellular assays for binding and function," enabling high-throughput screening
- Can be validated experimentally for a specified indication; therapeutic use might be broadened to additional indications
- Genomics and phenotypic screening may add to the understanding of the disease model and predictive validity of potential side effects (e.g., knockout mouse, somatic mutations, etc.)
- A mechanistic biomarker exists to monitor efficacy
- The use of the target does not infringe on the intellectual property rights of others (no competitors on target, freedom to operate)

SOURCE: Adapted from Gashaw et al., 2011.

In particular, Gandy's laboratory is interested in this last strategy for Alzheimer's disease: the prevention of β-amyloid production at the synapse through development of antagonists. Gandy and colleagues studied the generation of β-amyloid in synaptosomes[3] in a mouse with the human transgene for APP. When the investigators depolarized the synaptosomes, the depolarization activated secretases that selectively spliced APP into β-amyloid$_{42}$, but not β-amyloid$_{40}$ (Kim et al., 2010). That finding propelled them to search for transmitter signaling pathways that mimic depolarization. They found that an agonist for Group II metabotropic glutamate receptor also selectively produced β-amyloid$_{42}$ in the synaptosomes. Having established the signaling pathway, they then sought to block β-amyloid$_{42}$ production by pretreatment with a Group II metabotropic glutamate receptor antagonist, which was successful in inhibiting generation of β-amyloid$_{42}$ (Kim et al., 2010).

Employing this novel strategy led to administration of two different Group II glutamate antagonists in the transgenic mouse. The drug BCI-838 was found to reduce oligomeric β-amyloid accumulation. Behaviorally, the drug improved learning and reduced anxiety behaviors. Results also show increased neurogenesis using three different markers of proliferation. Gandy raised the question of whether neurogenesis can act as an

[3]Synaptosomes are isolated intact nerve terminals.

unconventional biological antagonist of β-amyloid toxicity. He and colleagues are now testing BCI-838 in Phase I studies. Thus far, they have shown that BCI-838 is well tolerated in healthy controls. The next step is to test the drug in a geriatric population diagnosed with prodromal or mild AD. Gandy and colleagues are also considering the drug for use in tauopathies and TBI. In summary, Gandy suggested that the drug discovery paradigm for AD and other diseases could potentially change through the use of novel approaches outlined.

A NEED FOR BETTER BIOMARKERS

Sperling discussed the utility of biomarkers for AD. Their greatest utility, in her view, is for selecting participants for clinical trials who have target pathology by measuring and predicting disease progression or prognosis and assisting with patient stratification (IOM, 2011). However, the greatest challenge is that there are deficiencies in the number of biomarkers currently available that track and predict therapeutic response. Two clinical trials of monoclonal antibodies against β-amyloid showed lower β-amyloid with positron emission tomography (PET) amyloid imaging as the biomarker. The issue was that the antibodies did not improve cognition in these Phase II studies (Ostrowitzki et al., 2012; Rinne et al., 2010). Better biomarkers are needed of synaptic dysfunction, which, according to the β-amyloid hypothesis, occurs much earlier than cognitive decline. Biomarkers of synaptic dysfunction—using new imaging modalities such as task-functional magnetic resonance imaging (fMRI) and resting state (task-free) functional connectivity, or fc-MRI—could be studied along with PET amyloid imaging to determine the benefits of anti-β-amyloid therapies. For example, fMRI and PET amyloid imaging were combined to study asymptomatic and minimally impaired older individuals to demonstrate that amyloid pathology was linked to neural dysfunction of the default network in cortical regions implicated in AD (Sperling et al., 2009). Imaging modalities may be better as useful measures of therapeutic response, because cognitive impairment occurs too late in the disease process of AD. However, imaging does not constitute a surrogate endpoint, but rather a correlate that is a measurement of biological activity (Fleming and Powers, 2012).

Sperling suggested potential solutions for targeting and developing biomarkers for β-amyloid that might also apply to other nervous system disorders:

- embed multiple biomarkers in Phase I/IIa trials in order to develop pharmacodynamic profiles quickly;
- develop synaptic and other biomarkers in humans that can give a functional readout in a short timeframe;
- test drugs aimed at upstream processes before irreversible downstream damage;
- find more potent drugs without dose-limiting toxicity; and
- use combination therapies and start them before symptoms appear.

In the case of psychiatric disorders and *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria, John Krystal, Robert L. McNeil, Jr., professor of translational research and chair of the department of psychiatry at Yale University School of Medicine, commented there needs to be a willingness to explore subgroups of patients with mechanistic homogeneity. Connecting genetic networks and quantitative traits might build the case for proof-of-concept studies; the studies would be based on quantitative information rather than behavioral readouts and could be tested in specific patient groups. In summary, Chas Bountra, head of the Structural Genomics Consortium and professor of translational medicine at the University of Oxford, noted that unless biomarkers are discovered, the field faces continued high failure rates in Phase IIa clinical trials. At this stage of drug development, the majority of novel compounds fail (Paul et al., 2010). As a result, target validation, or invalidation, is delayed.

PORTFOLIO ASSESSMENT TOOL FOR TARGET VALIDATION AND QUALIFICATION

Merchant provided her perspective on factors considered when making investment decisions in neuroscience portfolios. Merchant began by noting that attrition in drug development is very high in Phase II studies, with an approximate rate of 66 percent. Major causes of failure in Phase II are related to inadequacies in efficacy, safety, the overall strategic plan, and bioavailability and pharmacokinetic properties (Paul et al., 2010). High attrition underscores the need for better target validation and biomarkers to avoid selection of the wrong target, the wrong patient population, or the wrong dose. Merchant suggested that target validation is best accomplished in humans, while animal models are important for

target qualification, which is a step in the process to determine the scientific validity and safety of a target (see Figure 4-1).

Target Validation

There are three major components of target validation using human data: tissue expression, genetics, and clinical experience. For each of these components, several metrics might guide decisions to invest in a particular therapy (see Figure 4-1). Merchant identified specific metrics that might apply in ascending order of priority (see Table 4-1).

Merchant noted that each step toward target validation provides an increasing level of importance on how to interpret data and build confidence in what projects to bring forward. All the components—tissue expression, genetics, and clinical experience—can inform disease pathways. It is an iterative learning problem. How can what is learned from tissue expression integrate with genetics and integrate with the clinic?

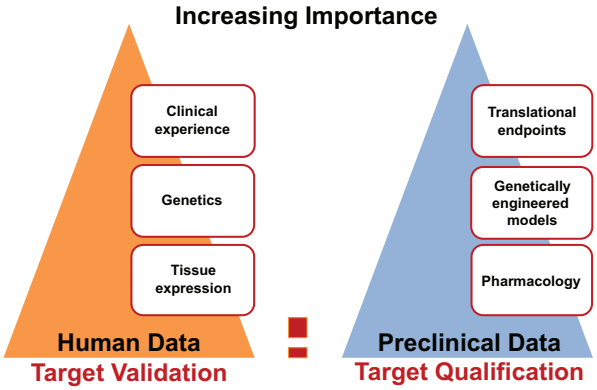

FIGURE 4-1 Major components of target validation and qualification.
SOURCE: Merchant presentation and Lilly Research Laboratories, April 9, 2013.

TABLE 4-1 Metrics of Target Validation

Components of Target Validation		Metrics Increasing Confidence →		
Increasing Importance ↓	Pharmacology	Target protein is expressed or active in the desired organ/ subregion/cell types	Target mRNA expression is altered by the disease	Target protein expression is altered in disease/tissue
	Genetically Engineered Models	Genetic association with disease occurs in small, under-powered, or non-replicated studies without knowing the function of the variant	Polygenic association with modest effect size and known function of the variant, or association with common, low-risk variant in a gene that also has rare variant associated with large effect size, or in the best case	Monogenic association with large effect size and known function of gene variant
	Translational Endpoints	Clinically relevant efficacy observed in a small trial, but knowledge of engagement of specific target/ pathway is lacking	Clinically relevant efficacy is observed with at least one ligand with a different mode of target modulation or with two ligands on biomarkers previously shown to predict efficacy	At least one ligand with an analogous mode of action on the target/target pathway has "approvable" efficacy in the indication of interest and robust evidence of target engagement

NOTE: mRNA = messenger ribonucleic acid.
SOURCE: Merchant presentation, April 9, 2013.

Target Qualification

Target qualification consists of evaluating a target to ensure that it has a clear role in the disease process (Cambridge Healthtech Institute, 2013). Three major components of target qualification in preclinical data, according to Merchant, are pharmacology, genetically engineered models, and translational endpoints (see Figure 4-1). For each component, Merchant specified metrics that could be used to guide decisions and in what order of priority (see Table 4-2).

Merchant concluded by saying that the outlined metrics and components could be used as a portfolio management tool for target assessment. Merchant also emphasized the need for researchers to conduct molecular phenotyping of disorders in order to create molecularly defined disease states and not simply syndromes. During the discussion, a participant asked how researchers can know, definitively, when a target is invalidated. Merchant suggested examining target engagement in clinical trials within the targeted population.

Several participants noted that it is possible to move directly into clinical trials for highly validated targets. However, Krystal said researchers cannot go directly into the patient population without knowing whether the biology of the animal models applies to healthy humans. The drug development process is exploratory; it is an iterative process of testing specific mechanistic hypotheses across cellular and animal studies, healthy human subjects, and clinical trials. A participant asked if going into first-in-human trials would be an appropriate risk–benefit decision for serious conditions with short life expectancies such as amyotrophic lateral sclerosis. Merchant agreed that it would be appropriate and said that is the case for oncology drugs in which researchers and companies go to first-in-human trials in patients with clear biomarkers. Target validation is a multilayered step in drug development that is critical to the success of a drug. Validated targets and biomarkers, along with assessment tools, are needed to ensure that the drug is actively engaging the target to produce an expected therapeutic effect.

TABLE 4-2 Metrics of Target Qualification

Components of Target Qualification		Metrics Increasing Confidence →		
Increasing Importance ↓	Pharmacology	A pharmacological tool (e.g., a small molecule, antibody, or peptide) modulates disease associated with pathway in vitro or in heterologous cell lines at appropriate concentrations	Ligands with the intended mode of action modulate disease-associated pathway ex vivo or in native tissue, or in the best case	Ligands with intended mode of action modulate disease-associated pathway in vivo and target engagement–activity relationships are established
	Genetically Engineered Models	Genetic modulation in a non-mammalian model organism produces disease- or treatment-relevant phenotype	Genetic modulation in a rodent/non-human primate produces disease-relevant endophenotype	Human pathogenic mutation of the target in a rodent/primate mimics disease pathway and/or genetic modulation of the target mitigates the same
	Translational Endpoints	Target or pathology is known and demonstration of target pharmacology identical to human native tissue assays	PK/PD relationship and margin of safety are established using a translational biomarker of target engagement/ modulation	PK/PD relationship and margin of safety are established using a translational biomarker historically associated with clinical efficacy

NOTE: PK/PD = pharmacokinetic/pharmacodynamic.
SOURCE: Merchant presentation, April 9, 2013.

5

Opportunities to Improve and Accelerate the Drug Development Pipeline

Key Points

- The molecular medicine approach could be used for drug development by understanding the underlying pathophysiology of disease in order to identify and validate drug targets.
- Using investigational drugs as clinical probes, to identify and/or verify a target in healthy human populations, could aid investigators in making go/no-go decisions.
- Emerging tools and technologies based on scientific utility criteria that are relevant to the field today, such as diversity and competition, are needed.
- Shifting the conventional paradigm of drug screening to one that requires more rigorous preclinical and clinical experiments could increase the likelihood of identifying successful targets and mechanisms.
- Human phenotypes may better inform drug discovery; therefore, starting in humans first, then validating in animal models, may be more beneficial to drug development.
- Due to the complexity and heterogeneity of patients, a greater emphasis on multipronged approaches using combination therapies, might result in an increased number of successful drugs.
- Public–private partnerships and the extension of the precompetitive space among academia, industry, and government could help de-risk research.
- Increasing standards and sharing of preclinical data might help to improve reproducibility, thereby strengthening the drug development pipeline.
- Several factors could influence investment decisions that researchers might consider to increase the probability that their drug will be successful.

NOTE: The items in this list were addressed by individual speakers and participants and were identified and summarized for this report by the rapporteurs, not the workshop participants. This list is not meant to reflect a consensus among workshop participants.

Novel approaches and infrastructure changes to the current drug development pipeline might improve the efficacy of research and support a more efficient process. Although there are several bottlenecks in the current pipeline, several participants discussed opportunities to facilitate drug development for nervous system disorders through methodological approaches, shifts in current processes, and changes to the infrastructural components in drug development.

METHODOLOGICAL APPROACHES

Due to the array of challenges the field is currently facing, several participants discussed the advantages of considering novel methodological approaches that address all stages of the development pipeline, including target identification and validation. According to Mark Bear, professor of neuroscience at the Massachusetts Institute of Technology, by examining the genetic basis of a disease first, a molecular medicine approach might provide insight into underlying pathophysiology to identify and validate targets. John Krystal, Robert L. McNeil, Jr., Professor of Translational Research and chair of the department of psychiatry at Yale University School of Medicine, discussed the utility of the experimental medicine approach to improve translation between preclinical and clinical studies through an exploratory process of using drugs as clinical probes to identify and verify targets.

Molecular Medicine Approach

Bear began by outlining the promise of molecular medicine, an approach that starts with a disease, proceeds to find its cause, and teases apart how the cause exerts pathophysiological effects by conducting basic research. This process results in a mechanistically inspired identification of a molecular target. After validation of the target succeeds, novel drugs aimed at the target can be tested first in animal models and then in clinical trials.

The molecular medicine approach has successfully led to ongoing clinical trials for Fragile X syndrome, which is the most widespread single-gene cause of autism. The genetic cause, reported in 1991, was found to be a transcriptional silencing of the Fragile X Mental Retardation 1 (FMR1) gene, resulting in absent expression of the FMR1 protein

(FMRP). By 1994, the first FMR1 knockout mouse was made. Eight years later, in 2002, research on basic neurobiology revealed that knockout animals showed an abnormal type of synaptic plasticity marked by exaggerated function of the metabotropic glutamate receptor 5 (mGluR5). This key finding was validated in 2007 by the demonstration that numerous Fragile X phenotypes are corrected in FMR1 knockout mice by genetic reduction of mGluR5 protein production (Dölen et al., 2007). With the target validated, animal studies and clinical trials ensued with inhibitors of mGluR5.

This line of investigation led to the mGluR theory of Fragile X, which holds that many of the syndrome's psychiatric and neurological abnormalities are a downstream consequence of exaggerated mGluR5 activation (Bear et al., 2004). The normal FMRP is an mRNA-binding protein that functions at many synapses to repress local protein synthesis stimulated by mGluR5 (Bhakar et al., 2012).

One part of the Fragile X story worth noting is that it was a "community" effort: 40 distinct phenotypes were catalogued in knockout animals, including flies, zebrafish, and mice, in at least 31 different publications (Bhakar et al., 2012). The lessons learned from the Fragile X story, according to Bear, are (1) defined genetic etiology led to valid animal models; (2) fundamental synaptic biology revealed signaling defects; (3) core pathophysiology is evolutionarily conserved; (4) disease-modifying treatments are feasible; (5) treatments can be successful after symptom onset; and (6) multiple mutations may converge on a common signaling pathway.

Bear was careful to point out the risks incurred at every stage of the process, most notably in the design of clinical trials of mGluR5 inhibitors. He observed that fulfilling the promise of molecular medicine requires many educated guesses about the following:

- Drug formulation
- Patient selection (e.g., age, ratings at baseline, etc.)
- Dose selection
- Treatment duration
- Number of subjects
- Number of clinical sites
- Choice of endpoints
- Statistical analysis plan
- Agreement with the U.S. Food and Drug Administration (FDA) on all of the above

- Training of sites in Good Clinical Practice so that data are acceptable to FDA

Experimental Medicine Approach

The most challenging step in the drug development process, Krystal said, is the translation of cellular or animal models to healthy human subjects and then to patients. Krystal noted that researchers cannot go directly into the patient population without knowing whether the biology of the animal models applies to healthy humans. The drug development process is exploratory; it is an iterative process of testing specific mechanistic hypotheses across cellular and animal studies, healthy human subjects, and clinical trials, Krystal said.

The experimental medicine approach, according to Krystal, involves the ability to evaluate the effects of a putative therapeutic agent in humans and examine outcomes at various levels (e.g., behavior, cortical activity, and brain imaging). The goal is to produce therapeutic change in a pathophysiologic process, quickly, and in a laboratory setting. This approach uses drugs as clinical probes in order to identify or verify a target and/or study mechanisms of disease. Similar to proof-of-concept clinical trials, this approach examines the ability of a drug to act on a pathological target and affect a biological endpoint as measured by a biomarker. In general, the experimental medicine approach relies on human studies rather than animal models (Insel, 2012b).

The approach could be useful in several ways to advance and accelerate drug development, said Krystal. First, for go/no-go decisions, using positron emission tomography (PET) imaging, researchers can determine whether a drug enters the brain and reaches the target. Second, the experimental medicine approach can increase or decrease confidence in a particular drug, especially in Phase II. Proof-of-mechanism and proof-of-principle studies could be conducted using this approach to accelerate the development process for several reasons:

- Studying healthy subjects in pathology models instead of patients is cheaper and quicker.
- Biology readouts can be based on short-term rather than long-term exposure (limited toxicology).
- Human pharmacology studies might often be more tractable than studying the disorder because researchers can reduce heterogene-

ity and the impact of placebo response while probing specific mechanisms.
- Experimental medicine approaches model pathology, which is often necessary to see a therapeutic drug effect.

Krystal used this approach when deploying the drug ketamine to probe pathological mechanisms underlying schizophrenia. Krystal and colleagues demonstrated that ketamine, if given to healthy subjects, produces both positive symptoms of schizophrenia—hallucinations and delusions—and negative symptoms—withdrawal, apathy, and lack of motivation (2005). The schizophrenia-like effects of ketamine are not altered by medications such as benzodiazepine, lorazepam, or two antipsychotic drugs, haloperidol and olanzapine. Findings suggest that there are a variety of biological mechanisms underlying schizophrenia, and the ketamine model, in particular, is related to glutamate circuit dysfunction.

Pharmacologic studies drive translation from animal to human to patient, noted Krystal, and can be useful for asking specific questions that inform the drug development process. Still, it is important to point out that the experimental medicine approach, particularly with regard to ketamine, is designed to probe specific mechanisms, not the full biology, of the disease. Krystal concluded that pharmacologic studies might be used in a thoughtful and hypothesis-based way to inform the testing of specific therapeutic mechanisms in an iterative process that could to lead to drug discovery efforts.

The molecular and experimental medicine approaches are just two ways to improve drug development by rethinking conventional methodologies. Examining the pathophysiology of diseases and changes that occur from drug interactions in humans may improve translation from preclinical to clinical studies. In addition to the use of novel approaches, Krystal noted paradigm changes to the current drug development pipeline are needed to facilitate a more efficient process.

OVERARCHING CHANGES TO THE CURRENT PIPELINE

The current drug development pipeline is characterized by a number of challenges that are impeding innovation and the development of novel therapeutics in the field, as discussed in Chapter 2. Jason Karlawish, professor in the department of medicine, medical ethics, and health policy at the University of Pennsylvania, discussed the need for new tools and

technologies that fulfill specific criteria needed to answer research questions and test hypotheses in the field. Nicholas Brandon, senior director of the Neuroscience Innovative Medicines Unit (iMED) at AstraZeneca, offered a new paradigm to screen drugs more effectively in order to increase the probability of advancing to clinical trials. Scott Small, professor of neurology at Columbia University Medical Center, and Read Montague, director of the computational psychiatry unit at Virginia Tech and professor at University College London, highlighted the utility of adopting a top-down approach, or a reversal of the current pipeline direction. Finally, Christopher Austin, director of the National Center for Advancing Translational Science, discussed combinational strategies, emphasizing the use of more than one therapy to treat nervous system disorders.

New Scientific Utility Criteria

Karlawish said that the scientific community might opt for revised scientific utility criteria, namely, diversity, competition, degrees of validity, innovation, and value to patients in the selection of future tools and technologies. Karlawish provided a historical overview of the use of the inbred mouse and discussed how new tools and technologies might be developed to reflect the current needs of the field. Karlawish opened by describing a current trend in translational failures: the inability of some drugs that show promise in preclinical animal models to translate into successful therapeutics. Another way to frame this problem is that the inbred mouse, which dominates drug discovery, has not had a commensurate return on investment. This problem is not unique to the neurosciences, said Karlawish, and holds true in most other fields of medicine, especially cancer and infectious disease.

For more than 70 years, the inbred mouse has dominated science. Karlawish noted that the inbred mouse, in particular, was chosen as "a matter of policy" due to its small size, easy maintenance, and low cost. During its initial use, the underlying scientific utility or "value" of the inbred mouse included efficiency, standardization, collaboration, and communication among laboratories, and its ability to produce high-volume data and increase fundamental knowledge. Today, roughly 60 percent of animals used for research protocols are mice (European Commission, 2010). Although inbred mice have substantially increased knowledge, the benefits of their use need to be weighed against potential

risks—namely, premature standardization, which can stall progress, said Karlawish.

Heavy reliance on the inbred mouse might be precluding the use of a better tool or technology for generating new knowledge and treatments, noted Karlawish. The inbred mouse was not necessarily the wrong choice for the past 70 years, but rather, a choice that reflected scientific and society needs at the time, he continued. Although, there are several benefits to animal models, the inability for some drugs that show promise in preclinical studies to translate to clinical trials is still an issue. Commonly used animal models, such as the inbred mouse, do not always fully recapitulate human diseases, and therefore may limit the array of questions that can be answered (Bolker, 2012). Karlawish reiterated this point, stating that when the field is not sure where to go, it may be beneficial for researchers to be open to collegial competition and diversity. Researchers might consider utilizing other models that are also aligned with their specific research questions, taking into account environmental and other external factors (Bolker, 2012).

New Paradigm for Drug Screening

Brandon spoke about the need for a paradigm shift in screening nervous system drugs. As an example, Brandon used the conventional drug-screening paradigm for producing non-innovative, "me-too" compounds, which are pharmacologically similar to older drugs, but have reduced side effects (Rizzo et al., 2013). Conventional screens begin with high-throughput screening of large chemical libraries, resulting in identification of lead compounds for which in vivo screening and assessment of efficacy is conducted. Those steps are followed by demonstration of efficacy relative to standard of care, determining side effects, and extended characterization. But this paradigm has been largely unsuccessful at finding novel targets and mechanisms because the targets studied are generally not relevant to disease, Brandon noted.

Brandon outlined components of a potential new drug-screening paradigm that might produce greater success (see Table 5-1). Additional components include

- target modulation to demonstrate a pharmacological effect, which is typically a behavioral effect, not necessarily related to efficacy, at doses that occupy the target;

- evidence for efficacy potential using a relevant perturbation in a disease model;
- modulation of physiology endpoints;
- side-effect profiling; and
- screening to identify drugs whose effects may translate across assays.

Finally, Brandon suggested that understanding why drugs fail and then repeating the experiment may help in avoiding the abandonment of new drugs (Rizzo et al., 2013). Brandon's experience with an inhibitor of phosphodiesterase 10A (PDE10A) exemplifies the limits of the conventional paradigm for drug screening. PDE10A is expressed primarily in medium spiny neurons of the striatum. Because PDE10A degrades cyclic

TABLE 5-1 Paradigm Shifts Aimed at Improving Identification of Potential Therapeutics

Paradigm Shifts	
Before	**After**
Poor target identification	Target identification dependent on human genome data
Screens done quickly and without thought	Thoughtful and relevant (e.g., iPSCs)
Behavioral endpoints dominated	Electrophysiological circuit-based endpoints dominated
Normal animals used	Transgenics, lesion animal used
Acute dosing	Dosing regiments explored
Target engagement optional	Target engagement obligatory (demonstrate in vivo or ex vivo target occupancy in the brain)
Mechanism unknown	Mechanism explored
Knowledge in patient population optional	Biology of patient explored
Walk away after failed Phase II trials	Repeat experiments

NOTE: iPSCs = induced pluripotent stem cells.
SOURCE: Brandon presentation, April 8, 2013.

adenosine monophosphate (AMP), its inhibition results in a robust elevation of AMP. The PDE10A inhibitor showed acute efficacy in animal models of schizophrenia and Huntington's disease (Brandon et al., 2008; Giampà et al., 2010). Efficacy was shown in a stimulated locomotor assay and in other assays used in conventional drug screening paradigms. Despite showing efficacy in multiple conventional screening assays, the drug failed to show efficacy in Phase II trials in schizophrenia. Had investigators evaluated the drug's potential according to Brandon's suggested new paradigm, it might not have passed the screen. The drug showed target engagement and target modulation, but no evidence of reversal of positive symptoms, negative symptoms, or cognitive deficits in schizophrenia. It also did not show modulation of physiology endpoints in positive symptoms, cognitive symptoms, and brain network activity. Failure in the new screening paradigm, in other words, may explain why the drug did not work in human clinical trials. Brandon and colleagues, alongside the National Institute of Mental Health (NIMH), are considering more experiments to determine specific reasons for the failure and whether target occupancy in healthy volunteers and patients might be a critical component.

The lesson Brandon learned from the failure of the PDE10A inhibitor clinical trial is that investigators cannot rely on the conventional paradigm for drug screening. The PDE10A inhibitor showed promise in preclinical studies and Phase I trials, but failed in Phase II. Due to this experience, Brandon suggested a new drug screening paradigm with more rigorous components that could be beneficial to accelerate the drug development process (see Table 5-1). Brandon concluded that the field has misinterpreted animal data, oversold the same data, and has been reluctant to do experiments in humans. To develop therapeutics, researchers need to be willing to do the difficult experiments in both preclinical models and in an experimental medicine setting and accept some loss of speed (see Leaf, 2013).

Reversing the Pipeline

As previously highlighted in Chapter 2 by William Potter, senior advisor in the Office of the Director of NIMH, the current development pipeline moves from cellular/molecular mechanisms to animal models to control populations, and finally to the patient population. Several speakers noted that reversing the experimental pipeline by starting in

humans for target identification and validation, then moving to animal models for target engagement, may improve the drug development process.

Imaging

As previously discussed, Small suggested that translational imaging using a top-down approach, starting with humans and then validating findings using animal models, has the potential to accelerate the discovery of novel molecular targets (see Chapter 3). He emphasized the notion of regional vulnerability and the ability to identify underlying mechanisms using imaging, which could serve as future biomarkers for potential therapeutics and assist with patient stratification.

Computational Neuroscience

Montague discussed the use of computational neuroscience to accelerate development through reversal of the model organism pipeline by studying phenotypes of cognition (simple learning and conditioning behaviors) in humans first and then validating those measures in animal studies. Montague defines "computational neuroscience" as the study of nervous system function by processing patterns of information with an emphasis on neurons and their connections. Understanding nervous system function in computational terms exposes the underpinnings of healthy and diseased conditions and suggests neurobiological mechanisms that can be important for drug discovery and development, said Montague. The use of model-based brain and behavioral responses may help to generate potential genetic targets.

Montague asked, How do we validate rodent behavioral models as models of humans? For example, if there were a rodent model of empathy, what steps might be taken to ensure that it is in fact a model of what is observed in humans? Montague suggested that it might be beneficial to reverse the model organism pipeline and start in humans before moving into animal models for several reasons:

- Cognitive phenotyping using model-based behavioral probes is beneficial when seeking mechanisms in comparison to subjective diagnostic categories.
- Computational modeling can connect behavior and neural responses.

- Complete "theories of cognition" are not necessary.
- The use of model-based brain and behavioral responses may help generate potential genetic targets.
- Conducting research in humans first to develop phenotypes that include computational model-based parameter extractions from their behavior may help to develop new ways to characterize and identify genetic variation and substrates that contribute to disease.

Montague provided several examples in support of this view. Dopamine pathways play a central role in normal cognition—motivation, reward seeking and processing, working memory, and conditioned behavior—and disorders in these pathways are associated with addiction and schizophrenia (Montague et al., 1996). Behavioral tasks can probe the underlying mechanisms of normal and abnormal cognition and how dopamine systems are involved. For example, one behavioral task, of valuation and choice, asks subjects if they want $100 today or $117 in a week. The amounts and timeframe can be manipulated (e.g., $300 today or $330 next week) to determine the value of the future income relative to the present. Drug addicts will always choose the immediate reward, whereas healthy controls make choices based on the amount and timeframe. However, drug addicts were similar to healthy controls when there was a risky bet versus a "sure thing." Montague said the study goal is to understand valuation and choice and catalogue human phenotypes. The phenotypes include computational model-based behavioral parameters and human imaging using functional magnetic resonance imaging (fMRI) when making decisions. Using this information, Montague noted that he could identify genes—particularly those that might be involved in the synthesis and distribution of dopamine or the construction of the system—that may be a part of process and input them into a model organism.

Montague's laboratory is now focused on computational modeling of fairness games (Kishida et al., 2010). One fairness game is the ultimatum game, in which one person is given $100 and asked to split it with a second player. The second player can accept or reject the offer. If the second player accepts the offer, the two split the money, whereas if the player rejects the amount, neither gets money. Montague's research has shown that the second player rejects the offer 50 percent of the time if the first person only offers $20 of the $100 (an 80/20 split). The second player is incensed by the unfairness of the split and foregoes money for

both players. This simple exchange, when extended to multiple rounds and different amounts of money, requires important cognitive functions such as (1) response to "fair" reciprocity (social norms); (2) depth of thought; (3) sensitivity to horizon (planning); (4) sensitivity to history of play (working memory); and (5) ability to learn and to model the other person. Using fairness and other types of complex decision-making games, Montague and coworkers examine the behaviors of healthy individuals in comparison to people with psychiatric disorders to develop phenotypes of each group. Montague's goal is to design behavioral probes of the dopamine system to make computational predictions about complex human decision making and behavior.

Combination Therapy

Austin highlighted the value of combinatorial strategies in drug development. Combinatorial strategies have become popular in diseases where the target cell mutates, such as in cancer and infectious disease. But the nervous system is adaptable in a more rapid way: it can adapt on a scale of microseconds. Therefore, it should not be a surprise that the nervous system is resistant to interventions, said Austin. When monotherapy does not work, perhaps the conclusion should be that the system adapted, rather than the more typical conclusion that the target was not valid. Combinatorial strategies should be considered in nervous system disorders for these reasons, reiterated Austin.

Changing scientific approaches to the drug development pipeline to address current challenges in the field may be beneficial to the development of therapeutics for nervous system disorders. Several speakers stated that changes to the current paradigm are needed to facilitate a more efficacious drug development pathway to include developing new tools and technologies that are based on scientific utility criteria desired from the field today; shifting the drug-screening process from conventional practice to one that produces innovative therapeutics; reversing the development pipeline by starting in humans first; and considering combination therapies for nervous system disorders.

INFRASTRUCTURAL OPPORTUNITIES

In addition to shifting current scientific practices, many participants noted a number of opportunities to improve and accelerate drug development through infrastructural changes. Potter said that public–private partnerships are a means to share resources and risk among several entities (i.e., academia, industry, and government). According to Chas Bountra, head of the Structural Genomics Consortium and professor of translational medicine at the University of Oxford, extending the precompetitive space to facilitate collaboration in preclinical and clinical research could de-risk the drug development process and decrease repetitive research among organizations. Walter Koroshetz, deputy director of the National Institute of Neurological Disorders and Stroke (NINDS), and Adrian Ivinson, director of the Harvard NeuroDiscovery Center at Harvard University, discussed several initiatives are currently under way, including opportunities sponsored by the National Institutes of Health (NIH), the Massachusetts Neuroscience Consortium, and the Collaborative CNS Screening Initiative. In addition, establishing preclinical standards and a repository to share and mine data, such as "www.preclinical trials.gov," may improve reproducibility, said Paul Aisen, director of the Alzheimer's Disease Cooperative Study and professor in the department of Neurosciences at the University of California, San Diego.

Develop Public–Private Partnerships to De-Risk Research

Collaboration and the ability to share risk and costs among entities are two reasons why public–private partnerships are important for successful drug development, especially with current resource constraints. In addition to pharmaceutical companies stepping back from the drug discovery process, venture capital (VC) typically does not take risks beyond 7 years. There is a need to spread the risk among discovery, preclinical proof of concept through Phase I and Phase II trials, a participant noted. Bountra commented that industry is good at processes that require scale and infrastructure (e.g., high-throughput screening, lead optimization, manufacturing); target discovery is the main challenge. Academia and industry could work together to help develop targets that can be converted to drugs. Potter agreed and stated that the current drug development model does not allow the field to translate molecular science into new therapeutics, and the idea of sharing risk across several groups (e.g.,

stakeholders, advocacy groups, government, industry, and academia) would help investments from industry to focus on compounds that are more likely to succeed. Lawrence Goldstein commented that rather than trying to de-risk, the field could try to identify key bottlenecks in the system that allow risk tolerance and a degree of uncertainty.

Bountra is among a group of researchers spearheading a public–private partnership aimed at overcoming the many challenges facing drug development for nervous system disorders (Norman et al., 2011). The partnership consists of academic researchers, regulators, and several pharmaceutical companies. The goals are to de-risk drug development, increase efficiency, and accelerate new knowledge. The group hopes to achieve these goals by

- focusing on epigenetic targets;
- making novel reagents freely available;
- evaluating drugs in human primary cells;
- publishing all data immediately; and
- pushing the precompetitive boundary to Phase IIa when evaluating novel targets in patients.

Bountra elaborated that he and his colleagues are creating a public–private partnership in which resources are shared, which in turn will help de-risk the drug development process to Phase II. Bountra concluded that pioneering drug discovery can be challenging for any single organization and suggested that advances might occur through pooled funds from both the public and private sectors, improved access to reagents, and collaborations with patient groups and regulators to de-risk novel targets. After a public–private partnership advances the preclinical space forward toward Phase IIa, industry could be better situated to generate new drugs with greater accuracy and less risk, Bountra said.

Kazumi Shiosaki, managing director at MPM Capital, agreed with Kiran Reddy, principal at Third Rock Ventures, that there is a need for public–private partnerships to help alleviate the risk for neuroscience venture investments. VC firms are continuing to invest in the preclinical stages of drug development and are optimistic about emerging therapeutic approaches and technologies in the field. Shiosaki described how VC firms such as MPM work to reduce the time between their investment and a pharmaceutical company acquisition liquidity event by using various types of structured acquisitions to share risks and rewards. In a structured acquisition, large pharmaceutical companies make the

bulk of their payments for the startup (known as "earn-outs") contingent on the success of clinical trials or commercial activities. More recently, when there are drugs in development, the acquisition is made using an "option to acquire" agreement for the pharmaceutical company to acquire the startup if programs advance successfully. The pharmaceutical company pays an option fee that brings in non-dilutive capital to advance the drug project. The startup and the pharmaceutical company need to have a clear agreement and definition of the milestones that trigger the option.

Several participants suggested there is an increasing trend for lead generation and other steps in preclinical testing to be done by organizations other than drug companies (e.g., government, academia, and biotechnology companies). Potter noted that some drug companies choose to minimize risk by devoting their resources to drugs that are farther along the development pathway. Consequently, NIH has become more actively involved in supporting preclinical drug development. Through its National Center for Advancing Translational Science (NCATS), NIH supports new programs in preclinical development, one of which is the NIH molecular libraries program.[1] The program consists of a network of national laboratories whose aim is to generate novel small molecule probes by performing high-throughput screening, secondary screens, and medicinal chemistry. In addition, NIMH is supporting the Fast-Fail Trials (FAST) initiative[2] in the discovery of psychiatric medications by providing a rapid means for researchers to test new or repurposed compounds for their potential therapeutic use.

NCATS is working with other NIH institutes involved in neuroscience research to establish a clinical network in which experimental medicine can be performed in an efficient way, said Austin. Koroshetz reiterated that smaller and medium-sized institutes that want to participate in translational research could benefit from leveraging what is expected to be larger and more stable resources from NCATS. The initiative is designed to forge a network of centers that have harmonized information (both non-disease-specific and disease-specific). To help investigators understand FDA requirements and to facilitate communication, NCATS is engaged in conversations with FDA about having FDA staff members serve as consultants to new investigators. A few participants noted that by supporting public–private partnerships, government

[1]See http://mli.nih.gov/mli.

[2]See http://www.nimh.nih.gov/research-priorities/research-initiatives/fast-fast-fail-trials.html.

partners, such as NIH, might improve and accelerate drug development through a focus on understanding disease mechanisms and the underlying biology.

Extend the Precompetitive Space

In addition to public–private partnerships, collaboration in the precompetitive space is important to identify and validate novel targets while reducing the replication of studies. Bountra suggested that by extending the precompetitive boundary to Phase II, academic and government investigators would be included in research that establishes proof of clinical mechanism of a drug in humans before industry makes a huge investment. Sharing the risk and cost among all sectors could help advance drugs along the development pipeline (Bunnage, 2011). Several initiatives are under way to encourage collaboration in the precompetitive space to facilitate drug development.

Efforts by the National Institute of Neurological Disorders and Stroke

Koroshetz provided several examples of the institute's portfolio of grants, contracts, and cooperative agreements that provide researchers with resources needed to build confidence throughout the drug development process, adding knowledge to the precompetitive space. The oldest program, which has been under way for 10 years, consists of cooperative agreements designed to give 5 years of dedicated funding for conducting preclinical research leading to an investigational new drug (IND) submission.[3] Today, the program is milestone-driven and includes criteria for go/no-go decisions. If investigators do not hit milestones in pursuit of an IND, funding can be halted. Each cooperative agreement is approximately $1–$1.5 million, primarily given to academic investigators; however, small businesses and industry partnerships with academia are eligible to apply, said Koroshetz.

A new program, Blueprint Neurotherapeutics,[4] is designed to fund preclinical research covering the "valley of death," so named because it is a gap in the drug development pipeline where NIH funding typically ends and pharmaceutical industry development begins. Blueprint Neurotherapeutics is dedicated to advancing promising compounds from

[3]See http://www.ninds.nih.gov/research/translational.
[4]See http://neuroscienceblueprint.nih.gov/bpdrugs/project_pipeline_fig.pdf.

lead optimization to candidate selection, preclinical safety, and Phase I clinical testing. Each project is led by a team composed of a principal investigator, industry consultants, and NIH staff. The team plans a research strategy and oversees implementation, which is often outsourced to contract research organizations that are better equipped to conduct testing in which most academic investigators typically do not specialize, said Koroshetz.

Another new program is NeuroNext,[5] which consists of a network of 25 sites around the country that conduct Phase II clinical trials. The network has its own data coordinating center and clinical coordinating center. Investigators are encouraged to share preclinical data that justify going forward with Phase II clinical trials. The funding under NeuroNext can be used to test therapies and develop biomarkers. The program is established for academics or members of industry who have a Cooperative Research and Development Agreement (CRADA) with NIH. All 25 sites use the same institutional review board (IRB), which allows for rapid implementation. The first study funded by NeuroNext—a biomarker for spinal muscular atrophy—was initiated in just 54 days. A NeuroNext network for stroke is to be established in 2014.

According to Koroshetz, NINDS also has several resources that are instrumental to translational research. One is a cell bank of iPSCs from patients with neurological disorders as well as controls. Another resource is a Small Business Innovation Research (SBIR) program for which there is 3 percent of dedicated funding set aside to help small business commercialize neuroscience diagnostics or therapeutics.[6]

Koroshetz concluded with some ideas about how NINDS might enhance translational and clinical programs. In addition to encouraging better animal models and more rigorous design of preclinical trials, Koroshetz suggested development of better biomarkers, improvement of translational knowledge at the level of grantees and NINDS staff, and integration of knowledge across nervous system disorders with overlapping mechanisms, such as abnormal protein deposition, which applies to Alzheimer's and Parkinson's disease, and amyotrophic lateral sclerosis. Koroshetz suggested that government efforts to support translational research might lead to new and innovative therapeutics and accelerate the drug development process for nervous system disorders. During the discussion, one participant noted that there is some concern

[5]See http://www.neuronext.org.
[6]See http://www.ninds.nih.gov/funding/small-business.

that congressionally directed money is not yielding return investment for the taxpayer. The participant proposed that a model be developed that would advance drug discovery and encourage early collaboration between taxpayer funding and pharmaceutical companies. Koroshetz stated that there is an experiment going on in Europe in which companies and the government are trying to partner to address this same issue.

Massachusetts Neuroscience Consortium and Collaborative CNS Screening Initiative

The Massachusetts Neuroscience Consortium[7] is another opportunity for entities to collaborate in the precompetitive space. It is a new initiative designed to accelerate preclinical research, introduce academic investigators to the challenges of targeted research and drug discovery, and forge industry–academic partnerships, said Ivinson. Consortium projects are centered on target identification and validation. Because the focus is on the precompetitive space, there is no impact on ownership of intellectual property. The funding available is approximately $250,000 per project. The projects are milestone-driven, with accompanying checkpoints and clearly defined timeframes. The data generated are shared among members and then published. The consortium is sponsored by the state of Massachusetts, and the program is administered through the Massachusetts Life Sciences Center.

Another new precompetitive program is the Collaborative CNS Screening Initiative. Under this initiative, university and industry partners pool their anonymous active compounds into a shared library. The eligible compounds have to exhibit potential in primary screens and have to be validated through secondary assays. The partner that discovers novel activity for the compound is then put in touch with the original sponsor of the compound to share results and ideas. The initiative began with academic partners, but will include industry partners as well. The funding comes from three foundations—the Alzheimer's Drug Discovery Foundation, the Beyond Batten Disease Foundation, and the National Multiple Sclerosis Society.

[7]See http://www.masslifesciences.com/neuroscience.html.

Improve Reproducibility by Increasing Preclinical Study Standards and Sharing

Public–private partnerships and collaboration in the precompetitive space create opportunities to identify areas of improvement in the field. Two points that several participants highlighted were the need to increase statistical and research standards of preclinical studies and the creation of a central portal to share preclinical data. The overall end goal is to improve the reproducibility of preclinical data, which could further researchers' understanding of what was or was not successful during preclinical trials before investing their time and resources into similar targets or drugs.

Statistical Standards for Preclinical Studies

According to several participants, more statistical rigor is needed for preclinical studies. The number of successful animal studies is high due in part to the widespread practice of a 0.05 statistical cutoff for positive findings. Aisen suggested that this cutoff is appropriate only if there is a single variable; however, the overwhelming majority of studies have numerous variables, making it easier to detect positive results at this cutoff point. This, in turn, may have an influence on the lack of negative data that are published in the field. From an investment standpoint, Shiosaki noted that consultants are used to guide companies in understanding the science and the risks when performing due diligence to assess the quality and interpretation of the data that have been submitted for startup funding. If needed, the data are replicated through contract research organizations (CROs).

Central Repository for Preclinical Data Sharing

Aisen asserted a need for researchers to be required to register animal studies in advance in the same way that clinical trials are registered. Aisen suggested that such a registry could include study design, drugs, route of administration, dose, duration, primary outcome measure, and statistical plan. These features could be captured in a centralized website akin to www.clinicaltrials.gov (e.g., "www. preclinicaltrials.gov") that would serve as a portal for sharing of experimental designs and results. A participant noted that there are several issues related to data sharing, particularly related to imaging technologies that lack standardization. Data that are

readily available, analyzable, and reproducible may be beneficial to the field.

VENTURE CAPITAL PERSPECTIVE ON OPPORTUNITIES TO IMPROVE DRUG DEVELOPMENT

VC firms are primary engines of drug development innovation, considering that VC firms, according to Reddy's analysis, backed 12 of 14 Fast Track drug approvals by FDA in 2011. During that year, the U.S. VC industry invested $28 billion in all industries; approximately $7–$8 billion was invested in the life sciences, including biotechnology, medical devices, and medical equipment sectors. When VC firms invest in preclinical stage projects, they have a high success rate in terms of return on investment and usually "exit" through large company acquisition or initial public offerings (IPOs). There is a misconception that VC firms are looking at 2- to 3-year investment horizons, when the actual figure is approximately 5 to 7 years, said Reddy.

Reddy offered several suggestions that could accelerate the therapeutic development process by helping investment decisions:

- Improve delivery technologies for blood–brain barrier biologics.
- Expand access to a diverse set of human iPSC lines.
- Promote more safe, well-controlled, "human lab" testing (i.e., iPSCs).
- Build mechanisms to encourage replication of important preclinical findings and publishing of negative results.
- Define objective biomarkers for behaviors (e.g., electroencephalogram, fMRI, diffusion tensor imaging, omics platforms, etc.).
- Obtain straightforward phenotypic/genotypic information of heterogeneous patient populations.
- Create patient registries that enable rapid and cost-efficient development.
- Provide approvals or "conditional" approvals based on surrogate endpoints with Phase IV requirements.
- Extend patent terms for nervous system indications associated with long development time lines (i.e., disease modifying/ preventative therapies).

Workshop speakers and participants discussed multiple opportunities and approaches that might improve and accelerate drug development for nervous system disorders. Novel methodological approaches, such as molecular and experimental medicine approaches, could facilitate the translation from preclinical to clinical more effectively than current methods. Many participants highlighted the need for overarching changes to the current drug development pipeline through the transformation of conventional practices and technologies to ones that encourage innovation. Capitalizing on infrastructural opportunities such as public–private partnerships, collaboration in the precompetitive space, and preclinical data sharing could alleviate the risk associated with drug development and limit unnecessary research. Finally, from a VC perspective, a number of strategies could aid in investment decisions for nervous system disorders (e.g., objective biomarkers, patient registries, technologies for blood–brain barrier biologics).

6

Perspectives on Next Steps

The end of the workshop provided an opportunity for session chairs to engage participants in discussing opportunities for improving and accelerating drug discovery as discussed in their respective sessions (see Box 6-1)[1]; session chairs' comments are summarized in this chapter.

Current Therapeutic Development Practices

David Michelson, vice president of clinical neuroscience and ophthalmology at Merck Research Laboratories, observed several key themes throughout the first session and identified next steps to aid in drug discovery. Michelson said several participants indicated that companies do not have confidence in choosing nervous system disorder targets and as a result choose to work in areas where the science is further along. Many times, this leads to a restriction of the focus of research to the disease areas that are best understood, which often are not within the neurosciences. To build confidence in the next stage of research and the investments made, many participants who spoke agreed there is a need to de-risk across steps in the development time line. Some researchers continue to prematurely proceed to clinical trials, without sufficient preclini-

[1]The topics highlighted in this chapter are based on the summary remarks made by each session chair during the final workshop session and at the end of his or her respective session. Additional comments by participants related to the closing remarks are also included. As noted in Chapter 1, comments included here should not be construed as reflecting any group consensus or endorsement by the Institute of Medicine or the Forum on Neuroscience and Nervous System Disorders.

cal data, resulting in high clinical failure rates (Leaf, 2013). When companies are at the point of making larger investments and commitments, the probability of success should high, said Michelson.

Several participants noted that the use of multiple models may be beneficial to discover and validate targets; there is no simple "yes" or "no" as to whether a specific animal model will be useful, but little is gained by continuing to pursue a target when data suggest it may be futile. Increasing reagents for novel targets in laboratories and establishing better biomarkers by considering the patient group in which the mechanism of the disease is likely to be homogeneous (patient stratification) could also help de-risk research programs. A few participants reiterated

BOX 6-1
Potential Opportunities to Accelerate Therapeutic Development

- Utilize combinations of animal and cell-based models to further understand underlying biological mechanisms of diseases and improve target identification.
- Improve biomarkers for nervous system disorders.
- Consider target invalidation in addition to validation.
- Extend the precompetitive space to identify and validate novel targets and eliminate replication of studies.
- Increase the availability of new and emerging tools and technologies (e.g., induced pluripotent stem cells [iPSCs], humanized animal models, neuroimaging, experimental medicine, computational neuroscience).
- Identify and use mechanisms (e.g., iPSCs, assays, clinical probes) to assist and accelerate go/no-go decisions.
- Reverse the experimental pipeline starting in humans for target identification and validation, then move to animal models for target engagement.
- Increase preclinical study standards and improve reproducibility.
- Share preclinical positive and negative data.
- Develop a www.preclinicaltrials.gov portal for sharing of experimental designs and results.
- Continue to establish public–private partnerships focused on target identification and validation to de-risk research.

NOTE: The items in this list were addressed by individual speakers and participants and were identified and summarized for this report by the rapporteurs, not the workshop participants. This list is not meant to reflect a consensus among workshop participants.

the need for public–private partnerships to de-risk investments as well as pushing the precompetitive boundaries to Phase IIa by evaluating novel targets in patients. Another concept mentioned by several participants is that large pharmaceutical companies are not the only places where drug discovery and development can occur. Biotechnology companies and federal agencies, for example, might also be resources to consider.

Regarding next steps, Michelson posed the following three questions:

1. What areas are the ripest for work?
2. What are the gaps, and how can they be addressed?
3. What are the steps in the drug discovery process that can be de-risked and provide confidence across the development pipeline?

Michelson noted that the focus should not be to accelerate the drug discovery process, but rather to make it better and more efficient.

The Regulatory Pathway

William Potter, senior advisor in the Office of the Director of the National Institute of Mental Health, highlighted how many basic scientists are unfamiliar with Food and Drug Administration approval procedures and resources at NCATS that may potentially resolve these issues. FDA, in its current case-by-case approach, views flexibility as a benefit and helps academic researchers better understand the guidance documents that may alleviate common mistakes and misconceptions. Echoing comments made by several participants, Potter asked, Where are the opportunities for increasing the probability of success? This is an area in which the neuroscience field has been struggling, he noted. Beyond these concerns, Potter stated, the fundamental question is, How can we create a better fit between preclinical assays and experimental human models? Is the field at a point where it can depend on one method, and can this be tested?

New and Emerging Tools and Technologies

There was an overall sense at that workshop that the cell is the smallest common denominator, as opposed to the gene or protein, said

session chair Rajesh Ranganathan, director of the Office of Translational Research at NINDS. Several participants noted that human phenotypes may better inform the translational space than animal models, and, if possible, measuring the same variables in humans and animals might be beneficial. Many participants who spoke agreed that creating a database, such as "www.preclinicaltrials.gov," as a repository to share data could further the understanding of nervous system disorders and provide a mechanism for researchers to share discoveries.

Ranganathan reflected on the Human Genome Project and asked whether there is a fundamental technology that could change the neuroscience space, and if so, should investment be increased in this specific area? Specifically, for neuroscience, said Ranganathan, target engagement is critical. Ensuring that there is target engagement, taking measurements that are pharmacodynamically related to the target, and testing where it truly matters are important, he added. Developing a better learning curve in clinical trials is needed to eliminate the common responses of "it did not work and we do not know why" or "it's the patient, not the drug." Ranganathan concluded by saying that the field should push to race ahead with a broad-based platform of investment to facilitate drug discovery.

Opportunities in Nervous System Disorders

Magali Haas, chief science and technology officer at One Mind for Research, observed that in the course of the workshop, the focus had been on the ability to predict outcomes and determine which steps are or are not informative in the development pipeline, rather than moving toward first-in-human trials from cellular models. During the session, participants discussed an array of topics, including the use of human data for target identification; the willingness of researchers to conduct rigorous experiments both in preclinical models and in an experimental medicine setting; and opportunities to accelerate the pathway to first-in-human trials when the severity of the disease warrants it. However, participants mainly focused their discussions on the investment portfolio in the neuroscience field and where there are opportunities for nonprofits, NIH, and pharmaceutical companies to reconsider their portfolios. There is a large investment in iPSC lines because of the potential to conduct functional pharmacology from a cell derived from a patient or normal individual. Although there was not much discussion about where the next

generation of genetic data, biomarkers, or phenotypes will fit into large-scale human trials, Haas noted that many participants and speakers agreed that this will happen through large-scale public–private partnerships. Several participants advocated for information technology platforms for sharing reliable data, such as a neuroscience community portal (which is currently under development), "neuromine," or "www.preclinicaltrials.gov" as suggested by a workshop speaker. In addition, Haas noted that there is a strong need to consider the use of new tools such as proteomics, transcriptomics, and computational modeling approaches.

Optimizing Therapeutic Development

Collaboration and the precompetitive space were two key themes in the workshop discussions, noted Daniel Burch, vice president and global therapeutic area head for central nervous system diseases at Pharmaceutical Product Development, Inc. (PPDi). Several participants identified a number of potential areas for collaboration, including target identification and validation, animal assays, and de-risking aspects of research. In addition, many participants highlighted the importance of extending the precompetitive space and establishing small-scale collaborative models. Burch stated that there is inefficiency within the translational space; researchers and groups are reinventing the wheel when it is unnecessary. The development of platforms to explore certain mechanisms might be beneficial, he added.

SUMMARY

Given the challenges surrounding current therapeutic development practices for nervous system disorders, this workshop sought to explore opportunities that could potentially make the pathway from discovery to approval more effective and efficient. Rather than focusing on accelerating the process from cellular models to first-in-human trials, workshop discussion focused on predicting outcomes and determining next steps in the development pipeline. Speakers and participants highlighted several limitations related to de-risking research, target validation and engagement, the regulatory process, inefficient research, and reproducibility. Although clinical outcomes cannot be predicted and additional research is needed, new and emerging tools and technologies, such as iPSCs, are

avenues that could potentially improve the drug development process, according to several participants. Patient stratification, target identification based on human data, systematic evaluations of failed clinical trials, and improved guidance on regulatory issues were just a few potential solutions that participants considered. Finally, several speakers and participants advocated for open data sharing among researchers and a centralized database for all preclinical trials to increase collaborative efforts and decrease replication in the field.

A

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B

Workshop Agenda

Accelerating Therapeutic Development for Nervous System Disorders Toward First-in-Human Trials: A Workshop

April 8 and 9, 2013

National Academy of Sciences Building, Lecture Room
2101 Constitution Ave., NW, Washington, DC

Background: In March 2012, the Forum on Neuroscience and Nervous System Disorders hosted a public workshop called Improving Translation of Animal Models for Nervous System Disorders. This workshop explored strategies for improving the processes of discovery and development of effective therapies for nervous system disorders with a focus on translation of results from animal models to clinical practice. Two themes that emerged from the workshop were that many have lost confidence in the ability of animal models to predict efficacy and that current animal models may, in fact, be screening out potentially effective compounds. Another theme was the need to combine animal models with emerging translational tools and technologies in therapeutic development. Following on these themes, the goal of this workshop is to explore opportunities to accelerate the pathway from discovery to approval of new therapeutics for nervous system disorders.

Meeting Objectives:

- Examine opportunities and challenges in neuroscience research for facilitating faster entry of potential treatments into first-in-human trials.
  - Discuss the role of new and emerging tools and technologies in accelerating therapeutic development.
  - Identify avenues for developing integrated strategies that utilize both animal and non-animal models.
  - Discuss potential benefits and risks of such an approach.
- Explore how emerging neuroscience technologies and techniques may improve the efficiency of research and facilitate a more effective and efficient pathway to first-in-human trials (e.g., induced pluripotent stem cells, in vitro neuronal circuits, connectomics, brain imaging, etc.).
- Consider regulatory mechanisms that may facilitate faster entry of potential treatments into first-in-human trials.
  - Discuss how new and emerging tools and technologies may accelerate progress toward first-in-human trials.
- Consider mechanisms for integration and proliferation of new technologies and techniques to facilitate drug development and discovery.

DAY ONE

8:30 a.m. Opening remarks
JOHN DUNLOP, *Co-Chair*
FRED GAGE, *Co-Chair*

8:40 a.m. Review of workshop on Improving Translation of Animal Models for Nervous System Disorders
RICHARD HODES
Director
National Institute on Aging

SESSION I: CURRENT THERAPEUTIC DEVELOPMENT PRACTICES

Session Objectives: Discuss the benefits and risks of accelerating therapeutic development into first-in-human clinical trials. Consider the need for new molecular targets for nervous system disorders. Examine therapeutic development practices with a focus on challenges presented by current tools and technologies.

8:55 a.m. Overview and session objectives
DAVID MICHELSON, *Session Chair*
Vice President
Clinical Neuroscience and Ophthalmology
Merck Research Laboratories

9:00 a.m. The therapeutic development pathway: From the lab to the clinic
WILLIAM POTTER
Senior Advisor
Office of the Director
National Institute of Mental Health

9:15 a.m. Meeting the medical need: The benefits and risks of aggressively moving compounds forward
JASON KARLAWISH
Professor of Medicine, Medical Ethics, and Health Policy
Perelman School of Medicine
University of Pennsylvania

9:30 a.m. Evolutionary conservation and divergence: The utility of animal models in development of therapeutics
DANIEL GESCHWIND
Gordon and Virginia MacDonald Distinguished Professor
Center for Autism Research and Treatment
University of California, Los Angeles, School of Medicine

9:45 a.m. Developing new molecular and clinical targets for nervous system disorders

SAMUEL GANDY
Professor of Neurology and Psychiatry
Associate Director
Mount Sinai Alzheimer's Disease Research Center

10:00 a.m. Therapeutic development practices: Challenges and limitations of current tools and technologies

CHAS BOUNTRA
Professor of Translational Medicine
Head of Structural Genomics Consortium
University of Oxford

10:15 a.m. Panel discussion with participants

DAVID MICHELSON, *Moderator and Session Chair*

10:45 a.m. BREAK

SESSION II: OPPORTUNITIES AND CHALLENGES FOR NEW AND EMERGING TOOLS AND TECHNOLOGIES

Session Objectives: Examine the role of new and emerging tools and technologies in accelerating the development of therapeutics for nervous system disorders. Discuss the readiness of these tools and technologies for integration into therapeutic developmental pathways. Examine the utility of specific new and emerging tools and technologies in relation to nervous system disorders.

11:00 a.m. Overview and session objectives

RAJESH RANGANATHAN, *Session Chair*
Director
Office of Translational Research
National Institute of Neurological Disorders and Stroke

Speakers will focus on the following questions:

- How could this area of research speed therapeutic development?

- What would the qualification process look like for this area?
- How long would it take for integration into therapeutic development pathways?

11:05 a.m. Induced pluripotent stem cells
LARRY GOLDSTEIN
Distinguished Professor, Department of Neurosciences
Director, University of California, San Diego (UCSD) Stem Cell Program
UCSD School of Medicine

11:25 a.m. Humanized animal models
IRVING WEISSMAN
Director, Institute of Stem Cell Biology and Regenerative Medicine
Professor of Pathology and Developmental Biology
Stanford University

11:45 a.m. Biomarkers/imaging
SCOTT SMALL
Herbert Irving Professor in Neurology
The Neurological Institute of New York
Columbia University Medical Center

12:05 p.m. Human models/experimental medicine
JOHN KRYSTAL
Robert L. McNeil, Jr., Professor of Translational Research
Chair, Department of Psychiatry
Yale University School of Medicine

12:25 p.m. Computational neuroscience
READ MONTAGUE
Director, Human Neuroimaging Laboratory
Director, Computational Psychiatry Unit
Virginia Tech Carilion Research Institute
Professor, Wellcome Trust Centre for Neuroimaging, University College London

12:45 p.m. Panel discussion with participants

- How would these new and emerging tools and technologies complement or replace current methods, including animal models?
- How could these new and emerging tools and technologies aid in the identification of new molecular and clinical targets?
- What are potential challenges for incorporation into current developmental pathways?

RAJESH RANGANATHAN, *Moderator*

1:15 p.m. LUNCH

2:00 p.m. Opportunities and challenges around incorporation of new and emerging tools and technologies into current research programs.

- Which tools and technologies show the most promise for the particular disease area?
- How could these tools and technologies best be positioned to positively bolster current research programs?

1) Neurodevelopmental disorders: Autism and schizophrenia
KEVIN EGGAN
Associate Professor
Harvard Stem Cell Institute
Harvard University

2) Mood disorders: Depression
WAYNE DREVETS
Scientific Vice President
Disease Area Leader in Mood Disorders
Janssen Pharmaceuticals Companies of Johnson & Johnson

3) Neurodegenerative disorders: Alzheimer's and Parkinson's
PAUL AISEN
Director, Alzheimer's Disease Cooperative Study
Professor, Department of Neurosciences
UCSD

4) Traumatic brain injury
RAMON DIAZ-ARRASTIA
Director of Clinical Research, Center for Neuroscience and Regenerative Medicine
Professor of Neurology
Uniformed Services University of the Health Sciences

3:00 p.m. Panel discussion with participants
RAJESH RANGANATHAN, *Moderator*

3:30 p.m. BREAK

SESSION III: EVALUATING THERAPEUTIC DEVELOPMENT PATHWAYS

Session Objectives: Explore mechanisms by which evidence is evaluated in decisions to commit to therapeutic development approaches. Discuss ways in which new and emerging tools and technologies could increase confidence in decision making.

3:45 p.m. Overview and session objectives
MAGALI HAAS, *Session Chair*
Chief Science & Technology Officer
One Mind for Research

3:50 p.m. Decision processes for committing to a therapeutic development approach
- What evidence is required for research programs to commit resources?
- How is evidence evaluated in the decision process? What evidence is given greater weight?

- When and how are decisions made to switch to a different approach?

1) Industry perspective
KALPANA MERCHANT
Chief Science Officer
Tailored Therapeutics, Neuroscience
Eli Lilly and Company

2) Government perspective
STORY LANDIS
Director
National Institute of Neurological Disorders and Stroke

3) Academic perspective
REISA SPERLING
Director, Center for Alzheimer's Research and Treatment
Professor of Neurology
Harvard Medical School

4:35 p.m. The contribution of animal models within the therapeutic development pathway

- What is the spectrum of animal models used in the therapeutic development pathway?
- How are research programs currently supplementing animal models in the development pathway?

NICK BRANDON
Senior Director, Neuroscience Innovative Medicines Unit (iMED)
AstraZeneca

4:50 p.m. Panel discussion with participants

- How can these tools and technologies help identify and validate molecular and clinical targets?

- Which of these tools and technologies show the best promise to help groups make these commitments?
- What combinations of new and emerging tools, technologies, and animal models have the potential to accelerate therapeutic development?

MAGALI HAAS, *Moderator*

5:20 p.m. Day one wrap-up
JOHN DUNLOP, *Co-Chair*
FRED GAGE, *Co-Chair*

5:30 p.m. ADJOURN

DAY TWO

8:30 a.m. Welcome
JOHN DUNLOP, *Co-Chair*
FRED GAGE, *Co-Chair*

SESSION IV: THE REGULATORY PATHWAY

Session Objectives: Examine the current regulatory processes and the use of new and emerging tools and technologies in applications. Discuss common mistakes in applications as guidance for developing accelerated pathways into first-in-human trials.

8:35 a.m. Overview and session objectives
WILLIAM POTTER, *Session Chair*
Senior Advisor
Office of the Director
National Institute of Mental Health

8:40 a.m. Lessons learned: Accelerating therapeutic development through a look at current regulatory applications
- What are key components of successful applications? What are common mistakes?

- What uses of new and emerging tools and technologies are subject to regulatory processes across the phases of drug development: investigational new drug (IND)/Phase I; Phase II; Phase III; and new drug application (NDA)?
- Are there mechanisms for moving into patients, children/adolescents faster? First?

IMRAN KHAN
Pharmacologist and Toxicologist
Office of New Drugs, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

9:00 a.m. Potential challenges facing integration of new and emerging tools and technologies into the regulatory process

- What potential challenges do these new and emerging tools and technologies face in the approval process?

ROBERT CONLEY
Distinguished Lilly Scholar
Regulatory Leader, Biomedicines
Eli Lilly and Company

ERIC BASTINGS
Deputy Director
Division of Neurology Products, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

NI KHIN
Medical Team Leader
Division of Psychiatry Products, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

9:30 a.m. Panel Discussion with Participants
WILLIAM POTTER, *Moderator*

SESSION V: ACCELERATING THERAPEUTIC DEVELOPMENT

Session Objectives: Explore mechanisms by which evidence is evaluated to make commitments to invest in clinical trials. Discuss ways in which therapeutic development paradigms can be optimized and accelerated. Identify potentially innovative methods to accelerate development of new therapeutics.

10:00 a.m. Overview and session objectives

DANIEL BURCH, *Session Chair*
Global TA Head Neurosciences–Global Product Development (GPD)
Pharmaceutical Product Development, LLC (PPDi)

10:05 a.m. Investment decisions in preclinical development and movement into clinical trials

- What is the level of proof needed to justify investment in a preclinical project for IND enabling or a Phase I activity?
- From an investment point of view, how attractive are neuroscience research areas when compared to other therapeutic areas? What could make it more attractive at the preclinical stage?
- How important is it to fully understand mechanisms and molecular pathways of action prior to initiation of the IND enabling package?

KIRAN REDDY
Principal
Third Rock Ventures

STEVE ELMS
Managing Partner
Aisling Capital

KAZUMI SHIOSAKI
Managing Director
MPM Capital

10:35 a.m. Panel discussion with participants

- How would new and emerging tools and technologies affect the decision process? Would they increase confidence in decisions?

DANIEL BURCH, *Moderator*

11:05 a.m. BREAK

11:20 a.m. Improving current therapeutic development approaches

- How could new and emerging tools and technologies provide solutions for challenges currently facing development of drugs for nervous system diseases?
- How could new and emerging tools and technologies be used in place of, or in addition to, animal models?

1) Discovery/basic research
DAVID GOLDSTEIN
Richard and Pat Johnson Distinguished University Professor
Director, Center for Human Genome Variation
Duke University

2) Target ID/validation
DANIEL WEINBERGER
Director and CEO
Lieber Institute for Brain Development

3) Screening/optimization
ADRIAN IVINSON
Director, Harvard NeuroDiscovery Center
Harvard University

4) Preclinical development
MARK BEAR
Picower Professor of Neuroscience
Investigator, Howard Hughes Medical Institute
Massachusetts Institute of Technology

12:20 p.m. Panel discussion with participants

- What balance between emerging tools and technologies and current methods (e.g., animal models) would be needed to increase confidence in selection of a particular development pathway?

DANIEL BURCH, *Moderator*

12:45 p.m. LUNCH

SESSION VI: NEW APPROACHES TO THERAPEUTIC DEVELOPMENT

Session Objectives: Discuss workshop concepts in the context of nervous system disorders. Identify tangible next steps by which identified mechanisms might be rapidly incorporated into current practices.

1:45 p.m. Overview and session objectives

STEVEN HYMAN, *Session Chair*
Director, Stanley Center at the Broad Institute
Distinguished Service Professor
Professor of Stem Cell Biology and Regenerative Biology
Harvard University

1:50 p.m. Imagining new therapeutic development pathways (with Q&A)

CHRISTOPHER AUSTIN
Director
National Center for Advancing Translational Sciences
National Institutes of Health

2:10 p.m. Next steps with workshop co-chairs and individual session chairs

- How could workshop concepts be rapidly incorporated into current therapeutic development practices?

JOHN DUNLOP, *Workshop Co-Chair*
AstraZeneca

FRED GAGE, *Workshop Co-Chair*
Salk Institute

DAVID MICHELSON, *Session I Chair*
Merck Research Laboratories

RAJESH RANGANATHAN, *Session II Chair*
National Institute of Neurological Disorders and Stroke

MAGALI HAAS, *Session III Chair*
One Mind for Research

WILLIAM POTTER, *Session IV Chair*
National Institute of Mental Health

DANIEL BURCH, *Session V Chair*
Pharmaceutical Product Development, LLC (PPDi)

3:30 p.m. Final comments
JOHN DUNLOP, *Co-Chair*
FRED GAGE, *Co-Chair*

3:45 p.m. ADJOURN

C

Registered Attendees

Susan Amara
National Institute of Mental Health

Aisar Atrakchi
U.S. Food and Drug Administration

Alex Bailey
U.S. Food and Drug Administration

Bruce Baron
Sanofi

Bruce Bebo
National Multiple Sclerosis Society

Francesca Bosetti
National Institute of Neurological Disorders and Stroke

Linda Brady
National Institute of Mental Health

Nathalie Breysse
Lundbeck Research USA

Katja Brose
Neuron

Wilson Bryan
U.S. Food and Drug Administration

Neil Buckholtz
National Institute on Aging

Elzbieta Chalecka-Franaszek
U.S. Food and Drug Administration

Jiu-Chiuan (J. C.) Chen
University of Southern California Keck School of Medicine

Charles Cywin
National Institutes of Health

Daryn David
National Institutes of Health

Hirsch Davis
National Institute on Drug Abuse

Jamie Driscoll
National Institute of Mental Health

Emmeline Edwards
National Center for Complementary and Alternative Medicine

Stephanie Fertig
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Linda Fossom
U.S. Food and Drug Administration

Lois Freed
U.S. Food and Drug Administration

Brandy Fureman
National Institute of Neurological Disorders and Stroke

John Gardenier
Independent

Turkan Gardenier
Independent

Jessica Goodman
Prize4Life

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Carol Hubner
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John Kehne
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Roxanne Khamsi
Nature Medicine

Violetta Klimek
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Elizabeth Kwasnik
Parkinson's Action Network

Woody Lin
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Yuan Luo
Center for Scientific Review, National Institutes of Health

Ernie Lyons
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Vince Macri
PreMotor Exercise Games

Laura Mamounas
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Ron McKay
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Matthew McMahon
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