Improving Translation of Animal Models for Nervous System Disorders: A Workshop

March 28 - 29, 2012

Institute of Medicine
Keck Building, Room 100
Washington, DC

Background: Nervous system disorders and diseases are highly prevalent and substantially contribute to the national disease burden. Animal models have significantly increased our understanding of nervous system disorders. Yet, in spite of these advances, there still remains a large gap in treatment options that are high in efficacy but low in side effects for many diseases. And for some diseases there are no treatment options. More than 80% of research projects fail to reach clinical trials. Of those nervous system drugs that do make it to clinical trials, only 8% end up being approved. These statistics translate to drug approval rates that are 50% lower than drugs for other therapeutic areas. Given the tremendous disease burden associated with nervous system diseases and disorders, the goal of this workshop is to bring together key stakeholders to discuss potential opportunities for maximizing the translation of effective therapies from animal models to clinical practice.

Meeting Objectives:

- Discuss key issues that contribute to poor translation of animal models in nervous system disorders.
    - Examine case studies that highlight successes and failures in the development and application of animal models.
- Consider strategies to increase the scientific rigor of preclinical efficacy testing.
    - Explore the benefits and challenges to developing standardized animal and behavioral models.
    - Identify methods to facilitate development of corresponding animal and clinical endpoints
- Identify methods that would maximize bidirectional translation between basic and clinical research
- Determine the next steps that will be critical for improvement of the development and testing of animal models of disorders of the nervous system.

DAY ONE

1:30 p.m. Opening Remarks

RICHARD HODES, *Co-chair*
STEVEN PAUL, *Co-chair*

SESSION I: EVALUATION OF CURRENT ANIMAL MODELS

Session Objective: Identify critical limitations impacting translation of therapies from animal models to clinical practice. Explore current expectations of animal models to predict therapeutic efficacy. Determine the impact of generalization of animal model capabilities. Examine the role of animal model derived data in making decisions about moving therapeutics into clinical trials.

1:40 p.m. Overview and Session Objectives

STEVIN ZORN, *Session Chair*

1:45 p.m. Examination of current expectations for animal models

STEVEN PAUL
Director
Helen and Robert Appel Alzheimer's Disease Research Institute
Weill Cornell Medical College

2:00 p.m. Choice and Validation of Animal Models for CNS Drug Discovery

MARK TRICKLEBANK
Director and Senior Research Fellow
Eli Lilly and Co.

2:15 p.m. Impact of Publication Bias

KATRINA KELNER
Editor
Science Translational Medicine

2:30 p.m. Q&A with speakers

SESSION II: CASE STUDIES

Breakout Objective: Conduct in-depth analysis of six case studies in which animal models have ranged in translational success. Specifically, breakout groups will focus on three key questions: 1) Would this research area benefit from a new or improved standardized animal or behavioral models (e.g. testing conditions, reference standards)? 2) Do animal and human endpoints match for this case study? 3) What is needed to bridge the gap between animal models and clinical science?

3:00 p.m. Overview and Session Objectives

RICHARD HODES and STEVEN PAUL, *Session Chairs*

3:10 p.m. BREAKOUT INTO GROUPS

3:25 p.m. Breakout 1: Animal models for Neurodegeneration

ROBERT FERRANTE, *Moderator*
Professor
Departments of Neurological Surgery, Neurology, and Neurobiology
University of Pittsburgh

TIM COETZEE, *Discussant*
Chief Research Officer
National Multiple Sclerosis Society

Breakout 2: Animal models for Alzheimer's disease

BRADLEY HYMAN, *Moderator*
John B. Penny Jr. Professor of Neurology
Harvard Medical School

RICHARD HODES, *Discussant*
Director
National Institute on Aging

SHARON ROSENZWEIG-LIPSON, *Discussant*
IVS Pharma Consulting

Breakout 3: Animal models for Stroke

CONSTANTINO IADECOLA – *Moderator*
George C. Cotzias Distinguished Professor of Neurology and Neuroscience
Weill Cornell Medical College

WALTER KOROSHETZ, *Discussant*
Deputy Director
National Institute for Neurological Disorders and Stroke

STEVEN PAUL, *Discussant*
Director
Helen and Robert Appel Alzheimer's Disease Research Institute
Weill Cornell Medical College

Breakout 4: Animal models for Schizophrenia: Cognition enhancement and antipsychotic efficacy

HOLLY MOORE – *Moderator*
Associate Professor
Clinical Neurobiology in Psychiatry
Columbia University

MARK GEYER, *Discussant*
Professor
Department of Psychiatry
University of California, San Diego

STEVIN ZORN, *Discussant*
Executive Vice President
Neuroscience Research
Lundbeck USA

Breakout 5: Animal models for Addiction

ATHINA MARKOU – *Moderator*
Professor
Department of Psychiatry
University of California, San Diego

ALAN LESHNER, *Discussant*
Chief Executive Officer
American Association for the Advancement of Science

GERARD MAREK, *Discussant*
Project Director
Neuroscience Development
Abbott Laboratories

Breakout 6: Animal models for Pain

A. VANIA APKARIAN– *Moderator*
Professor
Neuroscience Institute
Northwestern University

DAVID SHURTLEFF, *Discussant*
Acting Deputy Director
National Institute on Drug Abuse

4:15 p.m. Breakout groups Report Out and Panel Discussion with Participants (15 min/group)

- What common themes were identified in:
  - Standardization Needs
  - Endpoints
  - Basic Science/Clinical Research Gap

6:00 p.m. ADJOURN

DAY TWO

Note: continental breakfast will be available at 8:00 a.m.

SESSION III: THE VALUE OF STANDARDIZATION

Session Objective: Explore key components of animal model science that would benefit from standardization, such as behavioral paradigms. Examine the benefits and challenges to developing standardizations for animal and behavioral models. Discuss potential methods for dissemination of standards.

8:30 a.m. Overview and Session Objectives

WALTER KOROSHETZ, *Session Chair*

8:40 a.m. Standardization in preclinical models of anxiety: necessary but not sufficient

ANDREW HOLMES
Chief
Laboratory of Behavioral and Genomic Neuroscience
National Institute on Alcohol Abuse and Alcoholism

8:55 a.m. Developing new methods for cognitive translation from rodent to human

TIM BUSSEY
Professor
Department of Experimental Psychology
University of Cambridge

9:10 a.m. AD Models and the Risk/Benefit Ratio of Standardization

LENNART MUCKE
Director, Gladstone Institute of Neurological Disease
Professor, Department of Neurology
University of California, San Francisco

9:25 a.m. Discussion with speakers and participants

10:00 a.m. BREAK

SESSION IV: CORRESPONDING ANIMAL AND CLINICAL ENDPOINTS

Session Objective: Discuss methods to facilitate development of equivalent or surrogate animal research and clinical trial endpoints. Explore the value of surrogate endpoints for nervous system disorders. Identify components that require recapitulation in both animal studies and clinical trials.

10:15 a.m. Overview and Session Objectives

SHARON ROSENZWEIG-LIPSON, *Session Chair*

10:30 a.m. Prepulse inhibition – corresponding endpoints, but to what end?

NEAL SWERDLOW
Professor
Department of Psychiatry
University of California, San Diego

10:45 a.m. Choice of Endpoints – EAE to Approved Drug – One Huge Success; One Massive Failure

LARRY STEINMAN
Professor
Department of Neurology and Neurological Sciences
Stanford University

11:00 a.m. Improving Bidirectional Translation for Nervous System Disorders

MICHELA GALLAGHER
Krieger-Eisenhower Professor of Psychology and Neuroscience
Department of Psychological and Brain Sciences
Johns Hopkins University

11:15 a.m. Discussion with speakers and participants

11:45 p.m. LUNCH (*Will be provided for all participants*)

SESSION V: THE BASIC AND CLINICAL SCIENCE GAP

Session Objective: Explore methods for increasing bi-directional application of research findings between basic and clinical researchers. Examine regulatory requirements that may either facilitate or impede translation of animal models. Identify methods to increase confidence in the movement from animal models to clinical trials, including replication of studies.

1:00 p.m. Overview and Session Objectives

MARK GEYER, *Session Chair*

1:10 p.m. Developing better animal models of etiology and pathophysiology

RICHARD RANSOHOFF
Director
Neuroinflammation Research Center
Cleveland Clinic

1:30 p.m. Panel discussion on the session topic [15 min/speaker]

DEANNA BARCH
Professor of Psychology, Psychiatry and Radiology
Washington University

GERRY DAWSON
Chief Science Officer
P1Vital

HUGO GEERTS
Scientific Liaison Officer
In Silico Biosciences

THOMAS STECKLER
Senior Scientific Director
Neuroscience Drug Discovery
Johnson & Johnson

2:30 p.m. Discussion with speakers and participants

3:00 p.m. BREAK

SESSION VI: FUTURE DIRECTIONS & NEXT STEPS

Session Objective: Define important, yet practical, expectations for animal models in nervous system disorders. Identify opportunities and key stakeholders necessary for the success of improving translation of animal models. Identify key components of the infrastructure support that will be required for implementation.

3:15 p.m. Overview and Session Objectives

RICHARD HODES AND STEVEN PAUL, *Session Chairs*

3:25 p.m. Session Synopsis and Next Steps

STEVIN ZORN – *Session I Chair*

RICHARD HODES – *Session II Co-chair*
STEVEN PAUL– *Session II Co-chair*

WALTER KOROSHETZ – *Session III Chair*

SHARON ROSENZWEIG-LIPSON – *Session IV Chair*

MARK GEYER– *Session V Chair*

4:25 p.m. Discussion with speakers and participants

5:00 p.m. ADJOURN