



**Neuroscience Biomarkers and Biosignatures:  
Converging Technologies, Emerging Partnerships -  
Workshop Summary**

Miriam Davis, Sarah Hanson, Bruce Altevogt,  
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System Disorders

ISBN: 0-309-10890-X, 128 pages, 6 x 9, (2008)

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FORUM ON NEUROSCIENCE AND NERVOUS SYSTEM DISORDERS

# NEUROSCIENCE BIOMARKERS AND BIOSIGNATURES

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Converging Technologies, Emerging Partnerships

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WORKSHOP SUMMARY

Miriam Davis, Sarah Hanson, Bruce Altevogt, *Rapporteurs*

Forum on Neuroscience and Nervous System Disorders  
Board on Health Sciences Policy

INSTITUTE OF MEDICINE  
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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

This project was supported by contracts between the National Academy of Sciences and the Alzheimer's Association; Amgen, Inc.; AstraZeneca Pharmaceuticals, Inc.; the Department of Health and Human Services' National Institutes of Health (Contract No. N01-OD-4-213) through the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Aging (NIA), the National Institute on Drug Abuse (NIDA), the National Eye Institute (NEI), the NIH Blueprint for Neuroscience Research, the National Institute of Mental Health (NIMH), and the National Institute of Neurological Disorders and Stroke (NINDS); Eli Lilly and Company; GE Healthcare, Inc.; GlaxoSmithKline, Inc.; Johnson & Johnson Pharmaceutical Research and Development, LLC; Merck Research Laboratories, Inc.; the National Multiple Sclerosis Society; the National Science Foundation (Contract No. OIA-0647541); Pfizer Global Research and Development, Inc.; and the Society for Neuroscience. The views presented in this publication are those of the editors and attributing authors and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number-13:978-0-309-10889-8

International Standard Book Number-10:0-309-10889-6

Additional copies of this report are available from the National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area); Internet, <http://www.nap.edu>.

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Printed in the United States of America.

Suggested citation: Institute of Medicine. 2008. *Neuroscience biomarkers and biosignatures: Converging technologies, emerging partnerships, workshop summary*. Washington, DC: The National Academies Press.

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*“Knowing is not enough; we must apply.  
Willing is not enough; we must do.”*  
—Goethe



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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC'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 report as sound as possible and to ensure that the report 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 deliberative process. We wish to thank the following individuals for their review of this report:

**Joseph T. Coyle**, Harvard Medical School

**Allen D. Roses**, GlaxoSmithKline

**Ira Shoulson**, Department of Neurology, Pharmacology and Medicine,  
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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the final draft of the report before its release. The review of this report was overseen by **Dr. Theodore R. Marmor**, Yale University School of Management, Professor Emeritus. Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.



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## Summary<sup>1</sup>

Biological markers, or biomarkers, are quantitative measurements that provide information about biological processes, a disease state, or about response to treatment, providing much-needed insight into preclinical and clinical data.<sup>2</sup> Biomarkers hold the potential of a better understanding of the etiology and pathogenesis of a given disorder, providing researchers and clinicians with valuable insight into diagnosis, treatment, and prognosis for many debilitating disorders and diseases. The burden of the maladies described in the workshop affect every population; thus, the commitment to finding additional biomarkers is a major aim in neuroscience medical research.

While many advances have been made in the development of biomarkers for disorders other than those of the nervous system, e.g., cancer biology, advances in establishing biomarkers for disorders of the nervous system have been disappointing, given escalating research investment. This is a result of a combination of many factors, including, but not limited to, complexity of the nervous system, access to tissue and the blood brain barrier, and incentives for industry and academia, causing development to fall between the cracks of academic, government, and industry research programs. The public health burden of nervous system disorders is great—well over 1,000 different disorders, according to the

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<sup>1</sup>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.

<sup>2</sup>This definition of a biomarker was used throughout the workshop and is based on a definition developed by the FDA's Biomarkers Definitions Working Group; however, there are other definitions of biomarkers and biosignatures that capture other roles and applications that were not included in the scope of this workshop.

Society for Neuroscience—and yet only a handful of biomarkers are available. Focused attention is needed in neuroscience biomarker research and development, yet it is often difficult to categorize which areas are the most ripe for investment and should be further pursued.

Given the promising potential and high need for neuroscience biomarkers, the Institute of Medicine Forum on Neuroscience and Nervous System Disorders convened a workshop in Washington, DC, on February 26 and 27, 2007. The workshop brought together experts in various areas to discuss the most promising and practical arenas in neuroscience in which novel biomarkers will have the greatest near-term impact on the rate at which new treatments are brought forward for psychiatric and neurological disorders.

Several themes, including the following needs and opportunities, were highlighted by workshop participants:<sup>3</sup>

- a better understanding of the Food and Drug Administration (FDA) evaluation and qualification process to help promote and increase neuroscience biomarker submission;
- opportunities for public-private partnerships in a precompetitive space (i.e., the ability of organizations, including companies, sponsors, and developers, to work together on research and development without jeopardizing their intellectual property);
- combined tools and technologies in arenas such as proteomics, genomics, and imaging to refine specificity within findings;
- deconstruction of certain aspects of current characterizations and diagnostic criteria (e.g., *Diagnostic and Statistical Manual [DSM]* categorizations);
- standardization and pooling of resources and data, especially from current and completed clinical trials, including reporting of negative results; and
- development that draws upon successful models and lessons learned from outside fields.

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<sup>3</sup>Opinions and statements included in this workshop summary are solely those of the individual persons or participants at the workshop and are not necessarily adopted, endorsed, or verified as accurate by the National Academies.

### **Workshop Goals and Objectives**

A major objective of the workshop was to identify and discuss biomarker targets that are not currently being aggressively pursued but could be developed to practicality within the next 5 years by public-private partnerships. The biomarker could be useful in either diagnostic or therapeutic settings but, regardless, should have the potential for substantial clinical impact. Essentially, the key words used to define the parameters are “near term” and “high impact.” One potential mechanism discussed by participants was the new collaborative effort, the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium. The Consortium promotes public-private partnerships by facilitating collaborative research among the National Institutes of Health (NIH), academia, industry, and other foundations and patient advocacy groups to accelerate discovery, development, and qualification of biomarkers.

The planning committee for this workshop chose to discuss certain areas of biomarker research for nervous system disorders that may be ripe for development. The workshop and this summary are not meant to be a comprehensive review of all possible neuroscience biomarkers that may be ripe for development in the near term or in the future. Further, workshop participants were charged to highlight the opportunities and needs for biomarker research and discovery, not necessarily the application of a given biomarker.

### **Regulatory Considerations**

The evolution of biomarker application and the regulatory system is rapidly changing, incorporating new science and opportunities. The role of the FDA is to encourage qualification and use of new biomarkers while providing regulatory guidance on the design of qualification trials. Due, in part, to scientific, economic, and regulatory factors, biomarker development has lagged significantly behind therapeutic development. Some feel the biomarker qualification process by the FDA may present a hurdle for the submission of a biomarker. The FDA recently changed its definitions and requirements to include broader categories and to encourage submission of proposals. For instance, biomarkers may now fall under three categories: “possible,” “probable,” and “known.”



Another concern is the lack of clear understanding about how the FDA defines and qualifies different types of biomarkers, including surrogate endpoints. Thus, there are now clearer definitions of biomarkers, surrogate endpoints, and the “qualification process.” With increased transparency of the application process, the FDA hopes to encourage proposal submissions, qualifications, partnerships, and consortia geared toward increasing biomarker innovation and discovery.

### **Public-Private Partnership**

One successful partnership that was already under way before the creation of the FNIH but that is now funded through FNIH is the Alzheimer’s Disease Neuroimaging Initiative (ADNI). This public-private partnership has been extremely useful due to mechanisms set in place that allow for full data sharing in real time. Furthermore, ongoing results are published freely via the Internet. One of the greatest benefits of this partnership comes from the contributions of the special advisory committee members who have created both imaging and cerebrospinal fluid (CSF) protocols to help standardize collection. A major, if not the largest, accomplishment of the advisory committee came about through the push for higher rates of CSF sample collection from the public partners. The result was an increase in collection from 20 percent to 60 percent. However, this creates a new challenge and opportunity to expand ADNI to begin analyzing and categorizing collected biological samples. The success of the ADNI project is that it lies within the precompetitive space, allowing for broad applicability in future clinical trials and, in addition, fostering communication within otherwise proprietary realms in this area of research. Although ADNI is one example of a successful public-private partnership, there are many others that have been established that are also demonstrating similar successes; however, these were not discussed in detail at the workshop.

## **POTENTIAL TOOLS**

### **Genomics and Proteomics**

Partly as an outgrowth of the Human Genome Project and the International HapMap Project, there has been an increased interest in

genomics over the past several years. Genome-wide scanning in the search for a single nucleotide polymorphism that is associated with a disease is a relatively new tool that researchers have been using and developing in the hopes of identifying potential target loci for disease biomarkers. This technology has already been successfully utilized in Alzheimer's disease and shows promise for use in individuals with schizophrenia.

Although the technology is not yet available for whole-proteome scanning, proteomics is still a useful tool in helping to identify different patterns of expression of multiple protein biomarkers from CSF using, for example, liquid chromatography and mass spectrometry. Some researchers have found success in using samples obtained from CSF due to the greater concentration of potentially useful biomarkers it contains; for example, biomarkers found in the spinal cord have potential not only as a diagnostic test, but also as a measure of response to treatment. The capacity to report on the physiological state of the organism, which may not be reflected in genetic strategies, also make proteomics a valuable source of biomarkers, for example post-translational modifications and levels of protein activity that may not correlate to levels of gene transcription.

A need expressed during the workshop was for a larger number of samples to be collected and analyzed. Traditionally, analysis of CSF has been limited due to a perceived negative opinion among the public toward lumbar puncture. The ADNI project addressed this challenge by pointing out that attitude toward lumbar puncture was suggested to be improved as a result of subjects viewing an educational video that profiled the low risks associated with lumbar punctures.

### **Imaging Technologies**

Imaging tools are being used to discover surrogate biomarkers, guide therapeutic development, and detect and track disease progression; there is further hope in new, increasingly sophisticated technologies. Although the imaging field has many tools at hand, there is still no widely accepted surrogate biomarker for nervous system disorders using imaging tools. In addition, there are challenges to expansion that include validation of images, standardization of imaging protocols, and sophisticated informatics that would allow integration of various data. Another major challenge identified by workshop participants is the lack of radiotracers

for molecular defects. One effort under way is the establishment of a clearinghouse for radiotracers that would allow interested parties to share tracers. This concept is still under development; however, it is showing progress. Combining structural and functional imaging biomarkers (e.g., computed tomography and magnetic resonance imaging [MRI] with positron emission tomography [PET]) offers exciting opportunities for advancement in the future as well.

### FUTURE DIRECTIONS

Several future directions and next steps for biomarker development were identified by various workshop participants:

- Biomarker development should follow a process similar to drug development, with the same scientific rigor applied to analyzing and qualifying biomarkers. This suggests creating standardization in reporting and analysis, patient selection, and specimen and assay characterization.
- Clinical trials, ongoing and completed, offer a wealth of information and opportunities that can be utilized for biomarker development. First, clinical trials usually provide large amounts of stored tissues and other specimen that other researchers could potentially use. Second, data gleaned from clinical trials can be reanalyzed in light of new hypotheses. Third, incorporating potentially new biomarkers into clinical trials may shed light on future analysis, including identification of surrogate markers. Finally, reanalysis of data in light of a failed clinical trial is often encouraged by NIH and industry.
- Reporting negative results ascertained from various studies and experiments can save invaluable time and resources. The field should create a register of successful and failed scientific study findings for other researchers to reference (note: legislation being considered by Congress may serve to address this gap).
- More attention is needed in research that delves into the underlying pathophysiology and mechanisms of various neurological, psychiatric, and addiction disorders to help inform future opportunities in diagnostics and therapeutics. Animal models can be an important tool for elucidating these underlying mechanisms; however, better use and characterization is needed to advance this area of research. Thus, biomarkers that provide information on functional states and patterns of

neurocircuitry—using several approaches that combine brain imaging, animal models, and genotyping in conjunction with genetics, familial histories, and *DSM* categories—would help to refine diagnosis and treatment. Specific attention was focused on the current challenges and future opportunities for nervous system disorders in the areas of psychiatric and drug addiction disorders and neurological and eye diseases. Based on workshop presentations and discussions, participants identified a number of promising areas where a novel biomarker is nearerterm (Box S-1).

#### BOX S-1

##### Challenges and Opportunities for Nervous System Disorders

##### Psychiatric and Drug Addiction Disorders

**Depression:** Three genes have recently been identified as biomarkers for treatment of depression, signaling major advances in biomarker research. The serotonin 2A receptor may serve as an important biomarker for yielding information about antidepressant treatment outcome. In addition, two other genes are currently being researched and developed as a biomarker that may signal full remission. More research is needed, but the genotypic findings suggest a possible new direction that may take hold for treatment of depression. One interesting proposal includes using whole-genome scanning technologies for possible predictors of response and side effects for treatment of depression.

**Schizophrenia:** A few promising biomarkers utilize electrophysiology technologies to help detect cognitive dysfunction and working memory in the brain and have led to a few small clinical trials. The value of electrophysiology as a pathway to biomarker development for schizophrenia encompasses many opportunities that include a greater understanding of the neurocircuitry, including imaging, of psychiatric disorders and increased specificity for cognitive and behavioral tests.

**Addiction:** A biosignature, rather than a single biomarker, is used to track addiction. Brain imaging with PET is helping to identify biomarkers of vulnerability by allowing injected agents to be tracked in vivo. The search for additional biomarkers of addiction should involve genetic and animal model studies, given the success the field has seen in utilizing these paths. For example, studies outside the addiction field on genetic risks for impulsivity are shedding light on the likelihood of drug experimentation.

### Neurological and Eye Diseases

**Multiple Sclerosis (MS):** The current rating instruments for assessing the clinical course of MS are a major challenge to the field. Although there are other useful biomarkers to monitor the disease, there is no biomarker for the secondary, progressive stage of MS. Like those working in addiction, workers in the MS field have turned outside their field to cancer studies to glean valuable models that have proved successful. Most important, the cancer field was especially successful in setting up networks in the United States and Europe to foster growth in the design and conduct of, and report development for, cancer biomarker studies. The incorporation of potentially new biomarkers into clinical trials has the potential to be used in future analysis, including the possibility of identifying a surrogate marker.

**Stroke:** A promising biomarker for acute ischemic stroke, using MRI technology, may hold the key to applications for stroke clinical trials. The field of stroke research needs a formal way to share clinical trial and observational studies data, specifically during Phase II trials, which would help to standardize and optimize MRI data and patient selection and outcomes. Currently, a promising proposal for a multistage approach to standardize, optimize, and establish the use of MRI biomarkers in stroke drug development is being examined.

**Spinal Muscular Atrophy (SMA):** SMA is ripe for biomarker development, given the identification of a single defective gene over 10 years ago. It has been hypothesized that therapeutics that could increase the expression of this deleted gene may improve motor performance and muscular strength. However, this requires further delineation given that the detection of the SMA biomarker is only correlated with a certain subset of patients.

**Retinal Degeneration:** Major advances have been made, and are under way, for identifying biomarkers for retinal degeneration and even several neurodegenerative diseases such as MS. Advanced technologies such as optical coherence tomography and adaptive optics, in addition to metabolic biomarker candidates, are lending to further advancement in this area. However, despite the plethora of therapeutic targets, there is a need for increased understanding of the pathophysiology of the disorders.

## Introduction

*The impetus for the biomarkers workshop arose out of the scientific and therapeutic import of discovering and developing neuroscience biomarkers or biosignatures—more specifically biomarkers that are not currently being aggressively pursued but that hold the potential of near-term impact. The workshop drew upon experts from various fields to inform and provide discussion for the Institute of Medicine (IOM) Forum on Neuroscience and Nervous System Disorders about the challenges and opportunities in identifying biomarker targets that are not currently being aggressively pursued but that could be developed to practicality within the next 5 years by public-private partnerships. The goal of the workshop was focused consideration of potential biomarker, or biosignature, opportunities, including the current state of biomarker development and the resources needed to carry this effort forward.*

## BACKGROUND ON BIOMARKERS

The number of innovative medical therapies that have reached the market has been disappointing, given escalating research investment. One major reason for the slowdown has been the paucity of suitable biomarkers that might streamline the clinical testing of putative therapies. Biomarkers are quantitative biological measurements of many types that provide information about a disease state or a response to treatment, in addition to other disease characterizations.

One common category of biomarkers is used to identify people at risk for a disease; others are used to diagnose disease, assess its progression, or predict disease outcome. In the therapeutic setting, biomarkers can reveal information about whether a drug is adequately engaging its intended target or what therapeutic side effects or efficacy to expect. Of considerable interest to the pharmaceutical industry is the category of biomarkers known as “surrogate”<sup>1</sup> biomarkers, which are qualified indicators that can substitute for clinically meaningful endpoints in clinical trials (U.S. Department of Health and Human Services, 2006). Surrogate markers are sometimes used to substitute for clinical endpoints. Often they are used to reduce the time or study size needed to determine the response to a candidate treatment, thus shortening the path to use in a clinical setting. A biomarker of any type may be used individually; if a biomarker is used in combination with another biomarker, the two (or more) are sometimes referred to as a “biosignature.” An example of a biosignature would be a composite measure of imaging and genomics that offered improved diagnostic sensitivity and specificity compared to that of either measure alone.

The expected value of biomarkers to the pharmaceutical industry is to increase the efficiency of drug development, thereby permitting more drug candidates to be brought forward and perhaps increasing the information gleaned from the trials performed. The expected value to public health and to individual patients is to hasten access to safe and effective therapies. For these reasons, all potential partners have a stake in and stand to benefit from biomarker development.

There is a great need for new biomarkers for nervous system disorders, observed Dr. Dennis Choi, executive director of Strategic Neurosciences Initiative and Director of the Comprehensive Neuroscience

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<sup>1</sup>The Food and Drug Administration (FDA) defines a surrogate endpoint as “a biomarker that is used to predict clinical benefit (a direct measurement of how a patient feels, functions, or survives).”

Center in the Woodruff Health Sciences Center at Emory University and chairman of the planning committee for this workshop. Advances in basic neuroscience have identified a growing number of plausible therapeutic targets, but the gap between animal models of brain disorders and humans is profound. Estimating the potential of a putative new treatment is often impossible without clinical testing, which in many psychiatric, neurological, or retinal disorders has remained difficult and expensive and has been plagued by factors such as patient heterogeneity, lengthy trial durations, subjective readouts, and placebo responses. As a result, some potentially important experimental therapeutics are never explored. The availability of suitable biomarkers would likely significantly enhance the availability of needed treatments.

What has impeded the development of biomarkers for nervous system disorders? Certainly the complexity of the brain, limited access to brain tissue, and the blood-brain barrier are factors. But another key reason lies with incentives. Academic and government researchers already have provided a good scientific foundation for the preliminary identification of many biomarkers, several of which are described in this summary. But the industrial heavy lifting necessary to develop these candidate biomarkers into practical, reliable, and well-characterized tools ready for clinical use is usually not within the purview of academic researchers; it is too applied, process oriented, and resource intensive. Conversely, development is usually too remote from competitive-edge and commercial payoff to be justified within the research budgets of individual pharmaceutical companies. In other words, biomarker development may sometimes fall between the cracks of academic, government, and industry research programs. Some candidate biomarkers are likely to emerge only from large-scale molecular profiling efforts, whose assembly can require a daunting combination of resources, technology, and access to human subjects, often beyond the capabilities of individual organizations.

### **PUBLIC-PRIVATE PARTNERSHIPS**

A logical path forward is the formation of public-private research partnerships that bring together academic, government, and industry researchers. The partnerships would be tasked with developing nervous system biomarkers in the precompetitive space, which describes the ability of organizations, including companies, sponsors, and developers,



to work together on research and development without jeopardizing their intellectual property. The precompetitive space does not confer a competitive advantage to any individual pharmaceutical company. Bringing such biomarkers forward would broadly aid therapeutic development in given disease arenas, making it easier for any company to develop a successful treatment and giving no individual company a competitive advantage over another. An example of a public-private partnership in the neurosciences that has been extremely successful is the Alzheimer's Disease Neuroimaging Initiative (ADNI), a partnership launched several years ago by the National Institute on Aging (Table I-1).

This initiative, and the promise it holds for biomarker development, served as an impetus for a coordinated and focused process in biomarker development across multiple therapeutic areas (see agenda for further details). It led to the formation of the Biomarkers Consortium, launched in 2006 by the Foundation for the National Institutes of Health (FNIH), the National Institutes of Health, the FDA, and the Pharmaceutical Research and Manufacturers of America (Foundation for the National Institutes of Health, 2007).

The IOM Forum on Neuroscience and Nervous System Disorders (the Forum) was expressly created by the IOM in 2005 to bring together the public and private sectors, among other key stakeholders, to discuss issues of mutual interest and concern on topics of common and critical importance, particularly ones that stimulate partnerships to accelerate understanding and treatment of nervous system disorders. The Forum is a venue for convening stakeholders, sponsoring workshops, and producing workshop summaries intended to inform both the Forum membership and the general public.

In light of the aforementioned considerations, the time seemed right for the Forum to convene leaders from academic and industry organizations to assess the state of biomarker development and to consider strategies to galvanize public-private partnerships for nervous system diseases. For this purpose, the Forum sponsored a workshop, "Neuroscience Biomarkers and Biosignatures: Converging Technologies, Emerging Partnerships."

The organization of this summary essentially follows that of the sessions in the agenda (Appendix B). The first session describes the underlying goals of the workshop and includes an introduction to the FNIH and ADNI. Next, participants presented information on the potential

**TABLE I-1** Sponsors of the ADNI Initiative

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Alzheimer's Association  
Alzheimer's Drug Discovery Foundation  
Innogenetics  
Merck & Co, Inc.  
National Institute of Biomedical Imaging and Bioengineering  
National Institute on Aging  
National Institutes of Health  
Novartis Pharmaceuticals Corporation  
Pfizer, Inc.  
Wyeth Research

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SOURCE: Alzheimer's Disease Neuroimaging Initiative, 2007.

tools for biomarker and biosignature development, including discussion of the parameters that should be considered when developing a high-impact biomarker for neurological or psychiatric disorders. The next two sessions focused specifically on biomarkers for psychiatric diseases and drug addiction, and then neurological and eye diseases. The workshop concluded with a roundtable discussion on directions for the future.

This summary provides a synthesis of the workshop held on February 26 and 27, 2007, and presents insights made by participants at the workshop, but, in accordance with IOM policy, it does not make explicit consensus conclusions or recommendations.



# 1

## **Biomarker and Biosignature Principles**

*Workshop participants discussed the opportunities, challenges, principles, and best practices associated with identifying the necessary research tools, regulatory considerations, and partnerships for a biomarker that would provide a near-term impact. The Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium, which catalyzes new partnerships for the development of biomarkers that lie within the precompetitive space, was identified by participants as one potential mechanism that may facilitate additional collaboration and investment. Further, participants highlighted other models of public-private partnership that seek to accelerate development of new therapeutics, spanning effort across multiple areas of biomarker development, including the Alzheimer's Disease Neuroimaging Initiative (ADNI).*

## WORKSHOP GOALS

Organized by an independent planning committee, the Forum hosted a public workshop on biomarkers for nervous system diseases, inviting experts from industry, academia, government, and advocacy groups. The goal of the workshop was to discuss strategies to identify a high-impact biomarker, including a proof of concept, and provide a framework for how the Forum may facilitate its future dialogue and interactions among academia, government, and the private sector. Each speaker was asked to present data and stimulate discussion on the following questions:

- What processes can be used to accelerate scientific advances relevant to biomarker development?
- What models of public/private/academic partnerships have been successful in this and other arenas?
- What disciplines should be brought to bear? How can interdisciplinary perspectives be promoted?
- What tools are available? What tools are needed?

Besides stimulating discussion on these important topics, it was the Forum's ambition to contribute specifically to accelerating the availability of at least one important nervous system biomarker, both for its intrinsic value and for its value in exploring modes of Forum engagement. Thus, a stated goal of the workshop was to identify at least one high-impact biomarker, suitable for public-private partnership and potentially accomplishable in the near term, whose development might be accelerated by the Forum by facilitating interactions among stakeholders. It was recognized that to be suitable for public-private partnership, a biomarker would need to be useful to therapeutic development in industry context.

The chairman of the workshop's planning committee, Dr. Dennis Choi, described the workshop's goals in greater detail. He underscored the importance of setting realistic expectations for biomarker development, considering that few biomarkers (of varying qualification levels) besides risk genes have been developed for nervous system diseases to date. He and other members of the planning committee noted that biomarkers that reflected disease activity, drug safety,<sup>1</sup> or effectiveness were most likely to be of value in aiding clinical trials and, hence, to be of interest to industry. Yet a disease risk biomarker could also have quick im-

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<sup>1</sup>A safety biomarker can be used to identify patients at high risk for serious side effects, to monitor early signs of toxicity, or to predict the likelihood for severe toxicity.

pact on clinical trials—for example, if it helped to identify a subgroup of patients who had a higher probability of responding to a given candidate therapy. A 5-year time frame for development of a single biomarker is probably achievable, said Choi, but a longer time frame is needed for the biomarker to meet the Food and Drug Administration's (FDA's) rigorous regulatory requirements for qualifying as a surrogate marker (a topic later discussed by Dr. Janet Woodcock, deputy commissioner and chief medical officer at the FDA). While it is important to understand the regulatory requirements for a biomarker capable of serving as a primary end point in a clinical trial, Choi noted that exclusive focus on regulatory requirements at outset may deter innovation.

Another workshop goal was to help catalyze public-private partnerships. The partnerships could be cultivated through a variety of ways, including the FNIH Biomarkers Consortium, a new mechanism discussed by speaker Dr. Thomas Insel, the model provided by the ADNI, or, more narrowly, via a direct relationship between government and one private sponsor. Regardless, to be viable these partnerships must have sufficient commercial potential to engage the private sector and sufficient public health or research potential to engage the public sector.

### **FOUNDATION FOR NIH BIOMARKERS CONSORTIUM**

To facilitate public-private partnerships for biomarker development, Dr. Insel, director of the National Institute of Mental Health, outlined one major new mechanism, the FNIH Biomarkers Consortium. The mandate of the consortium is to accelerate biomarker discovery, development, and qualification. The creation of this consortium was among the prime motivations behind this workshop. This workshop will also serve to inform the Biomarkers Consortium, according to Insel, who is both a member of the Institute of Medicine's Forum and sits on governing bodies for the FNIH.

The Biomarkers Consortium was launched in October 2006 as a new initiative of the FNIH. The latter is a nonprofit organization associated with, yet independent of, the National Institutes of Health (NIH). FNIH is authorized by Congress to broker relationships between NIH and industry, academia, and philanthropies. Responding to scientifically worthy proposals, FNIH seeks funding from NIH institutes and pools their resources with those of private partners. One of the arrangements already created by this unusual pooling of public and private resources is an im-

aging project for lymphoma and lung cancer. NIH's partners under the Foundation's auspices are usually a group of pharmaceutical companies, rather than a single company. Projects vary in size, depending on their purpose and the Foundation's success at fund-raising.

Unlike an NIH institute, FNIH does not operate from a fixed budget; rather, it solicits funds from its public or private partners depending on the proposals it selects. FNIH is the administrative headquarters for each of the projects and is responsible for the entire process of proposal solicitation, proposal review and selection, and post-award management. Proposals can be submitted by any researcher and need not be restricted to those affiliated with organizations holding membership on the Foundation. Above all, FNIH's selection process is independent of the typical NIH peer-review system, and its criteria for selection are in keeping with its mission to expedite and expand the development of medically useful biomarker technologies and products.

The Biomarker Consortium's policy, like that of its parent Foundation, is only to solicit projects within the so-called precompetitive space. The concept is based on the premise that precompetitive projects are unattractive to academic, government, and industry partners alike, although for different reasons. For academicians and government researchers, developing biomarkers is too expensive and process oriented. For a single drug or device maker, biomarker development is too risky and removed from commercial payoff to justify the investment. The Consortium fills the gap by funding precompetitive projects that none of these entities would undertake on their own. Emphasis on precompetitive projects ensures that results are widely useful to the field as a whole. As elaborated upon by Choi, precompetitive projects sit somewhere between being not too hard to accomplish in a reasonable time frame and not so easy that individual companies can accomplish them and thereby gain competitive advantage.

One prominent example already funded through FNIH is the Alzheimer's initiative to identify biomarkers. It is precompetitive because it does not test any particular drug; rather, it is a prospective observational study that tracks the course of Alzheimer's disease. By contrast, a competitive project is one in which an individual company stands to gain financially, such as by testing a particular medication or diagnostic test for Alzheimer's disease. There are other mechanisms that enable those types of partnerships to occur outside the purview of the Consortium. Nevertheless, the Consortium is still so new that it has not defined the

exact boundaries between precompetitive and competitive space, according to Insel.

The Biomarkers Consortium faces many of the same policy issues as its parent Foundation. However, one key issue, conflict of interest, is less relevant to the Biomarkers Consortium because all members have agreed that all work will be public and, as described above, in the precompetitive space. In addition, device manufacturers and diagnostic companies are not represented in the Consortium, eliminating those who may see the biomarkers discovered as within their intellectual property space and of considerable value. Finally, all members sign extensive disclosure documents and agree to transparency in their interactions. Another issue concerns project solicitation and selection. Here, the obvious criteria apply: scientific merit, responsiveness, feasibility, and quality. But the most difficult issue is to find what types of scientifically meritorious projects are best suited to the Consortium's mission. The ongoing debate is whether scientific merit should be defined as having clinical impact as its foremost objective. A project can be of tremendous scientific value, for example, without having immediate clinical impact. On the other hand, a project can have immediate clinical impact without being at the cutting edge of science. Consortium members who sit on the committees that approve proposals often wrestle with these tensions.

The Consortium gained from the policy already developed by its parent Foundation regarding antitrust laws. Those laws normally preclude leaders of the pharmaceutical industry from meeting together and working on joint projects. Once the Foundation defined its role in facilitating projects in the precompetitive space, industry representatives were willing to participate without fear of violating antitrust laws. Two other thorny issues—intellectual property and data sharing—still are formidable because of the trade-off between encouraging commercialization, on the one hand, and meeting the public health need for transparency and openness on the other. For that reason, these issues are worked out on a project-by-project basis and are subject to the approval of the Foundation's oversight bodies.

### **REGULATORY CONSIDERATIONS FOR BIOMARKER DEVELOPMENT**

FDA is deeply concerned about the limited innovation of biomarkers, stated Dr. Janet Woodcock, deputy commissioner and chief



medical officer of the FDA. That concern prompted several policy initiatives, such as publication in March 2006 of FDA's Critical Path Opportunities Report. The document overtly encourages development of biomarkers and other tools to shorten the time necessary for new drug and device development and their clinical use (U.S. Department of Health and Human Services, 2006). In keeping with that landmark publication, Woodcock said that her presentation was designed to clear up misunderstandings about FDA's definitions of biomarkers and to explain the agency's regulatory requirements for different types of biomarkers. The misunderstandings, in her view, have set back biomarker development, because FDA's requirements for most types of biomarkers are erroneously perceived as too onerous. With the exception of surrogate biomarkers, most other types of biomarkers do not require a high bar for regulatory use, she stated.

FDA became concerned about the lag in biomarker development, relative to a surge in therapeutic development, when it realized that many biomarkers are discovered but never submitted for regulatory review. They are developed in academic laboratories and published in the biomedical literature as case series. They may even become commercially available as a lab service. But few are integrated into widespread clinical care because the evidence base is too slim or controversial. The main hurdles, according to Woodcock, are that academicians do not understand FDA's requirements and that the business model for diagnostic development is not as robust as that for therapeutics.

To clear up some of the misunderstanding, Woodcock began by giving FDA's current regulatory definition of a biomarker. The following definition was developed by an NIH-convened working group of which FDA was a part (Biomarkers Definitions Working Group, 2001):

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacological responses to a therapeutic intervention.

As it would for any other evolving field of medicine, FDA further modified the definition in its pharmacogenomics *Guidance* into possible, probable, and known valid categories of biomarker, depending on scientific evidence available to support the biomarker (Food and Drug Administration, March 2005).

Meanwhile, FDA has backed away from using the regulatory term “validation” of biomarkers because the term acted as a deterrent to biomarker development. To signal the lower threshold of evidence needed for most biomarkers (except surrogate markers), FDA began to refer to its regulatory process of evaluating biomarkers as a qualification process rather than a validation process. The purpose of a qualification process is “to evaluate the utility of a biomarker” (U.S. Department of Health and Human Services, 2006). Biomarker qualification is essentially an evaluation of a marker’s fitness for use, that is, whether the evidence supports a biomarker’s use for a given purpose. The level of evidence needed to qualify for fitness for use is highly variable. Many types of diagnostic biomarkers, for example, do not have a high threshold of evidence for approval by FDA. Biomarkers used in drug development that do not have an extremely high threshold of evidence, said Woodcock, include those used for safety assessment (e.g., markers that predict early signs of toxicity and/or signal potential for severe toxicity) (U.S. Department of Health and Human Services, 2006). Additionally, genetic tests for drug metabolizing enzymes or other determinants of starting dose may be utilized without undergoing the rigorous “validation” required for surrogate endpoints. Similarly, biomarkers used to stratify patients in order to enrich a trial with those who should receive therapy (e.g., as is the case with Herceptin for breast cancer) can usually be studied within a particular drug development program and do not need extensive separate trials.

A surrogate endpoint requires the most rigorous level of evidence. It is defined as a biomarker intended to substitute for a clinical endpoint. The surrogate is expected to predict clinical benefit (or harm, or lack of benefit) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. The clinical endpoint for which the surrogate is being developed is a characteristic or variable that reflects how a patient feels, functions, or survives (U.S. Department of Health and Human Services, 2006).

Woodcock proceeded to describe the multistep process that FDA requires for qualification of biomarkers. Qualification of any biomarker first requires analytic validation, a process that includes evaluation of test parameters such as stability of reagents, standardization of assays, assessment of sensitivity, specificity and predictive value of assays, and the biomarker’s robustness in various sites. Analytic validation is the area where academia falls short, in part because academic scientists are not well compensated or rewarded in the academic sector for applied science. The second step is clinical validation, which includes evaluating

the performance of the biomarker in clinical samples or in people with varying characteristics. The sponsor must establish that the assay continues to measure the same thing with reasonable accuracy under varying conditions or in different populations. The third step is to establish clinical utility, that is, to show that the biomarker has some clinical significance. Establishing clinical utility is not very onerous because many stand-alone diagnostic biomarkers can meet this criterion. Biomarkers that show ways to stratify patients based on prognosis, that show natural history of the disease process, or that predict pharmacokinetics based on variation in drug-metabolizing enzymes are the most common ways to establish clinical utility. A somewhat higher bar is reserved for biomarkers used to diagnose, or contribute to diagnosis of, pathology. In some cases, the purpose of biomarker qualification is to establish a linkage between the biomarker and a therapeutic intervention. These types of biomarkers are used to select patients to receive therapy (or not) or used for dose selection. These types of biomarkers do not have extensive regulatory requirements for clinical utility.

Woodcock stressed the point that biomarkers falling under any of the aforementioned categories may shorten the duration of clinical trials. A surrogate marker, in other words, is not the only type of biomarker that can hasten the process of drug development. Examples of nonsurrogate markers that can shorten trial duration are ones used to enrich trials with patients whose prognosis is worse or patients who are likely to exhibit a more rapid time to an event. For example, enrollment criteria often restrict entry to patients who meet certain prognostic criteria. New biomarkers such as gene expression arrays in cancer or markers of inflammation in heart disease may be used to identify individuals at high risk for recurrence or myocardial infarction, respectively.

Qualification of surrogate biomarkers requires great rigor, including evidence showing biological plausibility, statistical correlation with a clinical outcome, and success in clinical trials (Box 1-1). Although these criteria seem formidable, FDA has accumulated more than a decade of experience with surrogate markers. Over that time, its position on what constitutes a surrogate marker has evolved. Among FDA's key modifications, said Woodcock, is to understand that there is no gold standard for clinical outcome measurement of a particular disease. Patient outcomes are too multidimensional in that a single outcome measure can miss domains of interest. It is very difficult to capture with a single measure both the benefit and the harm predicted by a surrogate endpoint. Woodcock

**BOX 1-1**

**Qualification of Biomarkers for Use as Surrogate**

**Biological Plausibility**

- Epidemiological evidence that marker is a risk factor
- Marker must be consistent with pathophysiology
- Marker must be on causal pathway
- Changes in marker reflect changes in prognosis

**Statistical Criteria**

- Changes in marker must be correlated with clinical outcome (but correlation does not equal causation)

**Additional Support for Biomarkers as Surrogate**

**Success in Clinical Trials**

- Effect on surrogate has predicted outcome with other drugs of same pharmacologic class
- Effect on surrogate has predicted outcome for drugs in several pharmacologic classes

**Other Benefit/Risk Considerations**

- Serious or life-threatening illness with no alternative therapy
- Large safety database
- Short-term use
- Difficulty in studying clinical end points

SOURCE: Temple, 1999.

said she foresees the future of surrogate endpoint development as featuring composite outcome measurements (i.e., biosignatures). She also envisions responder rather than population mean analyses and individualized therapy based on biomarker-derived strata.

Regarding applications to nervous system disorders, Woodcock expressed optimism. Few nervous system biomarkers are available today because the disorders are marked by subjective diagnostic criteria, highly variable rates of responses, a high need for preventive interventions, and current therapeutic interventions with safety or adherence problems. All of these features create an opening for the development of new biomarkers. Woodcock views neuroscience as a leading candidate for new biomarker development.

To facilitate biomarker development, FDA has carved out several roles for itself. Through its Critical Path Opportunities Report initiative

and its “qualification” process, it hopes to encourage adoption of new biomarkers for preclinical and clinical product development. It also hopes to encourage partnerships and consortia to share the burden among all stakeholders who benefit from the new biomarkers. FDA participates in at least five other consortia dealing with other fields of medicine. Finally, FDA plans to develop regulatory guidance on pathways to market, and it plans to promulgate further advice on the design of qualification trials.

### **LESSONS LEARNED FROM A SUCCESSFUL PARTNERSHIP TO PROMOTE BIOMARKER DEVELOPMENT FOR ALZHEIMER’S DISEASE**

ADNI is an approximately \$60 million public-private partnership sponsored by FNIH in collaboration with other federal agencies, the National Institute on Aging (NIA), and private companies and organizations. Its overall goal, over a 5-year period, is to develop a validated biomarker for Alzheimer’s disease clinical trials. The emphasis of the initiative is to find biomarkers through neuroimaging, as the name of the initiative implies. Serial magnetic resonance imaging and positron emission tomography scans are being used to image several parameters of the brain, including the volume and boundaries of the hippocampus and the entorhinal cortex (two sites most affected by Alzheimer’s disease), whole-brain atrophy, and cortical thickness. But other biomarkers from cerebrospinal fluid and urine are also being collected that as described later, offer great interest and potential. The study’s costs are being borne by NIH (\$40 million) and the Alzheimer’s Association and several drug companies (\$27 million) according to Dr. William Potter, vice president, Franchise Integrator Neuroscience, at Merck Research Laboratories, the presenter who described the initiative and the lessons drawn thus far.

The study seeks to identify biomarkers for the progression of mild cognitive impairment and early Alzheimer’s disease. It is not a clinical trial testing a particular drug; rather, it is a prospective, naturalistic study tracking several groups of patients over the course of 2 to 3 years. One group (n = 400) has pre-Alzheimer’s (i.e., a mild cognitive impairment found in the earliest stages of Alzheimer’s disease). These patients constitute a critical population for prevention or for slowing further progression. Another group has early onset Alzheimer’s disease (n = 200), and the control group consists of cognitively normal older adults (n = 200).

Although ADNI commenced before creation of the Consortium, it illustrates the kind of public-private partnership envisioned by the Consortium for other nervous system diseases. ADNI will furnish one large dataset for analyzing a host of potential biomarkers or biosignatures over the course of disease, with the goal of determining the most useful ones. As such, it is a precompetitive project, with broad applicability for eventual use in wide-ranging clinical trials. In the past, clinical trials of the same agent had been plagued by inconsistent or conflicting findings partially attributable to the use of different biomarkers or different methods of analysis. ADNI's sponsors have agreed to full data sharing on a real-time basis; ongoing results are publicly accessible on the Internet.

What are the motivations behind the public and private partners? For the primary public partner, the NIA, the trial serves a crucial public health need to find a biomarker to stimulate development of new therapeutics. And that public health need is growing due to the demographic bulge of aging baby boomers. For industry partners, explained Potter, there are several reasons:

- the greater commercial demand due to the demographic growth in older persons;
- the longer period of patient usage based on the expectation that once a biomarker is identified, it will be possible to treat patients earlier in the course of disease;
- the desire to expedite NIA's research findings so that they can be applied to clinical trials more quickly;
- the ability to participate in study design; and
- the inexperience of industry partners in conducting prospective observational studies in which no drugs are being tested (as opposed to their wealth of experience in clinical trials).

On the downside, investment in Alzheimer's drugs is still considered highly risky because of the exorbitant costs of drug development, including clinical trials, and the poor return on investment. Several drugs have been unsuccessful in reaching the market, whereas other drugs that have reached the market have not met with high demand because of modest clinical gain.

The major lessons learned, observed Potter, come from the active role that industry members have carved out through a special advisory committee. Their contributions have been essential in two prominent areas of study design: the collection and standardization of cerebrospinal

fluid (CSF) and the standardization of imaging (Box 1-2). Industry members have collaborated so well, in the opinion of Potter and other workshop attendees, that they set a model for industry contributions to future Biomarkers Consortium projects.

While many advances are coming from the analysis of the image data, Potter expressed that collection of CSF may turn out to be more important than imaging biomarkers. This contribution was made possible through the advisory committee's success in working with its public partner to modify the study design to collect CSF at much higher rates than initially called for in the protocol and by encouraging more patients, via an educational video, to willingly undergo lumbar puncture. The protocol originally called for 20 percent of each group to undergo lumbar puncture; however, through the aforementioned strategies, investigators have been successful in collecting CSF from close to 60 percent of participants. With this success also comes the challenge of analysis of the CSF. ADNI was not originally designed to perform detailed analysis on this quantity of CSF; therefore, according to Potter, new partnerships are necessary to take advantage of this opportunity.

**BOX 1-2**

**Active Role of Industry's Participation in Study Design**

- Raised the percentage of patients for CSF collection from 20 percent to close to 60 percent
- Standardized collection, handling, and storage of CSF through development of a best practices protocol, which includes assays for proteins implicated in Alzheimer's disease
- Arranged for and cofunded an educational video to encourage contribution of CSF
- Developed best practices for a standardized approach to brain imaging
- Developed precompetitive algorithms for diagnosis
- Organized a training workshop for statisticians and database managers

SOURCE: Potter, 2007.

## 2

### **Potential Tools for Biomarker and Biosignature Development**

*Biomarker development hinges on the effective advancement and resourcing of currently available tools and technologies. Outcome measures include treatment efficacy, increased specificity in clinical trials and therapeutics, and identification of target study molecules. In Session II, workshop participants discussed the value of genomics, proteomics, and imaging as tools for biomarker discovery and development.*



## IMPACT OF GENOMICS

Genome-wide scanning is a relatively new genetic technology for finding biomarkers associated with disease. It is a method of scanning the entire genome in the search for single nucleotide polymorphisms (SNPs) that are correlated with disease. While the vast majority of SNPs are innocuous, SNPs associated with disease are identifiable in combination with other data, including epidemiology studies that compare large groups of individuals with the disease against other groups without the disease. When SNPs associated with disease are found on particular regions of the chromosome, these SNPs subsequently can be used to pinpoint disease-specific loci to the disease-related gene.

An outgrowth of the Human Genome Project and the International HapMap Project, genome-wide scanning has a myriad of applications, including the identification of targets for drug development. Dr. Allen Roses, senior vice president of GlaxoSmithKline, Inc., focused his presentation on genomics' impact for development of biomarkers for nervous system disorders. He pointed out that genotypes associated with disease eventually may be used to predict which patient groups are more susceptible to disease, which are more likely to experience adverse effects of drugs, or which are more likely to benefit from drug therapy and at what doses (among other applications).

Genome-wide scanning already has been applied successfully to at least one nervous system disorder, Alzheimer's disease (Martin et al., 2000), and is soon expected to yield results for schizophrenia, according to Roses. It is now well established that the gene APOE is a susceptibility gene for Alzheimer's disease (Roses, 1996). Drawing from this pioneering work, Roses first focused on the value and efficiency of genome-wide scanning as a method to validate and confirm genetic loci first found by previous methods that were more labor intensive (Lai et al., 1998). Genome-wide scanning, said Roses, has an equally important role in disconfirming other loci identified by earlier methods. Narrowing the search for the most important loci is essential before undertaking the laborious process of finer mapping and positional cloning to find, within the loci, specific genes that are defective. Genome-wide scanning also can be used, on its own, without being hypothesis-driven about which chromosomal regions to search. In other words, it can be used in a hypothesis-free manner to examine new regions of the genome not explored in earlier studies. Those studies were often small, family-based

association studies rather than the large population cohorts now being studied in association with genome-wide scanning.

With genome-wide scanning, around 500,000 SNPs are now used to examine the entire human genome to identify possible target loci for disease biomarkers. This figure represents a small subset of the 10 million SNPs found across the genome. The reason it is possible to examine only a small subset of SNPs is because of the correlation (linkage disequilibrium) that exists between SNPs in close proximity to one another. The 500,000 SNPs now available by commercial microarray technology capture 80 percent to 85 percent of the entire genome (and these figures are now growing with newer versions of the technology). After conducting the first analysis to find SNPs associated with disease, a series of replication analyses are performed with the same or with larger cohorts to eliminate false positives (considering the huge number of comparisons being made in a large cohort, as opposed to smaller, family-based associated studies, which are less sensitive to false positives). A combination of methods, for example, was used to implicate another gene associated with APOE. An analysis that focused on the gene SORL1 found no variants involved in defective processing of amyloid precursor protein in the pathophysiology of Alzheimer's disease (Rogaeva et al., 2007).

Roses also provided examples of the value of genotype biomarkers in clinical trial design. Results from clinical trials can be highly dependent on the genotype of the patient (Roses et al., 2007). Therefore, enriching trials with patients who have the receptive genotype is expected to enhance the likelihood of demonstrating drug efficacy and reduce the size of the trial. One example occurred during a trial of rosiglitazone, a drug targeted to combat the APOE defect in Alzheimer's disease. Overall, the combined group of patients with mild and moderate Alzheimer's disease did not improve with the drug, but after the patients were stratified by genotype, it was recognized that APOE4-negative patients improved with the drug, whereas those who were APOE4-positive failed to improve (Risner et al., 2006). Because the original data had been pooled together, the drug program would have been needlessly halted from lack of efficacy. Once the value of genotyping was established, subsequent phases of the clinical trial were redesigned and powered appropriately to ensure that the drug's effects would be realized among patients with the susceptible genotype. Three genotype-specific Phase III clinical trials are in progress for rosiglitazone, noted Roses, with a subset of patients carefully selected by genotype. Stratification by genotype also was crucial for choices about dose. Higher doses of the drug were needed to see a

positive effect in APOE4-negative patients. The concept of sequential analysis in clinical trial design—using each phase to help enrich subsequent phases with genotype-specific patients—has broad applications for drug development. The one major concern, however, is that the genotype being targeted by genome-wide scanning (or other methods) may be too specific in its physiological effect and, thereby, miss other candidate genes with broader therapeutic effects.

### IMPACT OF PROTEOMICS

Proteomics-based biomarker discovery is a relatively new field that can be harnessed to identify new central nervous system (CNS) biomarkers. In the broadest terms, proteomics seeks to understand the total protein complement in fluids or tissues by identifying individual or groups of proteins, their levels of expression, post-translational modification, and protein-protein interactions, among other characteristics from which protein and cellular function can be inferred. The field, however, does not yet have the capacity to conduct a whole-proteome scan to the same extent that the entire genome can now be scanned; proteomics can, however, identify hundreds to thousands of proteins in small samples of complex fluids or tissues. The proteome, unlike the genome, differs from cell to cell and, over time, changes dynamically within each cell in response to external stimuli. Its ability to report on the physiological state of the organism is what makes it valuable as a source of biomarkers but is also what makes proteomics more challenging.

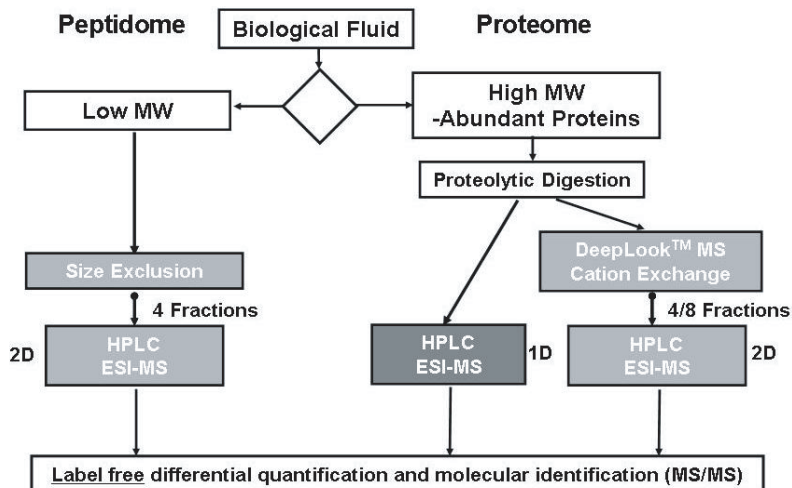
Against this fluctuating background in protein expression, the search for biomarkers and biosignatures of disease looks for reproducible changes expressly associated with disease or response to drugs. The study of CNS diseases, while in its infancy, will be greatly aided by identifying patterns of expression of multiple protein biomarkers in the same way that the measurements of HDL, LDL, and cholesterol are biosignatures of cardiac disease, noted Dr. Howard Schulman, vice president of R&D of PPD Biomarker Discovery Sciences.

Identification of potentially new protein biomarkers of disease first requires extraction of fluids or tissues, protein separation, identification, and quantification of relative levels of protein expression using advanced software. The most advanced methods of protein profiling rely on liquid chromatography combined with mass spectrometry (LC/MS), said Schulman. In his presentation, he described PPD's main approach to pro-

teomic discovery as “an unbiased screen of several thousand potential biomarkers in biological fluids or tissues.” The workhorse of proteomics historically has been the use of two-dimensional gels to separate proteins, but this method has lower sensitivity and throughput than LC/MS. These approaches compare with hypothesis-based approaches, using more narrowly targeted methods that typically use antibody reagents, for example, to find ratios in the levels of a small number of proteins. But the lack of antibody reagents has been a rate-limiting problem in the application of proteomics to the CNS. Hypothesis-based approaches or multiplexed screens with panels of antibodies can complement proteomic discovery by measuring low-abundance proteins. In general, the proteomics field is less developed for applications to the CNS than for other bodily systems, largely because fluids and tissues from the CNS are less accessible.

LC/MS generates *relative* concentrations of proteins by measuring signal intensity, but it cannot generate *absolute* concentrations. A major hindrance to protein profiling is the broad dynamic range of protein concentrations found in a complex mixture. To overcome this problem, one approach begins by affinity removal of the 80 percent to 90 percent of the protein mass contributed by the 6 to 12 most abundant proteins. Further fractionation of the mixture can yield certain proteome classes, such as low-molecular-weight (peptidome) versus higher-molecular-weight proteins (Figure 2-1). Peptidomes are often 10 times less abundant in the sample. Another approach is to subdivide proteins by attached chemical group, such as phosphoproteins, glycoproteins, and ubiquitinated proteins (i.e., the key to dealing with the problem of a wide dynamic range is through subsampling and fractionation).

For the purpose of discovery in CNS diseases, proteomics is best accomplished by examining samples from the cerebrospinal fluid (CSF) rather than from the blood, Schulman stressed. The CSF carries higher concentrations of biomarkers because it is closer to the source of the pathology and the physiological response to it (Huhmer et al., 2006). CSF is enriched with intracellular proteins and proteins in extracellular debris that are likely associated with disease (Schulman, 2006). The CSF also has a smaller dynamic range of protein concentrations to facilitate in-depth analyses, meaning that a smaller range exists between the most and the least abundant proteins. Its dynamic range is an order of magnitude less than that of blood. From about 1 mL of CSF it is possible to profile 1,000 to 2,000 proteins.



**FIGURE 2-1** Differential quantification: proteins and peptides.  
NOTE: Molecular weight (MW); high-performance liquid chromatography (HPLC); electrospray ionization mass spectrometry (ESI-MS); mass spectrometry (MS); combination of two or more MS experiments (MS/MS).  
SOURCE: Schulman, 2007.

Another obstacle is public attitudes, which view lumbar puncture as too invasive. This view is misplaced as long as the potential for benefit is strong, said Schulman, who notes that lumbar puncture is well accepted in Europe and Scandinavia. The evidence from one of the first CNS diseases for which biomarkers are being developed, Alzheimer's disease, justifies a shift in American attitudes. Proteins directly associated with the disease are detectable in CSF but are only poorly detectable in the blood, or their levels do not reflect changes in the CNS levels of the protein (Irizarry, 2004). A shift in American attitudes is likely to occur once more is known about the low risks associated with lumbar puncture. Schulman pointed out that in Potter's presentation, for example, attitude toward lumbar puncture was suggested to be improved as a result of subjects viewing an educational video that profiled the low risks associated with lumbar punctures.

In the case of CNS lymphoma, lumbar punctures are routinely done for cytological tests even though the results are not diagnostic, with lymphoma cells only detected in about 40 percent of the subjects with the cancer. Schulman reported that he and his colleagues are developing bet-

ter methods to diagnose CNS lymphoma with CSF, first by seeking to correlate potential biomarkers from CSF with imaging studies and other clinical indicators of disease. The initial set of biomarkers is already better than the existing cytological test (Rubenstein, 2005). Biomarkers found in the spinal cord have the potential not only as a diagnostic test but also as a measure of response to treatment. It is possible that after initial discovery of a useful biomarker from the CSF, a blood test can be created to check for that particular biomarker.

Apart from Alzheimer's disease, for which biomarkers are being developed, proteomics is only beginning to be investigated for diseases arising within the CNS. Some of the most obvious diseases for study include schizophrenia, depression, and autism (Box 2-1). Some of the major challenges in further expansion of the field are the limited number of reagents for enriching and subsampling classes of proteins, the wide dynamic range of concentrations of brain proteins (which means that many proteins would be missed), and improving the sensitivity of the LC/MS. To narrow the search, new methods need to be developed to eliminate the most abundant peptides. Reagents for depleting abundant proteins are typically designed for plasma proteins, but proteins in the CSF do not completely overlap with them. Finally, overcoming the public's attitude toward the invasiveness of lumbar puncture is key to CNS biomarker development with proteomics.

**BOX 2-1**

**Biomarker Opportunities in Neuroscience**

Comprehensive phenotyping (discovery- and hypothesis-based approaches; protein, genes, imaging, etc.) includes

- Antecedent markers in schizophrenia
- Patient responder/nonresponder stratification in depression
- Stratification of autism spectrum disorders
- Biomarkers of placebo effect (in depression)
- Antecedent markers in Alzheimer's disease

SOURCE: Schulman, 2007.

## IMPACT OF IMAGING TOOLS

Imaging not only occupies a singular place in the current practice of medicine, but also holds enormous prospects for future biomarker development, according to Dr. Bruce Rosen, director of the Center for Biomedical Imaging at Massachusetts General Hospital. Rosen opened by citing a survey of practicing internists who selected computed tomography (CT) and magnetic resonance imaging (MRI) as the leading medical advances of the past quarter-century. They were ranked first, superceding 30 other possible advances, including ACE inhibitors, statins, and mammography (Fuchs and Sox, 2001). Rosen profiled some existing biomarker advances, numerous cutting-edge opportunities, and several key barriers to progress for the two main types of imaging biomarkers—structural and functional. In years to come, both are likely to be integrated together in often creative and revealing ways.

The most common structural biomarkers being applied to the nervous system include CT and MRI, and functional biomarkers include positron emission tomography (PET; for neurochemistry), electrophysiology by electroencephalography and magnetoencephalography (MEG),<sup>1</sup> and functional MRI (fMRI); some of the imaging outcomes are described later in this section. Their ultimate value, from Rosen's perspective, is to provide surrogate markers for eventual qualification by the Food and Drug Administration. The markers they generate might represent early pathophysiologic indicators of disease, diagnosis, or treatment (especially dosing and response to treatment). Rosen noted that one of the major successes of the imaging field, which comes from oncology, is a structural biomarker showing tumor volume reduction in not only one but several colon cancer clinical trials. The reduced size of the tumor showed a strong correlation with overall survival and thereby could be developed as a surrogate to hasten the pace of drug development (Fleming, 2005). But for every success, there are failures. One guidepost for finding a successful biomarker, said Rosen, is to focus on those that participate in the pathophysiological process of the disease under study.

Rosen summarized the status of biomarker development in neuroimaging, emphasizing that the best *anatomical* biomarkers have been in quantitative morphometry and white matter conductivity. The greatest *functional* biomarkers have been in several areas of physiology, metabolism, receptor distribution, and electrophysiology (Box 2-2).

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<sup>1</sup>MEG measures magnetic fields produced by electrical activity in the brain.

In the near future Rosen anticipates the most progress in utilizing gray matter ultrastructure (which is especially important for developmental diseases), high-resolution cytoarchitectonic mapping, tomographic electrophysiology (which will enable identification of functional conductivity patterns), and the combination of imaging biomarkers with markers of gene and protein expression. As tantalizing as these prospects may be, Rosen anticipates that structural markers will continue to be a mainstay for a long time to come.

As one of many examples of the cutting-edge utility of imaging, Rosen highlighted some recent developments in Alzheimer's disease biomarkers. For years there has been debate about whether regional thinning in the brain of Alzheimer's patients reflects the disease process versus normal aging. New research reveals that Alzheimer's disease is indeed distinguishable from normal aging by distinct patterns of thinning in the parietal cortex, posterior hippocampus, and entorhinal cortex—nuclei long associated with Alzheimer's disease. These and related accomplishments are made possible by more sophisticated ways to increase resolution, allowing visualization of individual nuclei or tracts within the brain (Figure 2-2). The entorhinal cortex, for example, consists of nests of about 100 cells, each of which are about 250 microns in

**BOX 2-2**

**Neuroimaging as an Indicator for Neural States**

**Anatomy**

- Quantitative morphometry
- White matter "connectivity"
- Gray matter ultrastructure
- Cytoarchitectonic mapping

**Function**

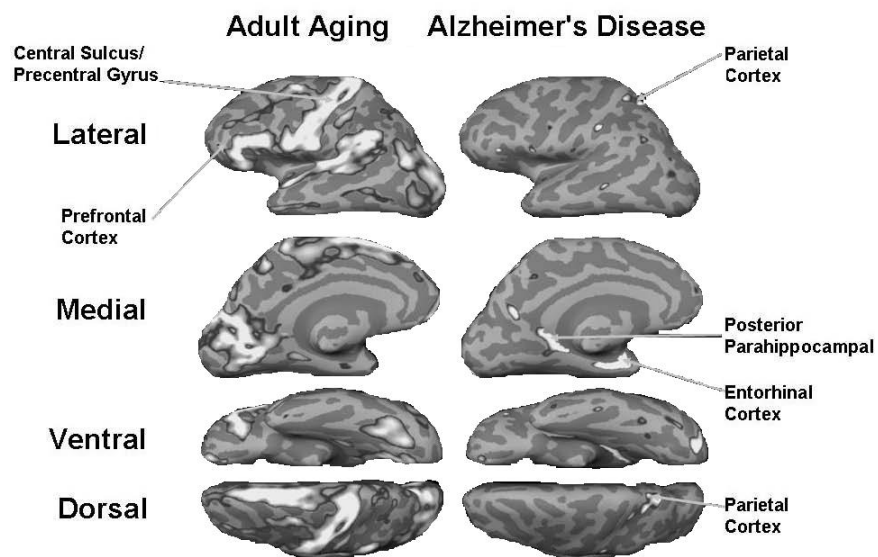
- Physiology (CBV, CBF, Hb/HbO<sub>2</sub>)
- Metabolism (CMRGlu, CMRO<sub>2</sub>)
- Receptor distribution
- Electrophysiology
- Tomographic electrophysiology/functional connectivity
- Gene and protein expression

SOURCE: Rosen, 2007.



size, said Rosen, who noted that this degree of resolution has not been heretofore achieved. This nucleus is highly important because it is the first group of cells to die during early Alzheimer's disease. A related example is from a study showing that in response to a cognitive task, people with attention deficit hyperactivity disorder (ADHD) fail to activate their anterior cingulate nucleus in comparison with normal controls (Bush et al., 1999).

The more distant prospects for neuroimaging are wide ranging. They include circuitry-based diagnosis of such disorders as ADHD, substance dependence, depression, schizophrenia, and obsessive-compulsive disorder; better contrast agents to increase sensitivity to visualize blood volume; imaging of gene expression through MR; and molecular imaging of substance abuse (Volkow et al., 2006) (or other brain-based disorders through PET scanning or pharmacologic MRI<sup>2</sup>).



**FIGURE 2-2** Selective regional thinning in Alzheimer's disease.  
SOURCE: Adapted from Salat et al., 2004.

<sup>2</sup>Pharmacologic MR uses pharmacological challenge to image neurocircuits and to track drug time course through hemodynamics.

An attractive goal, highlighted by Rosen, is to develop combination modalities that integrate structural and functional information, such as anatomical MRI in combination with functional and baseline perfusion MRI. In one early example, investigators compared five different modalities for imaging the hippocampus in Alzheimer's disease. The modalities are MRI, PIB (a radiotracer for an amyloid ligand), FDG (a radiotracer for glucose metabolism), ASL (arterial spin labeling MRI that measures blood perfusion), and fMRI. The combination of PET and MRI might enable study of receptor-specific functional activation through simultaneous physiology and receptor kinetics. The combined approach ultimately may add electrophysiology, predicted Rosen, who said that several modalities combined, rather than a single modality, may become the best markers for profiling nervous system diseases.

None of the opportunities are without barriers to development, the most common of which are

- the need for validation of images to ensure face validity (among other forms of validity testing);
- standardization of imaging protocols across centers, particularly as scanners are upgraded in field strength;
- the need for sophisticated informatics to integrate the information provided by markers from several different imaging modalities, in addition to levels of gene and protein expression;
- the formidable blood-brain barrier across which drugs or radiotracers must penetrate; and
- the insufficient number of radiotracers for PET studies that are tailored to proposed molecular defects. This problem was echoed by Dr. Nora Volkow, director of the National Institute on Drug Abuse, who pointedly called the lack of tracers the "strongest impediment to progress."

The absence of radiotracers has become such a rate-limiting problem that a new public-private initiative has been proposed to tackle it. The Radiotracer Clearinghouse (RCH) is a nonprofit organization providing a solution to help fast-track drug discovery and development processes for CNS and any other therapeutic areas. RCH was conceived as a vehicle to enable the pharmaceutical industry to share information on radiotracers within a secure environment designed to protect all parties' intellectual property. Within the RCH, scenarios may include sharing information (1) under strict confidence with minimum disclosure between parties and no

public disclosure or (2) with all parties involved with intent to publicly disclose information related to the biomarker, target, or specific imaging study in a timely manner. The latter scenario may be covered under RCH as a project with the Biomarker Consortium. In all cases, the rules of engagement for the scope and timing of information shared throughout the process will be established before each project begins by the RCH facilitator and the pharmaceutical companies/academic partner involved, according to Dr. Dean F. Wong, professor of radiology and psychiatry, vice chair radiology research and section director of high resolution brain imaging at the Johns Hopkins University.

### 3

## Psychiatric and Drug Addiction Disorders

*In assessing psychiatric and drug addiction disorders, there is a need to move from qualitative to quantitative measures. Biomarkers for psychiatric and drug addiction disorders will provide a valuable resource necessary to expand diagnosis and monitoring beyond the often qualitative categorizations revealed by clinical experiences and the manuals on mental health (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV] and the International Classification of Diseases, 10th Revision [ICD-10]). Quantitative measurements that could be gleaned from the biomarkers themselves offer better categorization of individuals, target treatments more effectively and earlier for patients, and determine vulnerability to disorders. In Session III the discussion centered on specific areas of psychiatric and drug addiction research where specific biomarkers are currently showing promise, as well as opportunities for further impact.*

## OVERVIEW

Psychiatric disorders, like most other nervous system disorders, lack biomarkers in clinical use. Instead, diagnosis of psychiatric disorders rests on patients' reports of their symptoms, signs from their mental status examination, and clinician observations of their behavior. To make a diagnosis, mental health professionals group those clues into distinct diagnostic categories listed in one of two classification systems, DSM-IV and ICD-10 (American Psychiatric Association, 2000; World Health Organization, 2007). The categories listed there are based on expert consensus that draws from both scientific evidence and clinical experience. The diagnostic categories are largely descriptive in orientation, with DSM actively professed to be "neutral with respect to theories of etiology" (American Psychiatric Association, 2000). But should the diagnostic categories of psychiatric disorder drive the search for biomarkers? Are there complementary alternatives to using standard diagnostic classifications? Those were the provocative questions raised by Dr. Steven Hyman, provost of Harvard University.

Growing evidence suggests that biomarker research might best be served by focusing elsewhere. Hyman proposed that biomarker research should focus less on current categories of disorder and more on underlying clinical states for which some knowledge of pathophysiology or neurocircuitry is available. Clinical states of this kind often transcend the boundaries of a single category of disorder. For example, the cognitive impairment observed in schizophrenia (including impairment of working memory) is associated with thinning of prefrontal cortex observed by structural MRI (Hyman, 2007b). Although it is responsible for substantial disability, it is not part of the DSM-IV criteria, which date to earlier understandings of schizophrenia as primarily reflecting psychotic symptoms such as hallucinations and delusions. A focus on biomarkers to follow working memory deficits involving prefrontal cortical circuits would seem more likely to succeed than searching for a biomarker of DSM-IV schizophrenia, which is a heterogeneous syndrome defined only by symptoms and course.

To understand the change in emphasis, Hyman first traced the intellectual and historical underpinnings of the current diagnostic classification systems and then argued that excessive reliance on current, consensus diagnostic categories—especially for the purpose of biomarker research—may lead researchers down blind alleys.

The criteria used to guide the current categorization of psychiatric disorders were developed in 1970 by pioneering epidemiologists (Robins and Guze, 1970). On the basis of their empirical research, they proposed that reliable and valid diagnoses should be based on five criteria: clinical description (symptom clusters), laboratory studies, delineation of one disorder from another, follow-up studies, and family studies. These criteria fueled the modern era of psychiatric diagnosis and helped to launch decades of empirical research, as opposed to the earlier emphasis on theory and small, nonrepresentative samples. With disorder classifications came the ability to study individual diagnoses and their causation. One of the most powerful lines of research dealt with family studies. This approach strongly influenced the current classification systems, most notably the DSM system of the American Psychiatric Association.

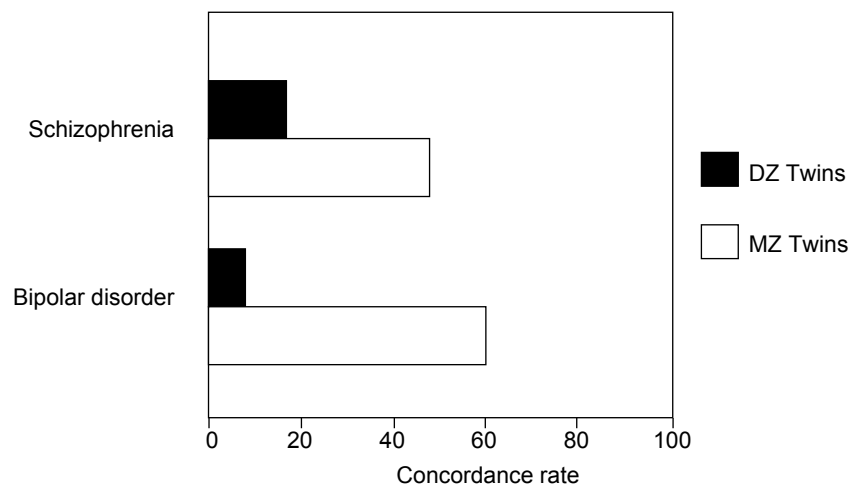
The benefit of the DSM system is the greater likelihood that two observers would agree on the diagnosis of an ill individual (reliability). The DSM diagnostic system facilitated epidemiology, clinical trials, and research on disease mechanisms by producing broad agreement on specific disease entities. The drawback of the broad acceptance of DSM criteria by journal editors, grant reviewers, and regulatory agencies is that boundaries drawn in the 1970s—without the benefit of objective tests, knowledge of pathophysiology, or identification of genetic risk factors—could not possibly mirror nature. Thus, imaging or genetic studies that use accepted criteria might be hobbled by starting with heterogeneous populations. An additional concern with the ability of current criteria to capture disease entities is that the DSM system conceptualizes all disorders as categories that are discontinuous with normal, whereas much evidence suggests that core symptoms of many disorders—including autism, schizophrenia, depression, attention deficit hyperactivity disorder, and personality disorders—might be better captured as dimensional or quantitative traits continuous with normal (Hoekstra et al., 2007; Kendler and Gardner, 1998).

These concerns are not meant to imply that the DSM criteria represent arbitrary constructions or chimeras. In fact, the cross-cultural similarity of symptoms for the major disorders (Kendler and Gardner, 1998) and the high rates of heritability that have been established suggest that, however imprecise, the criteria for the major disorders are picking out something real. At the same time, genetic studies also point out the limitations of the current criteria.

Studies of twins, starting in the 1970s, strongly implicated a genetic contribution to several psychiatric disorders. The evidence revealed that

diseases such as autism, schizophrenia, and bipolar disorder, in particular, had significant genetic components of risk. Monozygotic (MZ) twins (twins who share the same genetic endowment) were found more concordant for these disorders than were dizygotic (DZ) (twins whose genetic endowment was, on average, 50 percent similar to that of their siblings) (Figure 3-1). Nevertheless, as further evidence was collected, epidemiologic and genetic studies of families and twins called into question some of the categorical boundaries between disorders. For example, schizophrenia and bipolar disorder were sometimes found to occur in the same family pedigrees in distinct families (Pope and Yurgelun-Todd, 1990; Berrettini, 2000).

In another key example, two separate diagnoses that frequently co-occur—major depression and generalized anxiety disorder—were found to share risk genes (Kendler et al., 1987). This example suggests that the high rates of comorbidity that characterize psychiatric disorders may be partly artifactual (Kessler et al., 2005). Finally, symptom clusters of certain psychiatric disorders, such as bipolar disorder and psychosis or bipolar disorder and rapid cycling, failed to cosegregate across generations (Craddock et al., 2005).



**FIGURE 3-1** DZ and MZ twins concordance rate for schizophrenia and bipolar disorder.

NOTE: Monozygotic (MZ); dizygotic (DZ).

SOURCE: Gottesman and Wolfgram, 1991.

Additional problems cropped up to challenge the boundaries separating certain psychiatric disorders. DSM diagnoses, which were largely based on cross-sectional research and observation, may not remain stable over a lifetime, according to more recent longitudinal research. For example, early anxiety disorder may give way to depression (Wittchen et al., 2000).

Finally, many patients do not fit DSM-IV criteria. The DSM handles this problem by including, within groupings of related disorders, a category called “not otherwise specified” (NOS). Scrupulous clinicians often find themselves using such catch-all diagnoses (Fairburn and Bohn, 2005). In the long run the pathophysiology of psychiatric disorders will be understood. With modern genomic and genetic tools, such as high-density whole-genome association studies, which are beginning to yield results for other complex disorders, risk genes should be found for psychiatric disorders, assuming that large enough populations can be assembled for analysis (Altshuler and Daly, 2007). The question is how best to find biomarkers and drug targets in the mean time.

Hyman argues that the intermediate strategy is not to discard DSM, but to “deconstruct” some of the disorders into symptom complexes that can be related to known neural circuits. For example, schizophrenia could be reconceptualized in dimensional terms with dimensions that captured (1) positive symptoms (e.g., hallucinations and delusions), (2) negative symptoms (e.g., avolition<sup>1</sup>), (3) cognitive impairments (e.g., deficits in working memory), and (4) mood symptoms (e.g., depressive symptoms). The research community could focus on those aspects for which underlying neural circuits could reasonably be identified (Box 3-1). For example, much is known about the circuitry underlying working memory and cognitive control of behavior, whereas relatively little is known about the neural circuits involved in positive symptoms. Using structural and functional imaging, animal models, genotyping, and neuropharmacological, electrophysiological, and other methods, it might be possible to identify both biomarkers and drug targets.

In the case of cognitive impairments in schizophrenia, such approaches are already bearing fruit. For example, gray matter thinning and functional imaging abnormalities associated with working memory deficits have been identified (Cannon et al., 2002; Barch et al., 2001).

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<sup>1</sup>Avolition describes an individual’s perceived disinterest due to a decreased ability or inability to initiate and maintain goal-directed behavior.



**BOX 3-1**

**Potential Biomarkers  
Based on "Deconstruction" of DSM-IV Disorders**

- Executive function/working memory in schizophrenia and other conditions (e.g., frontal-striatal thalamic circuits)
- Abnormalities of conditioned fear that characterize multiple DSM-IV anxiety disorders (amygdala-based fear circuitry)
- Addiction, impulse control disorders, and possibly anhedonia in depression (mesotelencephalic and related reward circuitry)
- Mood regulation (more speculatively, circuits involving subgenual prefrontal cortex and its connections)

SOURCE: Hyman, 2007a.

The argument for this approach is that currently we have little chance of understanding the overall neurobiology of schizophrenia or other psychiatric disorders, but we can selectively understand important symptoms that might emanate from abnormal structure or function of prefrontal cortical circuits involved in executive function, in fear circuitry involving the amygdala, in mesotelencephalic reward circuits, and perhaps even in circuits involving mood regulation (Mayberg et al., 2005). Once we focus on neural circuits and their component cells and synapses, we are within more familiar biological paradigms with respect to discovering biomarkers and drug targets.

### **BIOMARKERS FOR DEPRESSION**

Treatment of depression is poised for major advances from biomarker research. New findings have identified at least three genes that might guide depression treatment. Those who possess these genes are more likely to experience a positive treatment response, according to convergent findings drawing on multiple methodologies: large clinical trials, human genotyping and imaging research, and animal models, said Dr. Husseini Manji, director of the Mood and Anxiety Disorders Program at the National Institute of Mental Health (NIMH).

Finding biomarkers to predict treatment response is extremely important for this highly prevalent condition, which is notoriously difficult to treat (U.S. Department of Health and Human Services, 1999). Treat-

ment response is markedly variable, with any given antidepressant only effective in about 50 percent of patients (there is a high placebo response, which lowers this figure considerably). The current state of treatment is left to a trial-and-error process consuming weeks to months—a delay during which many patients experience crippling disability, needless suffering, and, in severe cases, the possibility of suicide (Stewart et al., 2003; U.S. Department of Health and Human Services, 1999). The large variation in patients' treatment response may be partially attributable to genetics, according to at least two lines of indirect evidence: The outcome of treatment appears to run in families (Franchini et al., 1998), and it seems to vary less across illness episodes than across individuals (Fava et al., 2002; Franchini et al., 1998).

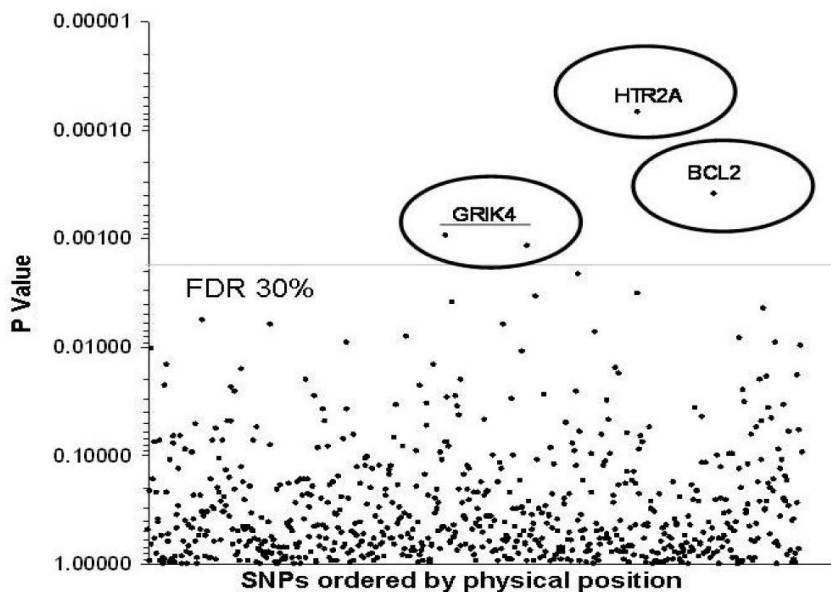
One candidate biomarker for treatment response is the gene encoding the serotonin 2A receptor (referred to by the acronym HTR2A). Serotonergic neurons are prime targets for the first-line pharmacologic class of treatment, the selective serotonin reuptake inhibitors (SSRIs). HTR2A is one of several subtypes of the serotonin receptor. HTR2A was identified by a large collaboration involving the National Institutes of Health and extramural teams as a candidate biomarker in a study that took advantage of the rich dataset from a large clinical trial, the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D). That major clinical trial of nearly 4,000 patients was a multisite effectiveness study aimed at real-world patients rather than the rarefied and more homogeneous samples of patients used in most clinical trials according to strict inclusionary and exclusionary criteria.

The SSRI citalopram was administered in the first step of the STAR\*D trial. The collaborative teams subsequently used the data from that first phase, collecting DNA samples from nearly 2,000 patients. They genotyped the samples, specifically sequencing more than 750 single nucleotide polymorphisms (SNPs) near 68 candidate genes (whole-genome scanning was neither financially nor technologically feasible at the time of the study). The study's specific goal was to find genes associated with a positive treatment outcome in both a test sample and a replication sample of patients. Although a positive outcome was defined by at least a 50 percent reduction in symptom severity with treatment, the investigators were most interested in biomarker genes in patients who became nearly asymptomatic. The analysis yielded a strong association between one SNP located in the HTR2A gene and a positive outcome with antidepressant treatment (McMahon et al., 2006). The association was also found to be stronger in Caucasians than in African Americans, a

finding that might explain what has been found in STAR\*D and other studies, namely that African Americans tend to have a poorer response to SSRIs than do Caucasians.

Patients with the HTR2A genotype exhibited greater binding potential of the serotonin transporter with positron emission tomography (PET) scanning, which confirms the importance of the HTR2A genotype (McMahon et al., 2007). The serotonin transporter is the target molecule for most SSRIs. The transporter's role is, in part, to reduce the concentration of serotonin in the synaptic cleft.

In addition to the SNP within the HTR2A gene, two other SNPs were found to be associated with a positive treatment response. Both implicated neurotransmission-related genes: Bcl-2 and GRIK4 (Figure 3-2). Bcl-2 is an oncogene that has been shown to have neurotrophic effects in promoting cell growth and survival in neural circuits that modulate mood, motor, and cognition. In the STAR\*D analysis, Manji's team found that individuals homozygous for the good response allele



**FIGURE 3-2** Genes associated with treatment response.

NOTE: False discovery rate (FDR); single nucleotide polymorphism (SNP); glutamate receptor, ionotropic, kainate (GRIK4); serotonin receptor 2A (HTR2A); B-cell CLL/lymphoma 2 (BCL2).

SOURCE: Paddock et al., 2007.

were 40 percent more likely to go into full remission with treatment. The GRIK4 gene is one of several genes forming subunits of the glutamate kainate receptor, a receptor that regulates the flow of ions across neuronal membranes during excitatory neurotransmission.

Considering the robust role of the Bcl-2 protein in treatment response, Manji's team turned to animal models to corroborate its role in treatment response and to probe its role further. Preliminary studies revealed that mice lacking one copy of the Bcl-2 gene displayed less neurogenesis. Depression treatment does not take effect until several weeks after initiation of treatment. Neurogenesis is one proposed mechanism that may explain the slow time line in treatment response, based on the fact that in separate experiments with knockout mice, mice heterozygous for Bcl-2 more quickly developed a depression-like behavior known as learned helplessness after a series of repeated shocks (Yuan et al., 2007). Not only did the mice develop learned helplessness at a markedly greater rate, but they also failed to respond to chronic treatment with citalopram, compared with wild-type mice. The Bcl-2 heterozygous rats also performed worse on other well-accepted behavioral tests of depression. Manji noted that his group is now investigating the possibility of an interaction between the Bcl-2 gene and the other two genes identified in his SNP analysis.

### THE ROLE OF GENES IN TREATMENT RESPONSE

Do genes also predict the likelihood of experiencing adverse effects with depression treatment? This is an important public health question because of the possibility that SSRIs may increase the risk of suicidal behavior in a small subgroup of children. That concern has led to a black box warning issued by the Food and Drug Administration. On the other hand, the large drop in sales of SSRIs after the warning took effect indicates that the black box warning deters physicians from prescribing SSRIs that many youngsters may desperately need (Gibbons et al., 2007).

The STAR\*D dataset is being used by Manji's team to determine whether certain genes increase the risk of suicidal ideation or behavior. His group found a subgroup of patients ( $n = 120$ ) who reported suicidal ideation after treatment with citalopram but none before. The SNP analysis revealed that these patients are more likely to possess one subtype of a kainate receptor (GluR6), said Manji (Lage et al., 2007). Furthermore,

knockout experiments are consistent with these clinical findings. GluR6 knockout mice display hyperlocomotion, aggression, and increased exploratory behaviors. Since GluR6 is also a putative bipolar susceptibility gene, these results suggest that individuals experiencing these side effects may be those with a subtle bipolar diathesis (Shaltiel et al., 2007). These behavioral findings fit with the interpretation that antidepressants, in a rare group of patients with a certain genotype, stimulate impulsive or aggressive behaviors, that, in turn, might be precursors to suicidal behavior.

More research needs to be performed to explore these intriguing findings, but what has been accomplished thus far points to the seminal role that genotype may play in treatment response. The field has managed to marshal clinical findings and animal models to launch potentially the first generation of genetic predictors of treatment response for a widespread, serious, and disabling disorder.

### **BIOMARKERS FOR SCHIZOPHRENIA**

Promising biomarkers are being investigated to identify and track schizophrenia's cognitive symptoms, said Dr. David Lewis, director of the University of Pittsburgh Translational Neuroscience Program. The specific gene discussed during the workshop was *CHRNA7*; however, a few highly replicable risk genes have been identified for schizophrenia, including *DISC1*, *G72 (DAOA)*, and *neuregulin*. These genes were not discussed in the workshop and are therefore not included in the summary.

Cognitive symptoms are generally underrecognized by the general public and include abnormalities in attention, verbal fluency, and working memory. The latter refers to the capacity to hold and manipulate information in the mind to guide behavior or to plan ahead. These and other cognitive characteristics are considered core symptoms of schizophrenia because they appear before disorder onset and, over the course of the disorder, are associated with the greatest level of dysfunction (Green, 1996; Heinrichs and Zakzanis, 1998). Although several effective medications have been marketed for decades to treat schizophrenia's most recognizable symptoms—hallucinations and delusions—no medications have been developed and marketed for improving cognition.

Two potential biomarkers of cognitive dysfunction rely on electrophysiology to detect patterns of activity within regions of the cerebral

cortex. The identification of these biomarkers has been so promising that it has already led to small clinical trials. Because the underlying defects captured by the biomarkers may actually contribute to the pathophysiology of schizophrenia *before* its onset, future clinical trials are also contemplated with another outcome in mind: the prevention of full-blown schizophrenia by interrupting its pathological progression.

The first biomarker is one of impaired attention, assessed by the P50 evoked potential. Its purpose is to detect the ability to filter (gate) sensory stimuli, without which deficits in sustained attention are produced. People with schizophrenia describe being barraged by an onslaught of sensory stimuli, thereby finding it difficult to sustain focus on any one stimulus. The laboratory of Dr. Robert Freedman at the University of Colorado Health Sciences Center has developed a test for filtering sensory stimuli by measuring auditory evoked potentials. The test introduces a tone and measures the evoked response in the subject via a scalp electrode right after the tone and then 50 milliseconds later. In normal adults, the second identical tone presented 50 milliseconds later produces a blunted response (as measured by amplitude of evoked response) in comparison with the first. But in schizophrenia, the so-called P50 amplitude in response to the second tone is the same as the first, or sometimes is even exacerbated. A similar or even exaggerated response means that the second stimulus is perceived as being as novel as the first, suggesting a defect in sustained attention.

Relatedly, animal models have provided some of the molecular underpinnings of this defect in sustained attention. Cholinergic stimulation of the  $\alpha_7$  nicotinic receptor on hippocampal interneurons is essential for the P50 reduction to the second stimulus. The failure to attenuate the P50 auditory evoked response in schizophrenia is associated with a polymorphism in the gene (CHRNA7) for the  $\alpha_7$  nicotinic receptor (Leonard et al., 2002). In addition, postmortem studies of people with schizophrenia reveal that  $\alpha_7$  nicotinic receptor expression is reduced. Piecing these findings together, Freedman's team undertook a small proof-of-concept clinical trial in which an  $\alpha_7$  nicotinic agonist was administered to a small group of patients with schizophrenia (Olincy et al., 2006). The trial found significant improvement in P50 inhibition to the second stimulus. It also found some improvement in subjects' performance on a test battery designed to assess neuropsychological functioning. The proof-of-concept clinical trial has galvanized efforts to conduct larger trials with nicotinic agonists.

Another potential biomarker for schizophrenia strives to capture electrophysiological measures of the neural abnormalities underlying the working memory impairments in the illness, said Lewis. This biomarker measures electrophysiological oscillations in the gamma band range (30 to 80 Hz) during an activity that requires working memory. Physiological activity at gamma band frequency is influenced by GABA neurons in the cerebral cortex, including one type known as the chandelier cell. A given chandelier cell supplies inhibitory input to the axon initial segment of 200 to 300 pyramidal cells and, by virtue of their connectivity and firing patterns, chandelier cells contribute to the synchronized firing of populations of pyramidal cells. In individuals with schizophrenia, chandelier cells in the dorsolateral prefrontal cortex (DLPFC) have reduced expression of GAD 67, an enzyme responsible for synthesis of GABA, and the presumed resulting deficit in GABA input leads to compensatory changes in pyramidal cell axon initial segments, including upregulation of GABA receptors that contain alpha<sub>2</sub> subunits (Lewis, et al., 2005). Thus, the postmortem findings predict that schizophrenia would be associated with a reduced capacity to generate gamma band oscillations in the DLPFC during working memory tasks, and exactly this abnormality has been observed in clinical studies (Cho et al., 2006). Lewis explained that the findings provided the rationale for a clinical trial, now in progress, using a GABA<sub>A</sub> alpha<sub>2</sub> selective agonist to treat the cognitive symptoms of schizophrenia and measuring gamma band activity during working memory tasks as one measure of the drug's effectiveness.

The two examples given here highlight the value of electrophysiology for biomarker development in schizophrenia. Electrophysiology's growing value draws from advances in understanding the molecular, cellular, and circuitry disturbances present in psychiatric disorders; knowledge of the molecular, cellular, and circuitry bases for particular patterns of electrophysiological activity; and cognitive and behavioral tests used to induce those patterns of activity. This convergence of information makes it possible to identify potential drug targets that are predicted to help normalize both the patterns of electrophysiological activity and the associated cognitive performance.

## BIOMARKERS OF ADDICTION

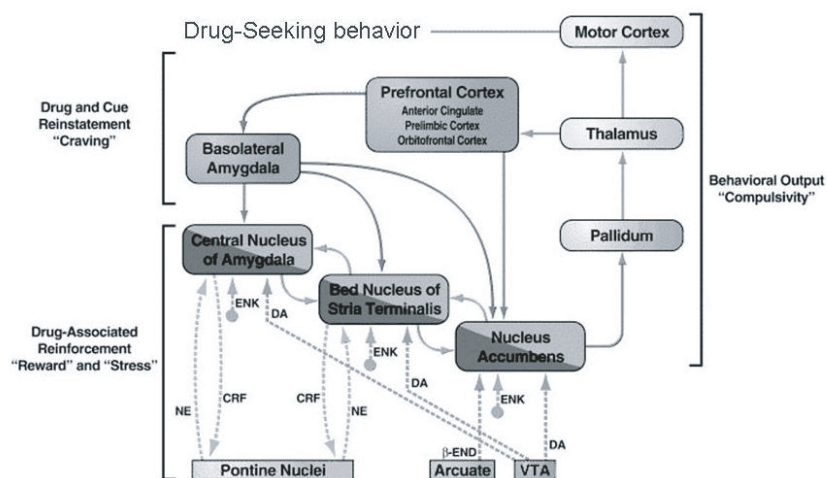
Imaging the brain with PET affords new opportunities for finding biomarkers of addiction, said Dr. Nora Volkow, director of the National Institute on Drug Abuse. One major aim is to identify biomarkers of vulnerability, since none are currently available for clinical use. The value of PET scanning is that numerous drugs and other agents can be labeled and injected and their temporal course tracked in vivo. Establishing temporal course is key to understanding addiction vulnerability because drugs with short- versus longer-term reinforcing effects are more likely to elicit frequent administration and thereby pose greater addiction potential. Cocaine, for example, exerts its reinforcing effects and exits the brain so swiftly that it is more prone to addiction than is the psychostimulant methylphenidate, which has longer pharmacodynamics in the brain. Although both bind to the same protein—the dopamine transporter, which is responsible for reuptake of excess dopamine in the synaptic cleft—their abuse liabilities are different.

PET scanning has begun to be harnessed to explore the genetic influences on the neurocircuitry underlying addiction vulnerability. The main neurocircuits depicted in Figure 3-3 are dauntingly complex, relying on multiple neurotransmitters and affecting numerous nuclei of the central nervous system (CNS). That complexity makes it unlikely that there are individual biomarkers of addiction and suggests instead that complex biosignatures will need to be identified. But, as Volkow describes, there is general agreement within the field for at least two major points. First, there are strong animal models used to complement clinical studies. Second, a large body of evidence implicates genetics in the vulnerability to addiction—perhaps accounting for 50 percent of the population variance.

Genetics plays a role in developing addiction in three ways: it determines the extent to which individuals are likely to experiment with drugs; it influences drug metabolism and pharmacological response once the drug is taken; and it influences why some people become addicted and others do not, a process that depends on plasticity within neurocircuits of addiction. However, individual genes underlying vulnerability have not been identified.

A striking example of genetic vulnerability—that is, how genotype may affect the likelihood of drug experimentation—comes from outside the addiction field. In a newly published study, a team of NIMH researchers used PET scanning in healthy human volunteers to investigate





**FIGURE 3-3** Key common neurocircuitry elements in drug-seeking behavior of addiction.

NOTE: Enkephalin (ENK); dopamine (DA); norepinephrine (NE); corticotropin releasing factor (CRF); β-endorphin (β-END); ventral tegmental area (VTA).

SOURCE: Koob, 2006.

neural mechanisms of genetic risk for impulsivity and violence (Meyer-Lindenberg et al., 2006). A common polymorphism in monoamine oxidase A (MAO-A) was found to exert profound effects on the structure and function of corticolimbic circuitry governing emotional regulation and cognitive control. The polymorphism affected the volume of gray matter of the cingulate gyrus and the amygdala. Subjects with high transcription rates of MAO-A had higher volumes, whereas those with lower transcription rates had smaller volumes. Subjects with high transcription rates also displayed a hyperresponsive amygdala and diminished reactivity of the prefrontal regions. Although the focus of the study was on impulsivity and aggression, these traits overlap with those involved in addiction. Impulsivity contributes to the likelihood of experimentation with drugs.

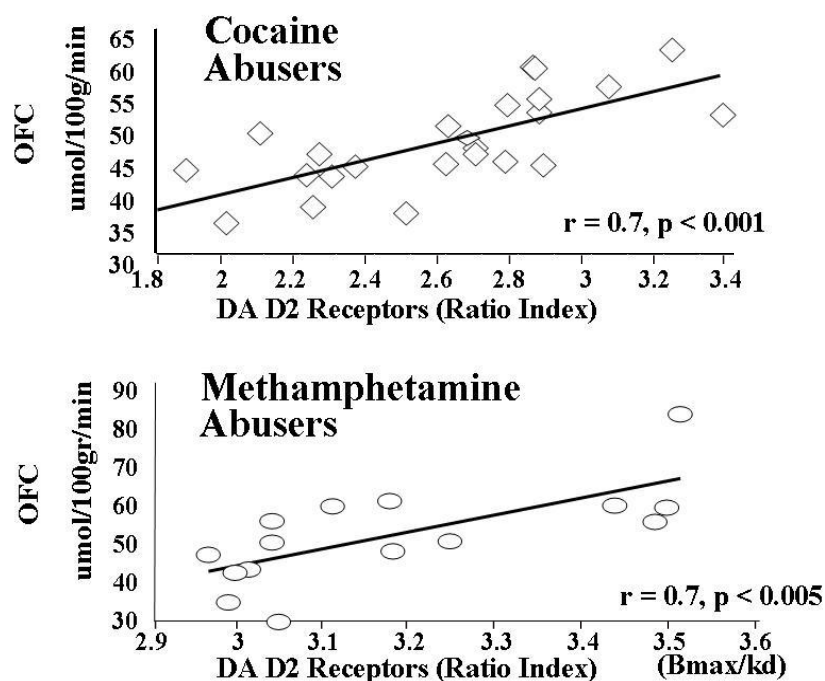
How can expression of a single enzyme, in this case MAO-A, have such profound effects on the structure and function of certain neurocircuits? From this study and other ongoing research in the addiction field,

Volkow hypothesized that the polymorphism exerts its effects during brain development. The human brain has a long developmental stage, relative to other organisms, during which time it remains vulnerable to genetic or environmental insults that affect structure and function into adulthood.

An example of the second role of genetics—that is, by drug metabolism and pharmacological response—comes directly from the addiction field. A large body of clinical studies, as well as preclinical research, has found that the dopamine D2 receptor is extremely important in regulating reinforcing responses to drugs of abuse. The evidence shows that drug abusers tend to have lower levels of dopamine D2 receptors (Kalivas and Volkow, 2005). The finding has been replicated in abusers of cocaine, methamphetamine, alcohol, and steroids. However, a reduced number of D2 receptors in the brain cannot be considered a biomarker of addiction because it lacks specificity; many nonabusers also have lower expression levels of D2 receptors. But it is possible that low expression levels eventually may be part of a biosignature of drug addiction, once other biomarkers are found to cluster with it, noted Volkow. Any biomarkers or biosignatures would be of special clinical utility if peripheral nervous system surrogate markers are found, which would obviate the need to sample CNS tissue. As yet, there is no peripheral surrogate marker for CNS D2 levels. Research is being done, however, to develop neurocognitive tasks that can predict expression of D2 receptors, reported Volkow.

PET scanning also has revealed that the levels of D2 receptors in the striatum are linearly related to levels of brain glucose metabolism (Volkow et al., 2006). More specifically, the greater the ratio of striatal D2 receptors, the greater the glucose metabolism in the orbitofrontal cortex and cingulate gyrus (two regions of the cerebral cortex involved in salience attribution, emotional reactivity, and inhibitory control in addiction) (Figure 3-4). The finding has been replicated by three or more different groups, according to Volkow.

Although it is tempting to interpret the evidence of an association as representing neuroplasticity occurring at the time of drug abuse and addiction, there is another possible interpretation, said Volkow. A new study by Dr. Eric Kandel's laboratory raises the possibility of a neurodevelopmental effect being responsible in another disorder affecting dopaminergic function (schizophrenia). He and coauthors performed an elegant study in which they selectively overexpressed the D2



**FIGURE 3-4** Correlations between striatal D2R and brain glucose metabolism.

NOTE: Orbitofrontal cortex (OFC); dopamine (DA).

SOURCE: Volkow et al., 2004.

transgene in the striatum during a restricted period in fetal development (Kellendonk et al., 2006). Yet they found that abnormalities in dopaminergic function in the prefrontal cortex persisted well into adulthood—long after the transgene had been turned off. This study—and others soon to be published regarding cocaine distribution to the fetus from maternal use—raises the possibility of lifelong structural and functional effects on brain neurocircuitry as a result of fetal exposure to drugs of abuse.

## 4

### Neurological and Eye Diseases

*The search for biomarkers for neurological and eye diseases has been under way for years, and technological advances, especially in retinal imaging, are showing promise in areas of research that encompass several neurological diseases. Of the approximately 600 neurological disorders, there are only a handful of biomarkers available, making it unclear which are best suited for investment. A rational approach to biomarker development hinges on two key elements: better understanding of the etiology and pathogenesis of a given disorder, and the use of data and stored biological samples from ongoing and prior clinical trials. In Session IV, workshop participants discussed several areas of neurological medicine where a high-impact biomarker could emerge, including Parkinson's disease, multiple sclerosis, stroke, spinal muscular atrophy, and retinal degeneration.*

### LESSONS FROM FAILED CLINICAL TRIALS

Uric acid has become a leading candidate as a biomarker for tracing the progression of Parkinson's disease, said Dr. Ira Shoulson, professor of neurology at the University of Rochester. Uric acid levels that are too high are responsible for gout, but higher uric acid levels at the middle ranges found in the Parkinson's clinical trials turned out to reduce the risk for progression of Parkinson's disease by approximately 25 percent, according to a published meta-analysis of observational studies, reported Shoulson (Weisskopf et al., 2007). The observational studies were spun off of three previous clinical trials of anti-Parkinson drugs. Not all the clinical trials turned out to be successful for their main purpose (i.e., finding a new treatment for Parkinson's), but collection of blood and cerebrospinal fluid (CSF) uric acid during the trials turned out to be vital.

Identification of uric acid as a putative biomarker came about fortuitously. It occurred during a meeting of investigators to determine why a clinical trial of an anti-Parkinsonian drug, sponsored by two pharmaceutical companies, had failed. One of the investigators ventured that patients with higher uric acid at baseline seemed to fare the best. Once Shoulson and the other investigators analyzed the data more closely, they reached the same conclusion. In this particular trial, they found that male patients with the highest levels of uric acid especially had reduced their risk of Parkinson's progression by about 50 percent, according to Shoulson, who described the data presented at a recent Society for Neuroscience meeting (Schwarzschild et al., 2006).

Furthermore, the results from the clinical trial suggested a possible mechanism for uric acid's role. Uric acid is a strong antioxidant, and it is the product of the metabolism of purines. The link between higher levels of uric acid and reduction of Parkinson's progression made mechanistic sense, they hypothesized, considering that oxidative mechanisms are implicated in the pathogenesis of Parkinson's disease and other neurological disorders (Floyd, 1999). But what specific target was protected from oxidation by uric acid?

The failed clinical trial provided a clue because it also had collected data on levels of the dopamine transporter in the striatum by using SPECT images of [<sup>123</sup>I] β-CIT uptake (the striatum's loss of dopamine transmission is one of the central lesions in Parkinson's disease). On subsequent analysis, investigators found that uric acid had a dose-dependent effect on the levels of dopamine transporter: patients with the lowest levels of uric acid had the highest loss of dopamine transporter over time,

whereas those with the highest levels of uric acid had the lowest loss of dopamine transporter over time. This dose response suggested at least one mechanism by which uric acid may exert its protective effects, according to Shoulson (Schwarzschild et al., 2006).

The analysis of the uric acid effect from this trial spurred investigators to reexamine results from the previous clinical trial (DATATOP), which studied 800 patients and had also collected data on uric acid levels. Researchers were able to use epidemiological methods to investigate the association between uric acid and Parkinson's disease progression and found that uric acid conferred dose-related beneficial effects: The higher the serum uric acid level, the lower the risk of developing Parkinson's disease disability. The findings from the CSF analysis of uric acid in this study were even more robust than those with serum uric acid.

The lesson from this experience with Parkinson's disease, said Shoulson, was that clinical trials provided a treasure trove of data that could be reanalyzed once potential biomarkers were identified. He also pointed out that the reanalysis of the clinical trial data was not only supported by the National Institutes of Health, but was also supported by pharmaceutical companies. He expressed the hope that DNA collection from clinical trials might allow whole-genome scanning to search for genotype markers related to biomarkers of risk, disease progression, or response to treatment.

### BIOMARKERS OF MULTIPLE SCLEROSIS

Several promising biomarkers are on the horizon for multiple sclerosis (MS), but all face significant, though not insurmountable, barriers to progress, asserted Dr. Gavin Giovannoni, professor of neurology at Queen Mary's School of Medicine and Dentistry, London. His presentation covered two main topics: (1) the types of organizational reforms needed for the neuroscience field as a whole to promote development of surrogate markers of sufficient validity to warrant Food and Drug Administration (FDA) qualification and (2) the more specific topic of developing promising biomarkers for MS, particularly ones for predicting prognosis.

The MS field faces one overarching hurdle spanning both topics: a flawed gold standard for assessing the disease's clinical course. Without a responsive and well-validated clinical outcome measure as a gold standard, biomarker development is thwarted from the start. For years, the

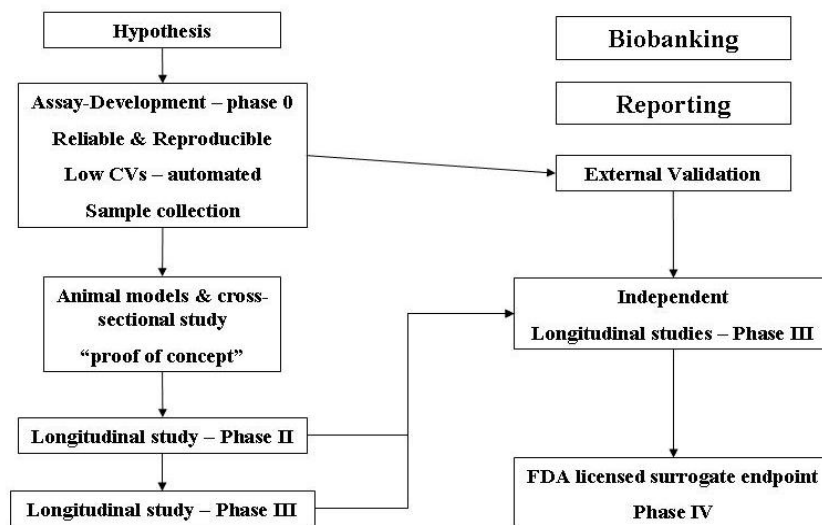
gold standard for MS has been the Expanded Disability Status Scale (EDSS). Developed before the era of rigorous psychometric evaluation, this scale would never have passed muster by today's standards. Recent research has exposed problems with the scale, including its inter- and intrarater reliability, ceiling and floor effects, nonlinearity, and large coefficient of variation (CV), which reduces statistical power to detect differences between study groups (Hobart, Freeman, and Thompson, 2000). The scale's psychometric problems became most apparent, Giovannoni recounted, with the publication of a 1998 paper showing only a modest correlation between the EDSS and a candidate biomarker for earlier stages of relapsing-remitting MS (Lycke et al., 1998). The levels of the biomarker in the CSF were associated with clinical exacerbations and exacerbation frequency; they steadily declined after the onset of the previous clinical exacerbation, but were only moderately associated with the EDSS.

MS does have other biomarkers that pertain to the early stages of disease, the relapsing-remitting stage. Relapse rate due to focal inflammatory disease activity correlates with the imaging biomarker of gadolinium-enhancing lesions on magnetic resonance imaging (MRI) (McFarland et al., 2002). But there are no well-validated biomarkers for the next stage—the secondary progressive phase—which typically occurs 5 to 15 years after first relapse. During this stage, patients become increasingly disabled without necessarily having superimposed relapses. A prognostic biomarker during this period is highly needed, said Giovannoni. A biomarker not only would predict prognosis, but also would enable researchers to have a gold standard for testing new treatments. One vitally needed treatment is a neuroprotective agent to modify the course of disease, considering that no treatment now serves this purpose. Generalized and regional brain and spinal cord atrophy measurements are currently being evaluated as potential primary outcome measures in exploratory neuroprotective trials.

The lack of a good biomarker for the progressive stage of disease motivated Giovannoni's laboratory to begin a decade-long search. In the process, he encountered major organizational and scientific impediments to biomarker development. One major conclusion he drew from the experience was that the problems transcend the MS field and extend across all brain disorders. Another conclusion was that the neuroscience field must approach biomarker development in as rigorous and scientific a manner as it does drug development.

Giovannoni laid out the scientific process he felt was needed for validation of a biomarker (Figure 4-1). In recognition of the necessity of biomarker development and validation, he said he turned to the cancer field, which, in his view, has become a model that neuroscience should emulate. The cancer field has set up a network in the United States and Europe, with one of its prime activities being to develop guidelines on how to design, conduct, and report biomarker studies (McShane et al., 2005). The guidelines are so important to the field that the same paper describing them was published simultaneously in seven of the top oncology journals. The oncology guidelines begin with the recognition that the guidelines given in the paper cover standardized reporting of materials and methods, including patient selection, specimen characteristics, assay methods, reporting of results, analysis and presentation, and discussion.

With the cancer field as its model, Giovannoni and his European colleagues have created a “BioMS Consortium.” They plan to issue at least three consensus papers, the first of which covers biobanking (i.e., the



**FIGURE 4-1** Scientific process for biomarker validation.

NOTE: Coefficient of variation (CV).

SOURCE: Giovannoni, 2006.



collection, processing, storage, and databasing of samples). The second paper will issue guidelines on reporting biomarker studies, as adapted from the oncology network.

Another major impediment to biomarker development is the failure of researchers to report negative results. If journals are reluctant to accept papers of this kind, it is incumbent upon the field to create a register of successful and failed biomarker studies so that other laboratories do not waste time and resources to repeat the analyses. Giovannoni emphasized that this is the foremost message of his presentation: to underscore the urgency of publishing negative results.

He then turned to specific steps that industry can take to advance biomarker research. The most important yet thorny issue is the incorporation of potentially new biomarkers into clinical trials. These are potential biomarkers that are not accepted outcome measures but that may become useful in the future with further analysis. Citing experience from the cardiac field, Giovannoni pointed out that industry has no incentives to incorporate novel biomarkers because they may uncover useful surrogate biomarkers that give competitors an edge in future trials. Establishing a surrogate biomarker may reduce study duration and thus helps competitors gain quicker access to market. For this reason, industry will need incentives to incorporate novel biomarkers in clinical trials (Box 4-1). The most important advance will be to find a replacement for the EDSS for assessing clinical course of MS, asserted Giovannoni. Without a new assessment tool as a gold standard, none of the prospective biomarkers can be carefully evaluated.

Giovannoni then turned to the specific biomarker his laboratory has been working on for the past 10 years: heavy chain neurofilaments as a prognostic biomarker for the later stage of MS, the stage when disease and disability are steadily progressive. Neurofilaments are intracellular proteins that form the internal cytoskeleton of the axon, maintaining its size, shape, and structure. Giovannoni's laboratory has established that heavy chain neurofilaments are a bulk biomarker of axon damage. Whenever axons are injured or destroyed, they release neurofilaments into the extracellular fluid that can be measured in the CSF. Giovannoni and his colleagues have proposed that the levels of heavy chain neuro-

**BOX 4-1**

**Organizational Steps to Advance Biomarker Research**

**Steps for the neurology field**

- Develop new gold standard for clinical course (EDSS is flawed).
- Develop large, organizational networks to facilitate science for biomarker development (e.g., European Biomarkers in MS, modeled on oncology networks).
- Standardize data collection and other scientific procedures needed for new biomarker development.
- Publish negative results through open-access publishing (e.g., *Journal of Negative Results*) and the creation of a biomarker study register, similar to clinical trial registers.

**Steps for industry**

- Incorporate potential biomarkers into clinical trials.
- Miniaturize and multiplex assays using emerging technologies, particularly for use in animal models. Biomarkers that are well validated in established animal models of specific diseases are more likely to be incorporated into clinical trials.
- Develop multiplex assays to minimize the volume of fluid required for performing assays.
- Develop real-time or rapid assays, which are particularly relevant in the neuro intensive care setting to allow biomarkers to inform clinical decision making in individual patients (e.g., head injury and stroke).

filaments might be useful surrogate markers of disability and prognosis (Petzold et al., 2002; Petzold, 2005). To determine the utility of the biomarker, his laboratory followed patients prospectively for 3 years. They found that a higher proportion of patients with progressive disease displayed higher levels of heavy chain neurofilaments over time than did those with relapsing-remitting disease or controls. Higher levels in CSF were correlated with three different disability scales (Petzold, 2005). The study concluded that cumulative axonal losses, as reflected by increased levels of heavy chain neurofilaments, are responsible for sustained disability in MS and convey a poor prognosis. This putative biomarker for poor prognosis may make it feasible to enrich studies with subjects more likely to progress and, therefore, improve the power of studies testing disease-modifying therapies. The high-neurofilament group of patients is likely to reveal a protective effect, if there is one, with administration of

a disease-modifying treatment. In fact, Giovannoni reported his participation in an exploratory study of the anticonvulsant lamotrigine—a potential disease-modifying therapy for progressive MS—to test this hypothesis.

Heavy chain neurofilaments are not the only biomarkers under consideration for MS. Other potential biomarkers are glial fibrillary acid protein and other markers of astrocytic and microglial activation that represent cellular response to any central nervous system (CNS) injury or challenge. Others include the neural cell adhesion molecule, which is thought to be a marker of axonal plasticity and synaptogenesis. A very promising marker that has already been included in the design of upcoming clinical trials due to its potential in cross-sectional studies is optical coherence tomography (Frohman et al., 2006). It is a noninvasive ultrasound imaging examination of the retina that is capable of measuring the thickness of the nerve fiber layer of the retina. Retinal nerve fibers are an accessible component of the CNS and are frequently targets of MS autoimmune attack. The loss of retinal axons indicates disease progression, albeit limited to the anterior visual pathway.

### BIOMARKERS OF STROKE

A biomarker derived from MRI shows promising, near-term impact for acute ischemic stroke, said Dr. Steven Warach, chief of the Section on Stroke Diagnostics and Therapeutics at the National Institute of Neurological Disorders and Stroke (NINDS). His presentation focused on the value and versatility of a single MRI-based biomarker. The single biomarker has several applications to stroke clinical trials: patient selection, dose finding, and evidence of drug efficacy. The current lack of valid biomarkers for acute stroke trials is largely responsible, in his view, for the failure over the past 2 decades of most drugs tested in acute stroke clinical trials. Rarely have trials required an objective confirmation of the presence of biological target for patient selection, and even less frequently have they required evidence of a drug's target biological activity to move a drug from Phase II to Phase III. He characterizes this enormous obstacle to progress as the “disconnect between laboratory successes and larger clinical trials” and argues that it must be tackled head-on by development of better biomarkers. In animal models, lesion volume reduction with treatment is both necessary and sufficient evi-

dence of treatment efficacy and is required to move a treatment from the laboratory to clinical trials.

The only effective therapy for acute ischemic stroke is the thrombolytic agent tissue plasminogen activator (tPA), which was introduced in 1996 (NINDS rt-PA Stroke Study Group, 1995). But only about 2 percent of eligible patients actually receive the drug, mainly because of the tight time window of only 3 hours in which the drug must be given after a stroke. Another related reason is the difficulty of arriving at the stroke diagnosis, which must be made on an emergency basis. Concern among emergency room physicians about the accuracy of making a positive diagnosis of ischemic stroke by clinical exam on the one hand and excluding a diagnosis of brain hemorrhage by computed tomography (CT) scan on the other have further limited the utilization of tPA (American Academy of Emergency Medicine, 2007).

The growing consensus regarding the value of MRI markers has been accompanied by growing recognition of the importance of data sharing, particularly from Phase II trials. But the efforts are still inchoate, said Warach. He wishes to launch more organized data sharing across industry and academic trials, as well as broader acceptance of MRI over CT to diagnose stroke in the emergency room. He and his collaborators established that MRI is better than CT for detection of acute ischemic stroke, although the two are of equal benefit for detection of acute intracranial hemorrhage (for which tPA is contraindicated) (Chalela et al., 2007). Current and previous clinical trial data are still valuable for pooling because new ways to analyze MRI results have been developed and thus can be applied to the raw data. The key to data sharing is to standardize procedures for acquisition and processing of MRI data and to standardize and fully validate certain parameters for selection of patients and outcomes.

The foremost parameter of interest, according to Warach, is the existence of tissue that is not already infarcted but is at risk for infarction as the lesion evolves. That at-risk tissue is the so-called ischemic penumbra. It is a ring of endangered tissue outside the immediate focal ischemia. The focal ischemia is a dynamic lesion—with time, the focal lesion may expand into the penumbra. But the penumbral tissue is potentially amenable to salvage by restoring blood flow (Kidwell et al., 2003). Natural history studies reveal the dynamic nature of the lesion: There is typically a one- to twofold increase in the volume size of the infarct from baseline to 3 months. Early and accurate identification of potentially salvageable tissue (i.e., the penumbra) is key, for it may enable selection of the best

candidate patients for early stroke therapies and also may minimize complications. The presence of penumbral tissue in greater volume than that of ischemic tissue renders a patient more amenable to treatment.

There is consensus in the field that relative lesion volume reduction within the penumbra holds the greatest promise as a biomarker to measure efficacy of a drug, according to Warach. MRI is used to measure the biomarker by revealing the mismatch between diffusion and perfusion. The diffusion-weighted imaging captures the core lesion of the stroke, which will infarct without adequate reperfusion and will enlarge within the penumbra, which is measured by the perfusion-weighted imaging.

The value of MRI biomarkers is already being tested in clinical trials. In these trials a strong relationship has been observed between clinical outcomes (to 3 months post-stroke) and a change in lesion volume from acute to chronic time points. Patients who achieved good clinical outcomes had smaller increases in lesion volumes than patients with poor outcomes. Having a mismatch on MRI where perfusion is greater than diffusion has been incorporated in two ways in clinical trials of another thrombolytic drug, desmoteplase, as a selection criterion and as a baseline measure of ischemic pathology against which to assess drug effect. It was an eligibility criterion for the trial, along with clinical criteria. MRI reperfusion 4 to 8 hours after treatment and good clinical outcome at 90 days were used as the efficacy outcome measures to select the dose that was taken forward in subsequent trials (Furlan et al., 2006).

To ensure high impact of this MRI biomarker, there is a need to pool clinical trial and academic observational studies into some repository and to reach consensus on how the data should be acquired and processed. There is also a need, said Warach, to refine our definition of the ideal “penumbral” patient for clinical trials, as well as to refine definitions for outcome and validation. The pharmaceutical industry has embraced this approach, and there are several ongoing international collaborations, but the effort needs to be greatly expanded to cover greater academic and industry participation, considering that there have been about 20 completed or ongoing acute stroke trials utilizing MRI. A major impetus for pooling data came from the stunning failure of AstraZenica’s NXY059, it followed all conventional wisdom for successful development of neuroprotective stroke therapies. The drug’s failure has led even biomarker skeptics to the view that a measure of biological activity should be a necessary step in stroke drug development. Finally, the repository might also collect DNA samples from patients to determine if there are any genetic contributions predisposing to stroke recovery. As the effort is launched,

the MRI biomarker must be validated against a clinically effective therapy (such as tPA), and it must be qualified by the FDA before it can become a surrogate marker.

### BIOMARKERS FOR SPINAL MUSCULAR ATROPHY

Spinal muscular atrophy (SMA) is a devastating motor neuron disorder affecting infants and young children. It is second to cystic fibrosis as the most common fatal genetic disorder in children. Approximately 1 in 35 people are carriers for this autosomal recessive condition. The 50,000 infants or children with the condition either fail to develop normally or progressively lose the ability to stand, sit, and eventually move. About 50 percent of affected children die before the age of 2. Despite the tragic nature of the disorder, there is much hope for treatment or cure, said Dr. Meg Winberg, director of research at the Spinal Muscular Atrophy Foundation. Her presentation touched upon many of the remarkable advances that have occurred in recent years, all of which have created a climate of opportunity for biomarker development and the prospect of well-designed clinical trials.

Progress in understanding the disorder has reached the point that NINDS has named SMA as a leading disorder for drug development. Several drugs are already being tested in investigator-initiated clinical trials supported by NINDS, although some are open-label and thus potentially vulnerable to what has been found in controlled trials: a large placebo effect. While large pharmaceutical companies are thus far non-committal with respect to SMA, Winberg stated that her organization foresees, with further progress in biomarker development, a sizable market—\$500 million to \$1 billion in annual revenues—that may be attractive to biotechnology firms (Box 4-2) (Spinal Muscular Atrophy Foundation, March 2007).

SMA is characterized as a single-gene disorder; the defective gene responsible for SMA was identified in 1995 (Lefebvre et al., 1995). In infants and children with SMA, the normal gene—Survival Motor Neuron 1 (SMN1)—is deleted, leaving them dependent on the activity of a closely related but defective backup gene, SMN2. The number of copies of SMN2 correlates with disease severity, said Winberg. One copy of the mutated gene is associated with the most severe form of SMA, known as type I, in which children never sit independently. Children with SMA

**BOX 4-2**

**Why Spinal Muscular Atrophy Is Ripe for Biomarker Development**

- Severe, often fatal, congenital neurological disease.
- Disease gene identified.
- Several treatments under investigation; efforts to validate SMN as a biomarker are in progress.
- One in 35 people are carriers.
- As common as cystic fibrosis and sickle cell anemia.
- Sizable market anticipated (\$500 million to \$1 billion annually).

SOURCE: Winberg, 2007.

type II, who have more copies of the mutated gene, are capable of sitting but generally do not achieve the ability to stand and walk independently. Children with SMA type III, who usually have the most copies of the mutated gene, are capable of standing and walking independently at some point but often lose this ability as the disease progresses, noted Winberg. The gene copy number effect also applies to animal models of transgenic mice lacking endogenous SMN who are given increasing SMN2 gene copy numbers (Monani et al., 2000). The relationship between copy number and severity of disorder has led to the hypothesis that drugs that increase the expression of full-length SMN would be expected to improve motor performance and muscle strength.

Compared with the normal SMN1 gene, the defect in SMN2 is a single point mutation that results in a splicing defect. The end product is a truncated SMN protein (Monani, 2005). The functions of the normal, full-length SMN protein are still actively being studied, but recent research points to its role in assembly of small nuclear ribonucleoprotein particles (Wan et al., 2005). SMN protein insufficiency also affects other aspects of RNA metabolism and axonal growth, especially of motor neurons.

Given the goal of increasing SMN expression, investigators have focused on SMN transcript and protein levels as biomarkers. Methods for SMN detection have been developed, but they have limitations (Sumner et al., 2006). In one study, SMN mRNA was assayed by quantitative reverse transcription polymerase chain reaction, and SMN protein was assayed by a cell immunoassay. Although both were measured with high reliability and temporal stability, their levels in the blood are only correlated with clinical severity in type I patients (Sumner et al., 2006). The

levels were not correlated with clinical severity of type II and type III patients. Still, if they respond to drug treatment, these biomarkers may prove useful in animal models and human clinical trials despite their limitations, said Winberg.

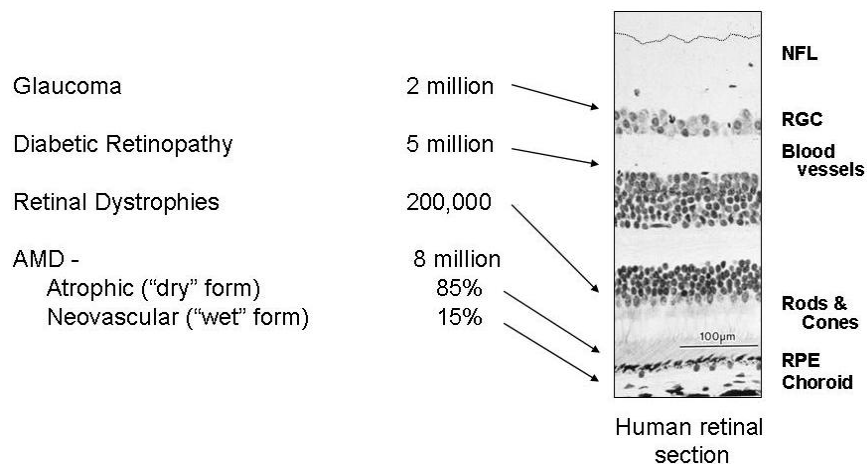
To facilitate biomarker development, Winberg first recommended a more practical, sensitive method for assaying SMN protein. Current approaches such as quantitative western blotting, cell immunoassay, or ELISA all require significant blood volumes due to the low level of SMN protein expression. Drawing a smaller volume of blood is more practical and ethically acceptable for infants and children. Her second recommendation is to understand more about the natural history of SMN. Little is known, for example, about the developmental profile of SMN transcript and protein levels during the prenatal, perinatal, and postnatal periods. The SMN protein may play a more critical role during certain periods of development, noted Winberg. In addition, little is known about blood levels of transcript or protein in relation to levels found in the spinal cord and other tissues, either cross-sectionally or longitudinally. Studies of this kind will require recruitment of additional patients, investigators, and sites. Such studies may uncover a surrogate marker that will shorten clinical trial duration, which now requires 6 to 18 months. These realistic goals for biomarker development should attract greater commercial interest in SMA.

### **BIOMARKERS FOR NEURODEGENERATIVE DISEASES OF THE RETINA**

Neurodegenerative diseases of the retina are exceedingly common in the general population, particularly among older people. Glaucoma, diabetic retinopathy, retinal dystrophies, and age-related macular degeneration collectively affect more than 15 million Americans, reported Dr. Paul Sieving, director of the National Eye Institute. Furthermore, their incidence is increasing as the U.S. population ages. Each of these disorders targets different cell layers of the retina and carries a great human toll, including blindness (Figure 4-2).

Sieving's presentation summarized the extensive advances that have been made in identifying biomarkers as well as mapping their genes. Just as vital, he reported, is compelling new evidence of the retina's value as a window for identifying biomarkers for other neurodegenerative

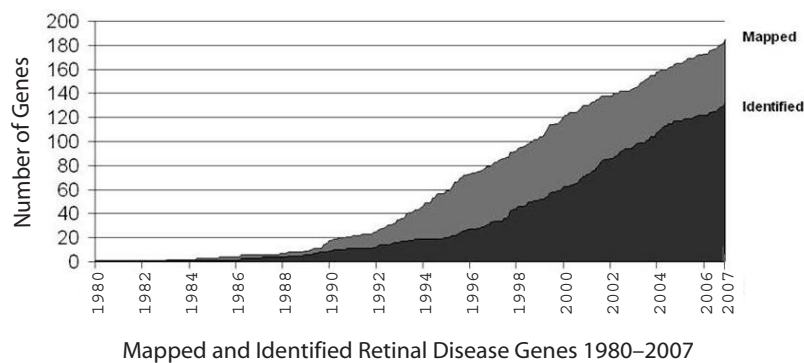




**FIGURE 4-2** Retinal neurodegenerative disease—clinical targets.  
NOTE: Numbers indicate number of affected Americans. Age-related macular degeneration (AMD); nerve fiber layer (NFL); retinal ganglion cell (RGC); retinal pigment epithelial (RPE).  
SOURCE: Sieving, 2007.

diseases such as MS. Because of its accessibility, the retina may hold enormous promise for finding biomarkers of other neurodegenerative diseases, for which tissue accessibility is a formidable obstacle. The retina's value depends on whether the potential biomarkers are expressed there and whether the other disorder has functional impact on vision.

Vision researchers have found a panoply of biomarkers for each of the retinal diseases. One familiar example is high intraocular pressure as a biomarker for glaucoma. High intraocular pressure leads to the demise of retinal ganglion cells, beginning with degeneration of their axons, said Sieving. Other markers, some of which have been available for 150 years, screen for disorders of photoreceptors found on retinal ganglion cells. More broadly, Sieving pointed out that the vision field has been remarkably successful for the past 20 years in identifying mutated genes associated with retinal neurodegenerative disorders. For example, nearly 200 genes have been found to be associated with the demise of the rods and cones (Figure 4-3). Yet the success of the field has had a paradoxical



**FIGURE 4-3** Retinal neurodegenerative disease genes: Disease pathophysiology correlates to developing new risk biomarkers.  
SOURCE: Daiger, 2007.

effect: it has uncovered too many therapeutic targets but not enough understanding of the contribution of each one to the pathophysiology of the disorders. Selecting the best therapeutic targets from a host of potential targets depends heavily on their playing a prominent role in pathophysiology, according to Sieving.

One disorder, age-related macular degeneration, appears to stand as a counterexample to this problem. Researchers have found that a few inflammatory biomarkers account for 74 percent of risk, said Sieving. The biomarkers are polymorphisms in several immune complement molecules, such as complement factor H, complement component 2, and complement factor B (Edwards et al., 2005; Haines et al., 2005; Klein et al., 2005; Moshfeghi and Blumenkranz, 2007). While investigators still do not yet know the full relationship of these complement molecules to pathophysiology, their epidemiological contribution to disease risk helps to identify them as important targets. These discoveries are not only of interest to the vision field, but may also have applications elsewhere: some of the complement proteins associated with macular degeneration are similar to those associated with other neurodegenerative disorders. The value of this overlap becomes even more evident with the new imaging technologies developed for retinal imaging.

### PROMISING TOOLS FOR USE IN OTHER APPLICATIONS

Retinal imaging has an illustrious history tracing back to 1850, when Hermann von Helmholtz invented the ophthalmoscope. Several of the newest imaging technologies may hold value to many neurodegenerative disorders besides those affecting the retina. The first is a structural technology known as optical coherence tomography. It allows each cellular layer of the retina to be visualized with  $3\mu$  axial resolution and image reconstruction. It carries applications for ocular diagnostics and therapeutic tracking, particularly for retinal ganglion cell axon loss in glaucoma and congenital X-linked retinoschisis (Apushkin et al., 2005). It also holds utility for MS by virtue of its ability to image loss of fibers in the retinal nerve fiber layer, which is a common manifestation of MS (Fisher et al., 2006).

Another new structural technology is adaptive optics. Its resolution is so great that it allows individual photoreceptors to be imaged. Pioneered by David Williams and colleagues at the University of Rochester, the technology has confirmed that human color vision depends on three color receptors—red, green, and blue cones—as first postulated in the early 1800s by Thomas Young.

A final tool is the development of metabolic biomarkers, which potentially could be localized together with structural imaging (Gu et al., 2003). Combination techniques would allow dynamic tracking of functional disruptions and pathophysiology with high resolution and in real time, said Sieving. He described an animal model in which monkeys' retinal ganglion cells are labeled and then, after their retrograde transport, are individually visualized in the retina. He stressed the potential for overlap with other neurodegenerative diseases, pointing out, for example, that elevated level of homocysteine is a metabolic biomarker not only for age-related macular degeneration but also for cardiac disease. He ended his presentation with the message that the science is poised to take advantage of ultra-high-resolution imaging tools to develop dynamic functional markers for studying neurodegenerative retinal diseases as well as other neurodegenerative disease. The insights gained can be applied to understanding pathophysiology as well as providing outcome measures for clinical trials.

## A

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## B

# Public Workshop on Neuroscience Biomarkers and Biosignatures: Converging Technologies, Emerging Partnerships

Monday, February 26, 2007  
Lecture Room  
The National Academy of Sciences  
2100 C Street, NW  
Washington, DC

### Workshop Objectives

- Discuss the most promising, and practical, arenas in neuroscience in which novel biomarkers will have greatest near-term impact on the rate at which new treatments are brought forward for psychiatric and neurological disorders.
- Discuss the necessary parameters for such a high-impact biomarker.
- Discuss potential partnerships needed to advance the development of biomarkers and biosignatures.

8:00 a.m. Continental Breakfast

8:30 a.m. Welcome and Introductions

ALAN LESHNER  
Forum Chair  
Chief Executive Officer, AAAS  
Executive Publisher, *Science*

**SESSION I: BIOMARKER AND BIOSIGNATURE PRINCIPLES**

- 8:40 a.m. Workshop Objective: What parameters should be considered when developing a high-impact biomarker?

DENNIS CHOI, *Workshop Chair*  
Professor of Pharmacology and Experimental Therapeutics  
Boston University

- 8:50 a.m. Introduction to the fNIH Biomarkers Consortium

TOM INSEL  
Director  
National Institute of Mental Health

- 9:10 a.m. Lessons Learned from Alzheimer's Disease and the NIA Alzheimer's Disease Neuroimaging Initiative

WILLIAM POTTER  
Vice President  
Merck Research Laboratories  
Clinical Neuroscience

**SESSION II: POTENTIAL TOOLS FOR BIOMARKER AND BIOSIGNATURE DEVELOPMENT**

**Session Objective:** Discuss which tools and parameters should be considered when developing a high-impact biomarker for the neurological or psychiatric disorders.

ALAN BREIER, *Session Chair*  
Vice President for Medical and Chief Medical Officer  
Eli Lilly and Company

- 9:30 a.m. What Impact Will the Genomics Field Have on the Immediate or the Near-Term Development of Biomarkers for Nervous System Diseases?

ALLEN ROSES  
Senior Vice President  
GlaxoSmithKline

- 9:50 a.m. What Impact Will Proteomics, Including CSF Analysis, Have on the Near-Term Development of Biomarkers for Nervous System Diseases?

HOWARD SCHULMAN  
Vice President  
PPD Biomarker Discovery Sciences

**10:10 a.m. BREAK**

- 10:30 a.m. What Imaging Tools May Be Utilized for the Development of Biomarkers for Nervous System Diseases?

BRUCE ROSEN  
Director  
Athinoula A. Martinos Center for Biomedical Imaging  
Massachusetts General Hospital

- 10:50 a.m. Panel Discussion with Meeting Attendees

ALAN BREIER, *Session Chair*

**11:30 a.m. LUNCH**

**SESSION III: PSYCHIATRIC DISEASES AND  
DRUG ADDICTION DISORDERS**

**Session Objective:** Identify specific areas of psychiatric medicine where the development of a novel biomarker could have a high impact.

TOM INSEL, *Session Chair*  
Director  
National Institute of Mental Health

- 12:30 p.m. Which Psychiatric Disorders Are Primed for Key Advances in Biomarker Development?

STEVEN HYMAN  
Provost  
Harvard University



12:45 p.m. Current and Near-Term Impact of Biomarkers for Depression

HUSSEINI MANJI  
Director, Mood and Anxiety Disorders Program  
National Institute of Mental Health

1:05 p.m. Current and Near-Term Impact of Biomarkers for Schizophrenia

DAVID LEWIS  
Endowed Professor of Psychiatry  
University of Pittsburgh Medical Center

1:25 p.m. Current and Near-Term Impact of Biomarkers for Disorders of Addiction

NORA VOLKOW  
Director  
National Institute on Drug Abuse

1:45 p.m. Panel Discussion with Meeting Attendees

TOM INSEL, *Session Chair*

**2:15 p.m. BREAK**

**SESSION IV: NEUROLOGICAL AND EYE DISEASES**

**Session Objective:** Discuss specific areas of neurological medicine where the development of a novel biomarker could have a high impact.

STORY LANDIS, *Session Chair*  
Director  
National Institute of Neurological Disorders and Stroke

2:30 p.m. Which Neurological Diseases are Primed for Key Advances in Biomarker Development?

IRA SHOULSON  
Professor of Neurology  
University of Rochester

2:45 p.m. Current and Near-Term Impact of Biomarkers for Multiple Sclerosis

GAVIN GIOVANNONI  
Professor of Neurology  
Institute of Cell and Molecular Science  
Queen Mary, University of London

3:05 p.m. Current and Near-Term Impact of Biomarkers for Stroke

STEVEN WARACH  
Chief  
Section on Stroke Diagnostics and Therapeutics  
National Institute of Neurological Disorders and Stroke

3:25 p.m. Current and Near-Term Impact of Biomarkers for SMA

MEG WINBERG  
Research Director  
Spinal Muscular Atrophy Foundation

3:45 p.m. Current and Near-Term Impact of Biomarkers for Retinal Degeneration

PAUL SIEVING  
Director  
National Eye Institute

4:05 p.m. Panel Discussion with Meeting Attendees

STORY LANDIS, *Session Chair*

**SESSION V: REGULATORY CONSIDERATIONS, NEXT STEPS, AND GENERAL DISCUSSION**

4:35 p.m. What Regulatory Considerations Are Important to Developing a Qualified Biomarker?

JANET WOODCOCK  
Deputy Commissioner and Chief Medical Officer  
Food and Drug Administration

4:55 p.m. General Discussion

- Which biomarkers have the greatest potential for near-term impact on the development of treatments or key diagnostics for nervous system diseases?
- What partnerships are needed to move forward?

DENNIS CHOI, *Workshop Chair*

Professor of Pharmacology & Experimental Therapeutics  
Boston University

5:30 p.m. **ADJOURN**

## C

### Workshop Attendees

**C. Anthony Altar**  
National Institutes of Health

**Oscar Alzate**  
Duke University

**C. Dennis Barton**  
Johns Hopkins University

**Sally Berry**  
Johnson & Johnson

**Linda Brady**  
National Institute of Mental  
Health

**Sarah Comley**  
International Observers

**Jeff Cossman**  
The Critical Path Institute

**Raymond Crowel**  
Mental Health America

**Mark Day**

**Maryellen de Mars**  
The Critical Path Institute

**Susan Feldman**  
New Jersey Medical School

**Jarlath French-Mullen**  
GeneLogic, Inc.

**Steve Foote**  
National Institute of Mental  
Health

**Philip Fung**  
National Institutes of Health

**Alycia Halladay**  
Autism Speaks

**Therese Heinonen**  
Critical Markers of Disease

**Julia Heinrich**  
Wyeth Research

**Bruce Hermann**  
Epilepsy Foundation

**Kazunari Hirata**

**Raquel Huerta**  
Rutgers University and  
University of Medicine and  
Dentistry of New Jersey

**Ekopimo Ibia**  
Merck Research Laboratories

**Carlayne Jackson**  
American Academy of  
Neurology

**John Lawson**  
Innogenetics

**Daniel Lee**  
Biogenidec, Inc.

**David Lee**  
Foundation for the National  
Institutes of Health

**Carole DeSpain Magoffin**  
National Minority Quality  
Forum

**Steven Marcus**  
Columbia University

**Amy McGuire**  
Foundation for the National  
Institutes of Health

**Roger Meyer**  
American College of  
Neuropsychopharmacology

**Thomas Miller**  
National Institutes of Health

**Ryan Mitchell**  
Pennsylvania State University,  
College of Medicine

**Susan Molchan**  
National Institutes of Health

**Avindra Nath**  
Johns Hopkins University

**Lisa Neuhold**  
National Institute on Alcohol  
Abuse and Alcoholism

**Steven Niemi**

**Patricia O'Looney**  
National Multiple Sclerosis  
Society

**Carlos Pardo**  
Johns Hopkins University,  
School of Medicine

**Mark Rasenick**  
University of Illinois,  
College of Medicine

**Dr J. Tilak Ratnanather**  
Johns Hopkins University

**Scott Reines**

Johnson & Johnson

**Judith Rumsey**

National Institutes of Health

**Joshua Schulman**

**Randall Smith**

University of Pittsburg, School  
of Pharmacy

**Jan Teller**

East Carolina University,  
Brody School of Medicine

**Hong Wan**

Wyeth

**David Wholley**

Foundation for the National  
Institutes of Health

**Dean Wong**

American College of  
Neuropsychopharmacology

**Jimmy Zhang**

Johnson & Johnson

**Yantian Zhang**

National Institute of Biomedical  
Imaging and Bioengineering



## D

### Biographical Sketches of Invited Speakers, Committee Members, and Staff

#### INVITED SPEAKERS

**Alan Breier, M.D.**, was named vice president for Medical and chief medical officer for Eli Lilly and Company in August 2003. He is a member of the Lilly Research Laboratories (LRL) Policy Committee and Lilly's Senior Management Council. He joined Lilly as an LRL research fellow in March 1997, the same year he was appointed adjunct professor of psychiatry at Indiana University School of Medicine in Indianapolis. He received a doctor of medicine degree from the University of Cincinnati School of Medicine and trained in psychiatry at Yale University School of Medicine. Dr. Breier was associate research professor of psychiatry at the University of Maryland School of Medicine and chief, Section on Clinical Studies, at the National Institute of Mental Health Intramural Research Program. In 1997 he began a career at Eli Lilly and Company, where he has focused on neuroscience drug development and led the Zyprexa Product Team. In his current role as chief medical officer, Dr. Breier leads Lilly's medical organization, which annually conducts clinical trials in over 60 countries spanning Phase I through Phase IV studies. He has been responsible for sponsoring the Principles of Medical Research, which encompasses ethical standards for medical research, and establishing Lilly's clinical trial registry, which is a publicly accessible web-based site for posting the initiation and results of clinical trials. He is the recipient of several awards, including the A. E. Bennett Neuropsychiatric Research Foundation Award and the Joel Elkes International Award. He is a fellow of the American College of Neuropsychopharmacology and has published over 225 scientific papers. He is included in *Best Doctors in America*.



**Gavin Giovannoni, Ph.D.**, holds the Chair of Neurology in the Institute of Cell and Molecular Science, Queen Mary, University of London; the Department of Neurology, Barts; and The London NHS Trust, London. He did his undergraduate medical training at the University of the Witwatersrand, South Africa. He moved to the Institute of Neurology, Queen Square, London, in 1993 after completing his specialist training in neurology. He was awarded a Ph.D. from the University of London in 1998. His special clinical interests are multiple sclerosis (MS) and other inflammatory disorders of the central nervous system (CNS). Specific research interests include MS-related neurodegeneration and MS biomarker discovery. He currently holds a program grant funded by the National MS Society and the MS Society of Great Britain and Northern Ireland to investigate novel neuroprotective and neurorestorative therapies in patients with MS. He runs an MS clinical trials unit and is chief investigator on several Phase II and III MS trials. He is particularly interested in optimizing MS disease-modifying therapies.

**David Lewis, M.D.**, is UPMC Endowed Professor in Translational Neuroscience in the Departments of Psychiatry and Neuroscience at the University of Pittsburgh and director of the Translational Neuroscience Program at Western Psychiatric Institute and Clinic. He also serves as director of a National Institute of Mental Health (NIMH) Conte Center for the Neuroscience of Mental Disorders, which is focused on understanding the role of prefrontal cortical dysfunction in the pathophysiology of schizophrenia. He received his medical degree from The Ohio State University, completed residencies in internal medicine and psychiatry at the University of Iowa, and received his research training at the Research Institute of the Scripps Clinic. Dr. Lewis has published over 250 scientific articles. He is currently the recipient of an NIMH MERIT Award, and he serves on the Scientific Council for NARSAD. In addition, he is deputy editor of *The American Journal of Psychiatry* and section editor of clinical neuroscience for *Neuroscience*. Recognition of Dr. Lewis's research accomplishments has included the NARSAD Lieber Prize for Schizophrenia Research, the Stanley Dean Research Award from the American College of Psychiatrists, and the American Psychiatric Association Kempf Award for Research Development.

**Husseini K. Manji, M.D.**, is chief, Laboratory of Molecular Pathophysiology, NIMH, and director of the NIMH Mood and Anxiety Disorders Program, the largest program of its kind in the world. He is also a

visiting professor in the Departments of Psychiatry at Columbia University and Duke University. Dr. Manji received his B.S. (biochemistry) and M.D. from the University of British Columbia. Following psychiatry residency training, he subsequently completed fellowship training in psychopharmacology at NIMH and obtained extensive additional training in cellular and molecular biology at the National Institute of Diabetes and Digestive and Kidney Diseases. The major focus of his ongoing research is the investigation of disease- and treatment-induced changes in gene and protein expression profiles that regulate cellular plasticity and resilience in mood disorders. In broad terms, his laboratories' scientific goals are to capitalize upon recent insights into our understanding of the signaling pathways mediating the effects of mood stabilizers, to understand the pathophysiology of severe mood disorders, and to develop improved therapeutics. He has received ongoing research funding for his work on signaling pathways, plasticity, and new medication development for severe mood disorders.

**Bruce Rosen, M.D., Ph.D.**, is professor of radiology at the Harvard Medical School in Boston and director of the Athinoula A. Martinos Center for Biomedical Imaging at Massachusetts General Hospital, Massachusetts Institute of Technology (MIT), and the Harvard Medical School. He received a doctorate in medical physics from MIT and an M.D. from the Hahnemann Medical College in Philadelphia and is currently board certified in medicine and radiology. Dr. Rosen is an international leader in the development and utilization of physiological and functional nuclear magnetic resonance (NMR) techniques. His current research in NMR technique development includes the measurement of the physiological and metabolic changes associated with brain activation and cerebrovascular insult and how functional imaging tools can be applied to solve specific biological and clinical problems. Dr. Rosen is author or coauthor of more than 125 peer-reviewed articles, book chapters, and reviews. He is the associate editor of *Human Brain Mapping* and is a member of the editorial boards of several scientific journals.

**Allen D. Roses, M.D., FRCP (Hon)**, was appointed as senior vice president, Pharmacogenetics for GlaxoSmithKline (GSK), in July 2006. Previously, he held the position of senior vice president, Genetics Research for GSK. In 1997, Dr. Roses joined Glaxo Wellcome and was charged with organizing genetic strategies for susceptibility gene discovery, pharmacogenetics strategy and implementation, and integration of genet-

ics into medicine discovery and development. In the GSK research and development (R&D) structure, genetics, genomics, proteomics, and bioinformatics are part of Genetics Research and support the entire R&D pipeline. Roses's group recently published the proof of principle experiments for using linkage disequilibrium mapping to identify susceptibility loci for drug adverse events. In 1997 when he left Duke University Medical Center, Dr. Roses was the Jefferson Pilot Professor of Neurobiology and Neurology, director of the Joseph and Kathleen Bryan Alzheimer's Disease Research Center, chief of the Division of Neurology, and director of the Center for Human Genetics. Dr. Roses was one of the first clinical neurologists to apply molecular genetic strategies to neurological diseases. His laboratory at Duke reported the chromosomal location for more than 15 diseases, including several muscular dystrophies and Lou Gehrig's disease. He led the team that identified APOE as a major, widely confirmed susceptibility gene in common late-onset Alzheimer's disease. Translation of these findings to pathway analyses, drug discovery, and development has continued at GSK.

**Howard Schulman, Ph.D.**, is vice president at PPD Biomarker Discovery Sciences, a position he has held since stepping down as head of neurobiology at Stanford University. In his current capacity he has worked with pharmaceutical and biotechnology company leaders to develop biomarker discovery programs that facilitate their drug discovery and validation as well as clinical development. Dr. Schulman received his B.S. in chemistry from UCLA in 1971 and his Ph.D. in biological chemistry at Harvard University in 1976 studying phospholipid metabolism with Eugene P. Kennedy. Subsequently he undertook postdoctoral research in neuropharmacology in the Department of Pharmacology at Yale University under the supervision of Nobel Laureate Paul Greengard. In 1978 he joined the faculty at Stanford University as an assistant professor in the Department of Pharmacology and subsequently in the Department of Neurobiology. He was most recently the chair of the Department of Neurobiology and cofounder and codirector of the Stanford Brain Research Center. He joined SurroMed in 2000 as vice president, a company whose biomarker assets were acquired by PPD in 2005 and where he now heads the biomarker discovery unit. As a scientist he has been a major contributor to progress in the field of molecular pharmacology research for more than 20 years, with over 100 primary articles. Dr. Schulman discovered one of the key protein kinases responsible for transmitting information from calcium-linked hormones, neurotransmitters, and cyto-

kines in heart, brain, and endocrine systems. He initiated two programs in pharmaceutical companies that are developing CaM kinase-based therapeutics in CNS (Roche) and cardiovascular (Scios—J&J) arenas. He was recently elected a fellow of the American Association for the Advancement of Science.

**Ira Shoulson, M.D.**, is the Louis C. Lasagna Professor of Experimental Therapeutics and professor of Neurology, Pharmacology, and Medicine at the University of Rochester School of Medicine in Rochester, New York. He received his M.D. (1971) and postdoctoral training in medicine (1971–1973) and neurology (1975–1977) at the University of Rochester and in experimental therapeutics at the National Institutes of Health (NIH) (1973–1975). He founded the Parkinson Study Group (1985) and the Huntington Study Group (1994), international academic consortia devoted to research and development of treatments for Parkinson's disease, Huntington's disease, and related neurodegenerative and neurogenetic disorders. He has served as principal investigator of the NIH-sponsored trials Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP), the Prospective Huntington At Risk Observational Study (PHAROS), and more than 25 other multicenter controlled trials. He is the director of the Experimental Therapeutics Program at the University of Rochester Department of Neurology, the chair of the executive committee of the Huntington Study Group, a consultant for the Food and Drug Administration, former member of the National Institute of Neurological Disorders and Stroke Council, associate editor of *Archives of Neurology*, and past president of the American Society for Experimental NeuroTherapeutics (ASENT). He has authored more than 230 scientific reports.

**Paul A. Sieving, M.D., Ph.D.**, became director of the National Eye Institute, NIH, in 2001. He came from the University of Michigan Medical School, where he was the Paul R. Lichter Professor of Ophthalmic Genetics and was the founding director of the Center for Retinal and Macular Degeneration in the Department of Ophthalmology and Visual Sciences. He served as vice chair for clinical research for the Foundation Fighting Blindness from 1996 to 2001. He is on the Bressler Vision Award Committee and serves on the jury for the annual \$1 million Award for Vision Research of the Champalimaud Foundation, Portugal. He was elected to membership in the American Ophthalmological Society in 1993 and the Academia Ophthalmologica Internationalis in

2005. He received an honorary doctor of science from Valparaiso University in 2003 and was named as one of The Best Doctors in America in 1998, 2001, and 2005. Dr. Sieving has received a number of awards, including the RPB Senior Scientific Investigator Award, 1998; the Alcon Award, Alcon Research Institute, 2000; and the 2005 Pisart Vision Award from the New York Lighthouse International for the Blind. In 2006 he was elected to the Institute of Medicine of the National Academy of Sciences, one of the highest honors in the fields of medicine and health.

**Steven Warach, M.D., Ph.D.**, received his B.S., M.A., and Ph.D. degrees from Michigan State University and his M.D. degree from Harvard Medical School. After receiving his Ph.D. in neuroscience and psychology for studies of cerebrovascular effects of cognitive tasks and gender, he did his postdoctoral work at the University of Pennsylvania in Dr. Martin Reivich's Cerebrovascular Research Center. Upon completion of his M.D., he did his neurology residency in the Harvard-Longwood Neurology Training Program. In conjunction with his residency, Dr. Warach completed an MRI fellowship with Dr. Robert Edelman at Beth Israel Hospital in Boston, Massachusetts. During this fellowship he began his work developing and using diffusion-perfusion MRI methods for the clinical diagnosis, management, and investigation of acute stroke. In 1993 he joined the faculty of the Neurology Department at Beth Israel Hospital, and in 1994 he was appointed chief of the Division of Cerebrovascular Diseases. Dr. Warach joined the National Institute of Neurological Disorders and Stroke in 1999 as chief of the newly formed Section on Stroke Diagnostics and Therapeutics. His section will be identifying promising experimental stroke therapies through the use of imaging surrogate markers.

**Meg Winberg, Ph.D.**, received her Ph.D. from the Massachusetts Institute of Technology in 1994. She then pursued postdoctoral studies in genetics and neurobiology with Dr. Corey Goodman at the University of California, Berkeley, defining the role of plexins and semaphorins in motoneuron guidance in a model genetic system. In 1999 she joined Exelixis, Inc., where she managed several efforts including genetics technology development for the company's proprietary discovery platform, and target identification and validation in support of a major corporate alliance. Since 2005, She has served as director of research for the Spinal Muscular Atrophy Foundation, where she is responsible for exe-

cuting the foundation's scientific plan, via sponsored research and collaborations with academic and industry investigators.

**Janet Woodcock, M.D.**, is deputy commissioner and chief medical officer, Food and Drug Administration (FDA). She is responsible for overseeing agency operations and cross-cutting regulatory and scientific processes at FDA. Dr. Woodcock served as director, Center for Drug Evaluation and Research at FDA (1994–2005). She previously served in other positions at FDA including director, Office of Therapeutics Research and Review, and acting deputy director, Center for Biologics Evaluation and Research. She received her M.D. from Northwestern Medical School and completed further training and held teaching appointments at the Pennsylvania State University and the University of California in San Francisco. She joined FDA in 1986.

#### COMMITTEE MEMBERS

**Alan I. Leshner, Ph.D. (Chair)**, is Chief Executive Officer of the American Association for the Advancement of Science (AAAS) and Executive Publisher of its journal, *Science*. Previously Dr. Leshner had been Director of the National Institute on Drug Abuse at NIH, and Deputy Director and Acting Director of NIMH. Before that, he held a variety of senior positions at the National Science Foundation. Dr. Leshner began his career at Bucknell University, where he was Professor of Psychology. Dr. Leshner is an elected member of the Institute of Medicine of the National Academies of Science, and a fellow of AAAS, the National Academy of Public Administration, and the American Academy of Arts and Sciences. He was appointed by the U.S. President to the National Science Board and is a member of the Advisory Committee to the Director of NIH. He received an A.B. in Psychology from Franklin and Marshall College and M.S. and Ph.D. degrees in Physiological Psychology from Rutgers University. Dr. Leshner also holds honorary Doctor of Science degrees from Franklin and Marshall College and the Pavlov Medical University in St. Petersburg, Russia.

**Huda Akil, Ph.D.**, is the Gardner Quarton Distinguished University Professor of Neuroscience and Psychiatry at the University of Michigan, and the co-director of the Molecular and Behavioral Neuroscience Institute. Dr. Akil has made seminal contributions to the understanding of the neu-

robiology of emotions, including pain, anxiety, depression, and substance abuse. Early on, she focused on the role of the endorphins and their receptors in pain and stress responsiveness. Her scientific contributions have been recognized with numerous honors and awards. These include the Pacesetter Award from the National Institute on Drug Abuse (NIDA) in 1993 and, with Dr. Stanley Watson, the Pasarow Award for Neuroscience Research in 1994. In 1998 she received the Sachar Award from Columbia University and the Bristol Myers Squibb Unrestricted Research Funds Award. She is past president of the American College of Neuropsychopharmacology (1998) and past president of the Society for Neuroscience (2004), the largest neuroscience organization in the world, with over 35,000 members. She was elected a fellow of AAAS in 2000. In 1994 she was elected to the Institute of Medicine of the National Academy of Sciences and is currently a member of its council. More recently (2004), she was elected to the American Academy of Arts and Sciences.

**Marc Barlow** joined the Strategic Marketing group at GE Healthcare as leader of the neuroscience area in 2005. In this role he is responsible for the development and delivery of disease area strategies for CNS. Before joining GE Mr. Barlow was the marketing director of Sanofi-Aventis in the United Kingdom. Prior to this he held a number of senior sales and marketing positions within the pharmaceutical industry both domestically in the United Kingdom and internationally based out of the United States and Switzerland. A large amount of Mr. Barlow's experience has been gained in the neuroscience area, particularly in epilepsy, Alzheimer's disease, and stroke. Mr. Barlow graduated from the University of Wolverhampton in 1983 with a focus in biological sciences and the Chartered Institute of Marketing with a diploma in Marketing Studies in 1987.

**Daniel J. Burch, M.D.**, is executive vice president of research and development and chief medical officer of CeNeRx Biopharma. Dr. Burch holds an M.D. from Vanderbilt University and an M.B.A. from the Wharton School, University of Pennsylvania. He completed a residency in internal medicine at Vanderbilt University School of Medicine and a fellowship in infectious diseases at Washington University School of Medicine. He has worked in the pharmaceutical industry for a total of 15 years at Abbott Laboratories, SmithKlineBeecham, and GlaxoSmithKline (GSK). His most recent post at GSK was senior vice

president, Neurosciences Medicines Development Centre. He was appointed to his current position in 2007.

**Dennis W. Choi, M.D., Ph.D.**, graduated from Harvard College in 1974 and received M.D. and Ph.D. degrees in 1978 (the latter in pharmacology) from Harvard University and the Harvard-MIT Program in Health Sciences and Technology. After completing residency and fellowship training in neurology at Harvard, Dr. Choi joined the faculty at Stanford University and began research into the mechanisms underlying pathological neuronal death. In 1991 he joined Washington University Medical School as head of the Neurology Department; there he also established the Center for the Study of Nervous System Injury and directed the McDonnell Center for Cellular and Molecular Neurobiology. From 2001 until 2006 he was executive vice president for neuroscience at Merck Research Labs. He is currently executive director of Emory University's Strategic Neurosciences Initiative and director of the Comprehensive Neuroscience Center in the Woodruff Health Sciences Center at Emory University. He is a fellow of the AAAS and a member of the IOM, the Executive Committee of the Dana Alliance for Brain Research, and the College of Physicians of Philadelphia. He has served as president of the Society for Neuroscience, vice president of the American Neurological Association, and chairman of the U.S./Canada Regional Committee of the International Brain Research Organization. He has also served on the National Academy of Sciences Board on Life Sciences and councils for the National Institute of Neurological Disorders and Stroke, the Society for Neuroscience, the Winter Conference for Brain Research, the International Society for Cerebral Blood Flow and Metabolism, and the Neurotrauma Society. He has been a member of advisory boards for the Christopher Reeve Paralysis Foundation, the Grass Foundation, the Hereditary Disease Foundation, the Spinal Muscular Atrophy Foundation, the Harvard-MIT Program in Health Sciences and Technology, the Queen's Neuroscience Institute in Honolulu, the Max-Planck Institute in Heidelberg, the Korea Institute for Advanced Study in Seoul, and the FDA, as well as for several university-based research consortia, biotechnology companies, and pharmaceutical companies.

**Timothy Coetzee, Ph.D.**, is the National Multiple Sclerosis Society's vice president for discovery partnerships. In this capacity, Dr. Coetzee is responsible for the Society's strategic funding of biotechnology and pharmaceutical companies as well as partnerships with the financial and



business communities. He received his Ph.D. in molecular biology from Albany Medical College in 1993 and has been involved with MS research since then. He was a research fellow in the laboratory of society grantee Dr. Brian Popko at the University of North Carolina at Chapel Hill and was also the recipient of one of the Society's Advanced Post-doctoral Fellowship Awards. After completing his training with Dr. Popko, Dr. Coetzee joined the faculty of the Department of Neuroscience at the University of Connecticut School of Medicine, where he conducted research that applied new technologies to understand how myelin is formed in the nervous system. He is the author of a number of research publications on the structure and function of myelin. He joined the Society Home Office staff in the fall of 2000.

**David H. Cohen, Ph.D.**, is professor of psychiatry and biological sciences at Columbia University, where he served as vice president and dean of the Faculty of Arts and Sciences from 1995 to 2003. Prior to joining Columbia, Dr. Cohen served as vice president for research and dean of the graduate school and subsequently as provost at Northwestern University. He has held professorships in physiology and/or neuroscience at Northwestern, SUNY Stony Brook, the University of Virginia School of Medicine, and Case Western University School of Medicine. Dr. Cohen has held various elected offices in national and international organizations, including president of the Society for Neuroscience and chairman of the Association of American Medical Colleges. He has served on varied boards including Argonne National Laboratory, the Fermi National Accelerator Laboratory, Zenith Electronics, and Columbia University Press. He has also served on numerous advisory committees for various organizations, including NIH, the National Science Foundation (NSF), the Department of Defense, and the National Academy of Sciences. Dr. Cohen received his B.A. from Harvard University and his Ph.D. from the University of California, Berkeley and was an NSF postdoctoral fellow at UCLA.

**Richard Frank, M.D., Ph.D.**, is vice president of clinical and medical strategy at GE Healthcare, Princeton, New Jersey. He has two decades of experience designing and implementing clinical trials in the pharmaceutical industry and built the Experimental Medicine Department at Pharmacia before joining GE Healthcare in 2005. Dr. Frank earned M.D. and Ph.D. (pharmacology) degrees concurrently and joined the pharmaceutical industry upon completion of his clinical training in 1985. He is past

president and founding director of the Society of Non-invasive Imaging in Drug Development and a fellow of the Faculty of Pharmaceutical Medicine, Royal College of Physicians. He serves on the scientific review board for the Institute for the Study of Aging and is a member of the editorial board of *Molecular Imaging and Biology*.

**Richard Hodes, M.D.**, is the Director of the National Institute on Aging at NIH. He is a diplomat of the American Board of Internal Medicine. In 1995 Dr. Hodes was elected as a member of The Dana Alliance for Brain Initiatives; in 1997 he was elected as a Fellow of the AAAS; and in 1999 he was elected to membership in the IOM of the NAS. He also maintains an active involvement in research on the NIH campus in Bethesda, Maryland, through his direction of the Immune Regulation Section, a laboratory devoted to studying regulation of the immune system focused on cellular and molecular events that activate the immune response. In the past Dr. Hodes acted as a clinical investigator in the National Cancer Institute, then as the deputy chief and acting chief of the Cancer Institute's Immunology Branch. Since 1982 he has served as program coordinator for the U.S.-Japan Cooperative Cancer Research Program and since 1992 on the scientific advisory board of the Cancer Research Institute. Dr. Hodes received his M.D. degree from the Harvard Medical School and completed a research fellowship at the Karolinska Institute in Stockholm and clinical training in internal medicine at Massachusetts General Hospital.

**Steven E. Hyman, M.D.**, is provost of Harvard University and professor of neurobiology at Harvard Medical School. From 1996 to 2001, Dr. Hyman served as director of NIMH. Before that, he was professor of psychiatry at Harvard Medical School, director of psychiatry research at Massachusetts General Hospital, and the first faculty director of Harvard University's Mind, Brain, and Behavior Initiative. In the laboratory, he studied the regulation of gene expression by neurotransmitters, especially dopamine, and by drugs that influence dopamine systems. This research was aimed at understanding addiction and the action of therapeutic psychotropic drugs. Dr. Hyman is a member of the IOM of the NAS, a fellow of the American Academy of Arts and Sciences, and a fellow of the American College of Neuropsychopharmacology. He is editor in chief of the *Annual Review of Neuroscience*. He has received awards for public service from the U.S. government and from patient advocacy groups such as the National Alliance for the Mentally Ill and the National Men-

tal Health Association. Dr. Hyman received his B.A. from Yale College in 1974 summa cum laude and an M.A. from the University of Cambridge, which he attended as a Mellon fellow studying the history and philosophy of science. He earned his M.D. from Harvard Medical School in 1980 cum laude.

**Judy Illes, Ph.D.**, is professor of neurology and Canada Research Chair in Neuroethics for the National Core for Neuroethics at the University of British Columbia. Dr. Illes received her doctorate in hearing and speech sciences from Stanford University in 1987, with a specialization in experimental neuropsychology. She returned to Stanford University in 1991 to help build the research enterprise in imaging sciences in the Department of Radiology. She also cofounded the Stanford Brain Research Center (now the Neuroscience Institute at Stanford) and served as its first executive director between 1998 and 2001. Most recently, she was acting associate professor of pediatrics (medical genetics) and director of the program in neuroethics at the Stanford Center for Biomedical Ethics. Dr. Illes has written numerous books, edited volumes, and articles. She is the author of *The Strategic Grant Seeker: Conceptualizing Fundable Research in the Brain and Behavioral Sciences* (1999, LEA Publishers, NJ); special guest editor of *Topics of Magnetic Resonance Imaging*, “Emerging Ethical Challenges in MR Imaging” (2002); and *Brain and Cognition*, “Ethical Challenges in Advanced Neuroimaging” (2002). Her latest book, *Neuroethics: Defining the Issues in Theory, Practice and Policy*, was published by Oxford University Press in January 2006. Dr. Illes is cochair of the Committee on Women in Neuroscience of the Society for Neuroscience, a member of the Internal Advisory Board of the Institute of Neurosciences, Mental Health and Addiction of the Canadian Institutes of Health Research, and a member of the Dana Alliance for Brain Initiatives.

**Thomas R. Insel, M.D.**, graduated from Boston University, where he received a B.A. from the College of Liberal Arts and an M.D. from the Medical School. He did his internship at Berkshire Medical Center, Pittsfield, Massachusetts, and his residency at the Langlely Porter Neuropsychiatric Institute at the University of California, San Francisco. Dr. Insel joined the National Institute of Mental Health in 1979, where he served in various scientific research positions until 1994, when he went to Emory University, Atlanta, as professor, Department of Psychiatry, Emory University School of Medicine, and director of the Yerkes Re-

gional Primate Research Center. As director of Yerkes, Dr. Insel built one of the nation's leading HIV vaccine research programs. He also served as the founding director of the Center for Behavioral Neuroscience, a Science and Technology Center funded by the NSF to develop an interdisciplinary consortium for research and education at eight Atlanta colleges and universities. Dr. Insel's scientific interests have ranged from clinical studies of obsessive-compulsive disorder to explorations of the molecular basis of social behaviors in rodents and nonhuman primates. His research on oxytocin and affiliative behaviors, such as parental care and pair bonding, helped to launch the field of social neuroscience. As director of NIMH, Dr. Insel oversees NIMH's \$1.4 billion research budget that provides support to investigators at universities throughout the country in the areas of basic science; clinical research, including large-scale trials of new treatments; and studies of the organization and delivery of mental health services.

**Story C. Landis, Ph.D.**, has been director of National Institute of Neurological Disorders and Stroke since September 1, 2003. As director, Dr. Landis oversees an annual budget of \$1.5 billion and a staff of more than 900 scientists, physician-scientists, and administrators. The Institute supports research by investigators in public and private institutions across the country, as well as by scientists working in its intramural laboratories and branches in Bethesda, Maryland. Since 1950, the Institute has been at the forefront of U.S. efforts in brain research. Dr. Landis joined NINDS in 1995 as scientific director and worked with Zach W. Hall, Ph.D., then institute director, to coordinate and reengineer the Institute's intramural research programs. Between 1999 and 2000, under the leadership of NINDS director Gerald D. Fischbach, M.D., she led the movement, together with NIMH scientific director Robert Desimone, Ph.D., to bring some sense of unity and common purpose to 200 laboratories from 11 different NIH institutes, all of which conduct leading-edge clinical and basic neuroscience research. A native of New England, Dr. Landis received her undergraduate degree in biology from Wellesley College (1967) and her master's degree (1970) and Ph.D. (1973) from Harvard University, where she conducted research on cerebellar development in mice. After postdoctoral work at Harvard University studying transmitter plasticity in sympathetic neurons, she served on the faculty of the Harvard Medical School Department of Neurobiology. In 1985 she joined the faculty of Case Western Reserve University School of Medicine in Cleveland, Ohio, where she held many academic positions including

associate professor of pharmacology; professor and director of the Center on Neurosciences; and chair of the Department of Neurosciences, a department she was instrumental in establishing. Under her leadership, Case Western's neuroscience department achieved worldwide acclaim and a reputation for excellence. Throughout her research career, Dr. Landis has made many fundamental contributions to the understanding of developmental interactions required for synapse formation. She has garnered many honors and awards and is an elected fellow of the Academy of Arts and Sciences, AAAS, and the American Neurological Association. In 2002 she was named president-elect of the Society for Neuroscience.

**Ting-Kai (TK) Li, M.D.**, is the director of the National Institute on Alcohol Abuse and Alcoholism. He earned his undergraduate degree from Northwestern University, and his M.D. from Harvard Medical School and completed his residency training at Peter Bent Brigham Hospital in Boston, where he was named chief medical resident in 1965. He also conducted research at the Nobel Medical Research and Karolinska Institutes in Stockholm and served as deputy director of the Department of Biochemistry within the Walter Reed Army Institute of Research. Dr. Li joined the faculty at Indiana University as professor of medicine and biochemistry in 1971. He subsequently was named the school's John B. Hickam Professor of Medicine and Professor of Biochemistry and later Distinguished Professor of Medicine. In 1985 he became director of the Indiana Alcohol Research Center at the Indiana University School of Medicine, where he also was the associate dean for research. Dr. Li is the recipient of numerous prestigious awards for his scientific accomplishments, including the Jellinek Award, the James B. Isaacson Award for Research in Chemical Dependency Diseases, and the R. Brinkley Smithers Distinguished Science Award. He has also served in many prominent leadership and advisory positions, including past president of the Research Society on Alcoholism and as a member of the National Advisory Council on Alcohol Abuse and Alcoholism and the Advisory Committee to the Director, NIH. Dr. Li was elected to membership in the IOM of the NAS in 1999 and is also an honorary fellow of the United Kingdom's Society for the Study of Addiction.

**Michael D. Oberdorfer, Ph.D.**, is the director of the Strabismus, Amblyopia and Visual Processing, and Low Vision and Blindness Rehabilitation Programs at the National Eye Institute of NIH. He is involved in a

number of trans-NIH initiatives and activities in neuroscience and other areas, including the Coordinating Committee of the NIH Blueprint for Neuroscience Research. Before coming to NIH he was a program officer at the National Science Foundation, where he was involved in a number of activities including directing the Developmental Neuroscience Program. Prior to that he was on the faculty of the University of Texas Medical School in Houston. He received his B.A. at Rockford College and his Ph.D. in zoology and neuroscience at the University of Wisconsin, Madison.

**Kathie L. Olsen, Ph.D.**, became deputy director of National Science Foundation in August 2005. She joined NSF from the Office of Science and Technology Policy (OSTP) in the Executive Office of the President, where she was the associate director and deputy director for science and responsible for overseeing science and education policy including physical sciences, life sciences, environmental science, and behavioral and social sciences. Prior to the OSTP post, she served as the chief scientist at the National Aeronautics and Space Administration (NASA) (May 1999–April 2002) and the acting associate administrator for the new Enterprise in Biological and Physical Research (July 2000–March 2002). As NASA chief scientist, she served not only as the administrator's senior scientific adviser and principal interface with the national and international scientific community, but also was the principal adviser to the administrator on budget content of the scientific programs. Before joining NASA in May 1999, Dr. Olsen was the senior staff associate for the Science and Technology Centers in the NSF Office of Integrative Activities. From February 1996 until November 1997, she was a Brookings Institute Legislative Fellow and then an NSF detail in the Office of Senator Conrad Burns of Montana. Preceding her work on Capitol Hill, she served for 2 years as acting deputy director for the Division of Integrative Biology and Neuroscience at NSF, where she has worked and held numerous other science-related positions. Dr. Olsen received her B.S. with honors from Chatham College, Pittsburgh, Pennsylvania, majoring in both biology and psychology and was elected to Phi Beta Kappa. She earned her Ph.D. in neuroscience at the University of California, Irvine. She was a postdoctoral fellow in the Department of Neuroscience at Children's Hospital of Harvard Medical School. Subsequently at SUNY Stony Brook, she was both a research scientist at the Long Island Research Institute and assistant professor in the Department of Psychiatry and Behavioral Science at the medical school. Her research on neural and

genetic mechanisms underlying development and expression of behavior was supported by NIH. Her awards include the NSF Director's Superior Accomplishment Award; the International Behavioral Neuroscience Society Award; the Society for Behavioral Neuroendocrinology Award for outstanding contributions in research and education; the Barry M. Goldwater Educator Award from the American Institute of Aeronautics and Astronautics—National Capital Section; the Barnard Medal of Distinction, which is the college's most significant recognition of individuals for demonstrated excellence in conduct of their lives and careers; and NASA's Outstanding Leadership Medal. She has also received honorary degrees from Chatham College, Clarkson University, and the University of South Carolina.

**Atul Pande, M.D.**, is senior vice president, Neurosciences Medicines Development Center at GlaxoSmithKline. Dr. Pande received his medical training in India and trained in psychiatry in India and subsequently at the University of Western Ontario in London, Canada. Following a mood disorders research fellowship at the University of Michigan Medical School, he served on the Department of Psychiatry faculty. In 1992 he joined the Lilly Research Laboratories in Indianapolis. Since then he has continued his career in pharmaceutical research and has held positions at Parke-Davis Pharmaceutical Research (now part of Pfizer), Pfizer Global R&D and Cenerx Biopharma. Dr. Pande has drug development and regulatory submission experience in a broad range of psychiatric and neurological disorders. He has over 50 peer-reviewed publications, six patents, and numerous book chapters, abstracts, and scientific presentations to his credit. He is a member of the Society of Biological Psychiatry and a fellow of the Royal College of Physicians and Surgeons of Canada, the American Psychiatric Association, the Canadian College of Neuropsychopharmacology, and the Collegium Internationale Neuro-Psychopharmacologicum.

**Steven Marc Paul, M.D.**, is executive vice president of science and technology and president of the LRL of Eli Lilly and Company. Dr. Paul joined Lilly in April 1993, initially as a vice president of the LRL responsible for CNS Discovery and Decision Phase Medical Research. In 1996 he was appointed vice president (and in 1998 group vice president) of Therapeutic Area Discovery Research and Clinical Investigation. In this position his responsibilities included all therapeutic area discovery research, medicinal chemistry, toxicology/drug disposition, and decision

phase (Phase I/II) medical research. He and his leadership team were responsible for meeting the pipeline performance objectives of LRL and improving R&D productivity, especially in discovery and the early phases of clinical development. In 2003 Dr. Paul was named executive vice president of Lilly and president of LRL with responsibility for all research and development at Lilly. In 2005 he was named chief scientific officer of the Year as one of the Annual Pharmaceutical Achievement Awards. Prior to assuming his position at Lilly, Dr. Paul served as scientific director of NIMH/NIH in Bethesda, Maryland. He received his B.A. degree magna cum laude with honors in biology and psychology from Tulane University in 1972. He received his M.S. degree in anatomy (neuroanatomy) and his M.D. degree, both in 1975, from the Tulane University School of Medicine. Following an internship in neurology at Charity Hospital in New Orleans, he served as a resident in psychiatry and an instructor in the Department of Psychiatry at the University of Chicago, Pritzker School of Medicine. In 1976 he was awarded a research fellowship in the Pharmacology Research Associate Training Program of the National Institute of General Medical Science to work with Nobel laureate Dr. Julius Axelrod in the Laboratory of Clinical Science, IRP, of NIMH. In June 1978 he became a clinical associate in the Clinical Psychobiology Branch of NIMH and served in that position for 2 years. In 1982, he was appointed chief of the Clinical Neuroscience Branch as well as chief of the Section on Preclinical Studies, IRP, NIMH. Dr. Paul also served as medical director in the Commissioned Corps of the United States Public Health Service and maintained a private practice in psychiatry and psychopharmacology. He is board certified by the American Board of Psychiatry and Neurology and has been elected a fellow in the American College of Neuropsychopharmacology (ACNP), served on the ACNP Council, and was elected president of the ACNP (1999). He is currently licensed to practice medicine in the state of Maryland. He also serves on the executive board of PhRMA's Science and Regulatory Committee and is incoming chair. Dr. Paul served as a member of the National Advisory General Medical Sciences Council, NIH (1996–1999), and was appointed by the secretary of health and human services to serve as a member of the advisory committee to the director of NIH (2001–2006).

**William Z. Potter, M.D., Ph.D.,** is vice president, Franchise Integrator Neuroscience, at Merck Research Laboratories. Prior to joining Merck he served as the executive director and Lilly Clinical Research



Fellow of the Neuroscience Therapeutic Area at LRL. He developed a Lilly/IU fellowship early in 1996 and was named professor of psychiatry at IUMC. Before being associated with LRL, he held the position of chief, Section on Clinical Pharmacology, Intramural Research Program at NIMH in Bethesda, Maryland. He had been with the Public Health Service and NIH since 1971. He has authored more than 200 publications in the field of preclinical and clinical pharmacology, mostly focused on drugs used in affective illnesses and methods for evaluating drug effects in humans. He has received many honors during his career. Some of those include the 1975–1977 Falk Fellow, American Psychiatric Association; the 1986 Meritorious Service Medal, United States Public Health Service; and, in 1990, St. Elizabeth's Residency Program Alumnus of the Year Award.

**Paul A. Sieving, M.D., Ph.D.** (biography in Invited Speakers).

**Rae Silver, Ph.D.**, is Helene L. and Mark N. Kaplan Professor of Natural and Physical Sciences and holds joint appointments at Barnard College and Columbia University. Dr. Silver is a fellow of the American Academy of Arts and Sciences. She has participated extensively in scientific and educational activities, including serving as chair for NASA's Research Maximization and Prioritization Committee reviewing Scientific Priorities for the International Space Station; Society for Neuroscience Program Committee (Theme E—Autonomic and Limbic System); chair, External Advisory Committee, NSF Center for the Study of Biological Rhythms at the University of Virginia; search committees for journal editors, department chairs, and provost at various institutions. She has been a panel member of a number of committees, including NASA: International Space Station Cost and Management Evaluation Task Force; NSF Center for Behavioral Neuroscience External Advisory Board member Georgia State, Emory, and other colleges; Society for Neuroscience Education Committee Ford Foundation Minority Fellowship Review panel. She was also president, Society Research in Biological Rhythms. As senior adviser at NSF, she worked with NSF staffers in all the scientific directorates to create a series of workshops to examine opportunities for the next decade in making advances in neuroscience through the joint efforts of biologists, chemists, educators, mathematicians, physicists, psychologists, and statisticians. Silver's studies of the biological clock in the suprachiasmatic nucleus of the brain were the first to conclusively demonstrate that this brain tissue can be readily trans-

planted and restore function at a very high success rate in an animal model. The laboratory is renowned for analysis of the input, output, and intraneuronal circuits underlying the function of the brain's master clock. A second line of research entails the study of mast cells (renowned for their role in producing allergic reactions) in modulating brain function and as a major source of brain histamine. The research has been supported without interruption by NIH and NSF, among other sources. Dr. Silver is deeply committed to educating undergraduate and graduate students, both at the national and institutional level and in the hands-on context of the laboratory. Consistent with this interest, she created the undergraduate program in Quantitative Reasoning at Barnard College and published, with colleagues, studies of mathematical learning. She initiated the undergraduate major in neuroscience, serving as its first program director. She also served as director of the graduate program in psychology at Columbia University.

**William H. Thies, Ph.D.**, is vice president for medical and scientific relations at the Alzheimer's Association, where he oversees the world's largest private, nonprofit Alzheimer's disease research grants program. Under his direction, the organization's annual grant budget has doubled, and the program has designated special focus areas targeting the relationship between cardiovascular risk factors and Alzheimer's disease, caregiving and care systems, and research involving diverse populations. He played a key role in launching *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, and in establishing the Research Roundtable, a consortium of senior scientists from industry, academia, and government who convene regularly to explore common barriers to drug discovery. In previous work at the American Heart Association (AHA) from 1988 to 1998, Dr. Thies formed a new stroke division that recently became the American Stroke Association. He also built the Emergency Cardiac Care Program, a continuing medical education program that trains over 3 million professionals annually. He has worked with NINDS to form the Brain Attack Coalition. Prior to joining AHA, he held faculty positions at Indiana University in Bloomington and the University of Pittsburgh. Dr. Thies earned a B.A. in biology from Lake Forest College, Lake Forest, Illinois, and a Ph.D. in pharmacology from the University of Pittsburgh School of Medicine.

**Roy E. Twyman, M.D.**, is vice president, Franchise Development in the Central Nervous System/Pain Area of Johnson & Johnson Pharmaceuti-

cal Research and Development. In this position, he oversees licensing and acquisition efforts for neurology, psychiatry, and pain franchises while coordinating strategic activities for CNS discovery optimization, early human studies and proof of concept, new technologies, and cross-company projects. Additional oversight includes the pharmacogenomics and neuroimaging teams that support broad-based pharma R&D across all therapeutic areas. Before his work at Johnson & Johnson, Dr. Twyman was on the faculty of the University of Utah and the University of Michigan. He received his B.S. degree from Purdue University in electrical engineering. He earned his M.D. from the University of Kentucky and completed a neurology residency at the University of Michigan.

**Nora D. Volkow, M.D.**, became director of the National Institute on Drug Abuse in May 2003. Dr. Volkow came to NIDA from Brookhaven National Laboratory (BNL), where she held concurrent positions including associate director for life sciences, director of nuclear medicine, and director of the NIDA-Department of Energy Regional Neuroimaging Center. In addition, she was a professor in the Department of Psychiatry and associate dean of the medical school at the State University of New York (SUNY), Stony Brook. Dr. Volkow brings to NIDA a long record of accomplishment in drug addiction research. She is a recognized expert on the brain's dopamine system, with her research focusing on the brains of addicted, obese, and aging individuals. Her studies have documented changes in the dopamine system affecting the actions of frontal brain regions involved with motivation, drive, and pleasure and the decline of brain dopamine function with age. Her work includes more than 350 peer-reviewed publications, three edited books, and more than 50 book chapters and non-peer-reviewed manuscripts. The recipient of multiple awards, she was elected to membership in the IOM of the NAS and was named "Innovator of the Year" in 2000 by *U.S. News & World Report*. Dr. Volkow received her B.A. from Modern American School, Mexico City; her M.D. from the National University of Mexico, Mexico City; and her postdoctoral training in psychiatry at New York University. In addition to BNL and SUNY Stony Brook, she has worked at the University of Texas Medical School and Sainte Anne Psychiatric Hospital in Paris.

**Frank D. Yocca, Ph.D.**, is currently vice president and head of CNS and Pain Drug Discovery for AstraZeneca at the Wilmington, Delaware, fa-

cility. His research focus is on new treatments for psychiatric diseases. Dr. Yocca received his Ph.D. in pharmacology from St. John's University in New York City. His work focused on the effect of antidepressants on circadian rhythms. Subsequently he was a postdoctoral fellow at Mt. Sinai Department of Pharmacology. Prior to joining AstraZeneca, he was executive director at the Bristol Myers Squibb Pharmaceutical Research Institute. He originally joined the Bristol Myers Company in 1984 as a postdoctoral fellow in CNS research. Utilizing techniques he learned from his academic postdoctoral position, Dr. Yocca helped to elucidate the mechanism of action of the anxiolytic drug Buspar. He then joined Bristol Myers as an employee and made significant advances in understanding the physiological role of the 5-HT<sub>1A</sub> receptor and its role in psychiatric disease states. During the 21 years spent with Bristol-Myers and then Bristol Myers Squibb, he supported a number of psychiatric discovery programs, helping to discover and develop the antidepressant Serzone. Throughout his tenure, he continued to work in the field of serotonin and advanced a number of agents to clinical trials including several antimigraine agents (avatriptan) as well as antipsychotics and anxiolytics. In the latter stages of his career at BMS, he also became involved in externalization and development. He contributed to the in-licensing and development of the novel antipsychotic agent Abilify. Additionally, Dr. Yocca was part of the externalization team that in-licensed to BMS the recently approved antidepressant agent Emsam, the first antidepressant to be administered through a patch. In development, he was early development project leader for CRF antagonists and was also involved in Phase IV clinical studies with Abilify. Dr. Yocca is a member of numerous scientific societies, including SFN and ACNP.

**Christian G. Zimmerman, M.D., FACS, M.B.A.**, is chairman and founder of the Idaho Neurological Institute (INI), adjunct professor of psychology at Boise State University, and past chief executive officer of Neuroscience Associates. He also served as a board member for the Idaho State Board of Health and Welfare. Dr. Zimmerman established the INI research facility to focus on nervous system injury, repair, and neuroplasticity; leads its various interdisciplinary research teams; and is co-professor for biology and cognitive neuroscience research students trained at the facility. Research projects include a 20-year longitudinal study of traumatic brain injury; investigations of spinal injury, stroke, aneurysms, arterial thrombolytic therapy intervention, neuropathology, CNS tumors, sleep disorders, deep brain stimulation, and movement dis-

orders; and five TATRC telemedicine grants. In his role as INI chairman, he has facilitated numerous symposia and workshops to provide educational opportunities for medical professionals and the general public. Additionally, he chairs prevention programs for Idaho's youth such as Think First. Dr. Zimmerman is diplomate of the American Board of Neurological Surgery and Pain Management and a fellow of the American College of Surgeons and Physician Executives. He received his M.B.A. from Auburn University.

**Stevin H. Zorn, Ph.D.**, is vice president and head of Central Nervous System Disorders Research at Pfizer Global Research and Development and also coleads Pfizer's CNS Therapeutic Area Leadership Team. He received a B.S. degree in chemistry from Lafayette College, Easton, Pennsylvania, and M.S. and Ph.D. degrees in biomedical sciences with an emphasis on toxicology and neuropharmacology, respectively. Dr. Zorn conducted postdoctoral research studies in Paul Greengard's Laboratory of Molecular and Cellular Neuroscience at Rockefeller University before joining Pfizer in 1989. He has coauthored numerous scientific research communications and patents and has contributed to the advancement of a wide variety of drug candidates, some of which are now helping to improve the lives of patients suffering from CNS-related illness.

#### IOM STAFF

**Bruce M. Altevogt, Ph.D.**, is a senior program officer in the Board on Health Sciences Policy at the IOM. His primary interests focus on policy issues related to basic research and preparedness for catastrophic events. He received his doctoral thesis from Harvard University's Program in Neuroscience. Following over 10 years of research, Dr. Altevogt joined The National Academies as a science and technology policy fellow with the Christine Mirzayan Science & Technology Policy Graduate Fellowship Program. Since joining the Board on Health Sciences Policy, he has been a program officer on multiple IOM studies, including *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem*, *The National Academies' Guidelines for Human Embryonic Stem Cell Research: 2007 Amendments*, and *Assessment of the NIOSH Head-and-Face Anthropometric Survey of U.S. Respirator Users*. He is currently serving as the director of the Forum on Neuroscience and Nervous Sys-

tem Disorders and a co-study director on the National Academy of Sciences Human Embryonic Stem Cells Research Advisory Committee. He received his B.A. from the University of Virginia in Charlottesville, where he majored in biology and minored in South Asian studies.

**Andrew Pope, Ph.D.**, is director of the Board on Health Sciences Policy and the Board on Neuroscience and Behavioral Health at IOM. With a Ph.D. in physiology and biochemistry, his primary interests focus on environmental and occupational influences on human health. Dr. Pope's previous research activities focused on the neuroendocrine and reproductive effects of various environmental substances in food-producing animals. During his tenure at the National Academies and since 1989 at IOM, Dr. Pope has directed numerous studies; topics include injury control, disability prevention, biological markers, neurotoxicology, indoor allergens, and the enhancement of environmental and occupational health content in medical and nursing school curricula. Most recently, Dr. Pope directed studies on NIH priority-setting processes, organ procurement and transplantation policy, and the role of science and technology in countering terrorism.

**Sarah L. Hanson** is a senior program associate in the Board on Health Sciences Policy at IOM. Ms. Hanson previously worked for the Committee on Sleep Medicine and Research. She is currently the senior program associate for the Forum on Neuroscience and Nervous System Disorders. Prior to joining IOM, she served as research and program assistant at the National Research Center for Women & Families. Ms. Hanson has a B.A. from the University of Kansas with a double major in political science and international studies. She is currently taking pre-med courses at the University of Maryland and hopes to attend medical school in the future.

**Lora K. Taylor** is a senior project assistant in the Board on Health Sciences Policy at IOM. She has 15 years of experience working at the NAS and, prior to joining IOM, served as the administrative associate for the Report Review Committee and the Division on Life Sciences' Ocean Studies Board. Ms. Taylor has a B.A. from Georgetown University with a double major in psychology and fine arts.

**James McGuinness** is a College of William and Mary student currently interning at the Institute of Medicine and aiding the Forum on Neurosci-

ence and Nervous System Disorders staff. In his third year now, he plans to major in neuroscience and pursue a career in the research or medical fields. At school he is active in many clubs and organizations and is planning on researching with one of his professors this fall.

### **IOM Fellow**

**Lisa F. Barcellos, Ph.D.**, is currently employed as Assistant Professor of Epidemiology in the School of Public Health at the University of California, Berkeley. Dr. Barcellos obtained her Ph.D. in Immunology from the School of Public Health, University of California Berkeley in 1996. She was awarded a National Multiple Sclerosis Society postdoctoral fellowship in 1997, and completed three years of postdoctoral training in Genetic Epidemiology in the Department of Neurology, University of California, San Francisco in 2001. While at University of California, San Francisco, she was also the recipient of a NIH/K12 clinical research and training award as part of the prestigious NIH-funded “Building Interdisciplinary Research Careers in Women’s Health” program for two years (2002–2004).

Dr. Barcellos currently holds faculty appointments in the Department of Neurology, University of California, San Francisco and Kaiser Permanente Division of Research Oakland. She serves as a co-investigator for the United States Multiple Sclerosis Genetics Group and the Multiple Sclerosis International Genetics Consortium. She is also a member of the Kaiser Permanente Autoimmune Disease Research Group and the National Multiple Sclerosis Society Task Force on Prospective Studies of Risk Factors in Multiple Sclerosis. Dr. Barcellos has significant expertise and training in areas of human genetics, genetic epidemiology, molecular genetics and statistical analysis of complex genetic diseases. She has actively participated in the design, implementation, analysis and interpretation of human genetic disease studies for the last ten years, including numerous investigations of candidate disease genes and genomic regions, as well as autoimmune phenotype characterization and the identification of genotype-phenotype correlations in studies of autoimmune disease.

In collaboration with colleagues at University of California, San Francisco and Kaiser Permanente Division of Research, Dr. Barcellos has established a strong NIH-funded research program with a primary focus

on the identification of genetic, social and environmental risk factors for particular autoimmune diseases including multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis and other conditions. Her current projects are comprised of large family-based and population-based studies, and include the application of novel analytical approaches to characterize gene-gene, gene-environment, parent-of-origin and maternal-child histocompatibility relationships underlying susceptibility to these diseases. Her research program also includes the application of state-of-the-art high throughput single nucleotide polymorphism (or SNP) genotyping methodologies. A major emphasis of her work is the comprehensive investigation of the major histocompatibility complex region genes on chromosome 6p21 in autoimmunity. Dr Barcellos has co-authored more than 35 publications in the scientific literature and is a member of the American Society of Human Genetics and International Genetic Epidemiology Society. She currently serves as a genetic epidemiology consultant to Celera Diagnostics in Alameda, CA, the March of Dimes California Birth Defects Monitoring Program in Berkeley, CA, and the Kaiser Permanente Program in Genes, Environment and Health in Oakland, CA. In addition to her autoimmune disease research program, Dr. Barcellos has also successfully developed and established graduate level curriculum in areas of human genetics, molecular and genetic epidemiology in the University of California, Berkeley, School of Public Health.



