



Training in  
**Neurotherapeutics Discovery and Development**  
*for academic scientists*

*A course supported by the  
National Institute of Neurological Disorders and Stroke  
and the NIH Blueprint for Neuroscience Research*  
Organized by the University of California, Davis,  
the Johns Hopkins Brain Science Institute, the Harvard  
NeuroDiscovery Center and Brigham and Women's Hospital  
and Northwestern University in collaboration with  
the American Society for Experimental NeuroTherapeutics.

February 19 – 22, 2014  
Bethesda North Marriott Hotel  
and Conference Center  
Bethesda, Maryland

Course Information



# Training in Neurotherapeutics Discovery and Development for Academic Scientists Schedule

Directed by the University of California, Davis,  
Johns Hopkins Brain Science Institute, Harvard NeuroDiscovery Center, Northwestern University,  
in collaboration with the American Society for Experimental NeuroTherapeutics

Supported by NIH/NINDS Grant 1R25NS077582

## Wednesday, February 19, 2014

7:45 am – 8:30 am	<b>Continental Breakfast</b>	Glen Foyer
8:30 am – 9:00 am	<b>Overview:</b> The Neurotherapeutics Discovery and Development Process <i>Course Directors</i>	Forest Glen
9:00 am – 10:00 am	<b>Lecture 1:</b> Target and Pathway Interrogation <i>Douglas Auld, PhD, Novartis Institutes for Biomedical Research</i>	Forest Glen
10:00 am – 10:10 am	<b>Break</b>	Glen Foyer
10:10 am – 11:10 am	<b>Lecture 2:</b> Biology Basics for Identifying Hits <i>William Janzen, BS, University of North Carolina, Chapel Hill</i>	Forest Glen
11:10 am – 12:10 pm	<b>Lecture 3:</b> Moving from Hit to Lead to Clinical Candidate <i>James Barrow, PhD, Johns Hopkins School of Medicine</i>	Forest Glen
12:10 pm – 1:30 pm	<b>Lunch</b> (Students paired with mentors)	Glen Echo
1:30 pm – 2:30 pm	<b>Lecture 4:</b> Medicinal Chemistry <i>Craig Lindsley, PhD, Vanderbilt University Medical Center</i>	Forest Glen
2:30 pm – 3:30 pm	<b>Lecture 5:</b> Alternative Approaches to Lead Generation <i>Sam Enna, PhD, University of Kansas</i>	Forest Glen
3:30 pm – 3:45 pm	<b>Break</b>	Glen Foyer
3:45 pm – 5:30 pm	<b>Engagement Exercise 1:</b> Clarify vision statement and begin to develop the components of mock translations grant application	Forest Glen
5:30 pm – 6:15 pm	Networking Reception	Glen Foyer
6:15 pm – 7:00 pm	<b>Dinner</b>	Glen Echo
7:00 pm – 8:15 pm	<b>After Dinner Talk:</b> Drug Discovery <i>Solomon Snyder, MD, DSc, DPhil, Johns Hopkins University</i>	Forest Glen

**Thursday, February 20, 2014**

7:15 am – 8:00 am	<b>Continental Breakfast</b>	Glen Foyer
8:00 am – 9:00 am	<b>Lecture 6:</b> ADME <i>Kennan Marsh, PhD, AbbVie</i>	Forest Glen
9:00 am – 10:00 am	<b>Lecture 7:</b> Preclinical Proof-Concept / Target Engagement Studies <i>Kalpna Merchant, PhD, Eli Lilly and Company</i>	Forest Glen
10:00 am – 10:10 am	<b>Break</b>	Glen Foyer
10:10 am – 11:10 am	<b>Lecture 8:</b> Toxicology <i>Adaline Smith, Ironwood Pharmaceuticals</i>	Forest Glen
11:10 am – 12:10 pm	<b>Lecture 9:</b> IND Enabling Studies and Preparation of the IND <i>William Bracken, PhD, DABT, AbbVie</i>	Forest Glen
12:10 pm – 1:30 pm	<b>Lunch</b> (Responsible conduct of research exercise)	Glen Echo
1:30 pm – 1:45 pm	Break	
1:45 pm – 5:45 pm	<b>Engagement Exercise 2:</b> Round-Robin – Students interact individually with each subject expert	Forest Glen & Glen Echo
5:45 pm – 6:30 pm	Networking Reception – ASENT Annual Meeting	Grand Ballroom C, Main Level
6:30 pm – 7:30 pm	ASENT Annual Meeting <b>Dinner</b>	Grand Ballroom A / B, Main Level
7:30 pm – 9:00 pm	Reserved for students to prepare mock translation grant applications; mentors available	Forest Glen and/or Glen Echo

**Friday, February 21, 2014**

7:15 am – 8:00 am	<b>Continental Breakfast</b>	Glen Foyer
8:00 am – 9:00 am	<b>Lecture 10:</b> Case Studies <i>Course Directors</i>	Forest Glen
9:00 am – 10:00 am	<b>Lecture 11:</b> Formulation and Route of Administration <i>Janet Wolfe, PhD, Wolfe Laboratories, Inc.</i>	Forest Glen
10:00 am – 10:10 am	<b>Break</b>	Glen Foyer
10:10 am – 11:10 am	<b>Lecture 12:</b> Rigor in Translational Drug Discovery and Development <i>Shai Silberberg, PhD, NIH/NINDS</i>	Forest Glen
11:10 am – 12:10 pm	<b>Lecture 13:</b> Intellectual Property <i>Kenneth Weber, PhD, Kilpatrick Townsend</i>	Forest Glen
12:10 pm – 2:00 pm	<b>Lunch</b>	Glen Echo
2:15 pm – 6:00 pm	<b>Pipeline Session</b> -ASENT 16 <sup>th</sup> Annual Meeting Brief presentations on ongoing corporate and academic neurotherapeutic R&D projects	Grand Ballroom A / B, Main Level
6:30 pm – 8:30 pm	<b>Restaurant Dinner – all invited</b> <i>Transportation leaves from Conference Center, Lower Level at 6:10 p.m.</i>	Positano Ristorante

**Saturday, February 22, 2014**

7:15 am – 8:00 am	<b>Continental Breakfast</b>	Glen Foyer
8:00 am – 9:00 am	<b>Lecture 14:</b> Funding Academic Drug Discovery Research <i>Rebecca Farkas, PhD, NIH/NINDS</i>	Forest Glen
9:00 am – 10:15 am	<b>Engagement Exercise 3:</b> Student Presentations – Description of mock translational grant application followed by critique	Forest Glen, Seneca, Strathmore, Cabin John
10:15 am – 10:30 am	<b>Break</b>	Glen Foyer
10:30 am – 11:45 am	<b>Engagement Exercise 3:</b> Continued	Forest Glen, Seneca, Strathmore, Cabin John
11:45 am – 12:00 pm	<b>Lecture 15:</b> Where Do We Go From Here? Presentation of Plan for Continued Mentoring, Engagement and Course Evaluation over Two-Year Period <i>Course Directors</i>	Forest Glen
12:00 pm	Adjourn	

**Training in Neurotherapeutics Discovery and Development  
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Program Director and Faculty List**

**Program Directors**

**Marcia Glicksman, PhD**

Co-Director, Lab for Drug Discovery in Neurodegeneration  
Harvard NeuroDiscovery Center  
Assistant Professor, Department of Neurology  
Brigham & Women's Hospital  
65 Landsdowne St.  
Cambridge, MA 02319

**Michael Rogawski, MD, PhD**

Professor  
Department of Neurology  
University of California, Davis  
4860 Y St., Suite 3700, Rm. 3715  
Sacramento, CA 95817

**Karl Scheidt, PhD**

Associate Professor  
Department of Chemistry  
Northwestern University  
2145 Sheridan Rd.  
Evanston, IL 60208

**Barbara Slusher, PhD, MAS**

Director, NeuroTranslational Program  
Johns Hopkins Brain Science Institute  
855 N. Wolfe St., Suite 277  
Baltimore, MD 21205

## **Faculty**

### **Douglas Auld, PhD**

Novartis Institutes for Biomedical Research  
250 Massachusetts Ave.  
Cambridge, MA 02139

### **James Barrow, PhD**

Lieber Institute for Brain Development  
Johns Hopkins School of Medicine  
855 N. Wolfe St., Suite 273  
Baltimore MD 21205

### **William Bracken, PhD, DABT**

AbbVie  
Global Pharmaceutical Regulatory Affairs  
200 Abbott Park Rd., Dept PA70, Bldg. AP34-3  
Abbott Park, IL 60054

### **Sam Enna, PhD**

Department of Molecular and Integrative Physiology  
University of Kansas Medical Center  
3901 Rainbow Blvd., MS4016  
Kansas City, KS 66160

### **Rebecca Farkas, PhD**

Neuroscience Center  
NIH/NINDS  
6001 Executive Blvd., Rm. 2109  
Bethesda, MD 20892

### **William Janzen, BS**

Division of Medicinal Chemistry and Natural Products  
University of North Carolina  
Campus Box 7363  
Chapel Hill, NC 27599

### **Craig Lindsley, PhD**

Department of Pharmacology  
Vanderbilt University Medical Center  
1205 Light Hall  
Nashville, TN 37232

**Kennan Marsh, PhD**

AbbVie  
Experimental Sciences  
100 Abbott Park Rd.  
Abbott Park, IL 60045

**Kalpana Merchant, PhD**

Eli Lilly and Company  
Indianapolis, IN

**Shai Silberberg, PhD**

NIH/NINDS  
Neuroscience Center  
6001 Executive Blvd., MSC 9521  
Bethesda, MD 20892

**Adaline Smith, PhD, DABT**

Preclinical Development  
Ironwood Pharmaceuticals  
301 Binney St.  
Cambridge, MA 02142

**Kenneth Weber, PhD**

Kilpatrick Townsend  
Two Embarcadero Center, 8th Floor  
San Francisco, CA 94111

**Janet Wolfe, PhD**

Wolfe Laboratories, Inc.  
134 Coolidge Ave.  
Watertown, MA 02472



**Training in Neurotherapeutics Discovery and Development  
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Attendee List**

**Ryan Altman, PhD**

Assistant Professor  
Medicinal Chemistry Department  
University of Kansas  
4046A Malott Hall  
1251 Wescoe Hall Dr.  
Lawrence, KS 66045

*Fluorinated Peptide Probes to Modulate Biophysical Properties of Neuropeptides*

**Noelle Anastasio, PhD**

Postdoctoral Fellow  
Center for Addiction Research  
University of Texas Medical Branch  
301 University Blvd., Route 0615  
Galveston, TX 77555

*Novel Serotonergic Strategy for the Treatment of Addiction*

**Matthew Banghart, PhD**

Postdoctoral Fellow  
Neurobiology Department  
Harvard Medical School  
220 Longwood Ave.  
Boston, MA 02115

*Biased Allosteric Modulators of the Kappa Opioid Receptor for Analgesia without  
Dysphoria*

**Melissa Barker-Haliski, PhD**

Senior Research Analyst  
Anticonvulsant Drug Development Program  
University of Utah  
417 Wakara Way, Suite 3211  
Salt Lake City, UT 84108

*Restoring Alzheimer's disease-induced Arc mRNA-dependent memory deficits with PatA*

**Bruno Benitez, MD**

Research Instructor  
Department of Medicine  
Washington University in Saint Louis  
6<sup>th</sup> Floor Southwest Tower, Room 644  
660 S. Euclid Ave.  
Saint Louis, MO 63110  
*Cell-Based High-Throughput Screening Assay for a NCL*

**Joshua Dunaief, MD, PhD**

Associate Professor  
Ophthalmology Department  
University of Pennsylvania  
Stellar Change Labs, Room 305  
422 Curie Blvd.  
Philadelphia, PA 19104  
*Iron chelation for neuroprotection of the retina and brain*

**David Graber, PhD**

Research Associate/Instructor  
Pathology Department  
Geisel School of Medicine at Dartmouth  
One Medical Center Dr.  
Lebanon, NH 03756  
*Developing Therapeutic Inhibitors of Parenchymal Neuroinflammation with Phenotypic Screening System*

**Ye Han, PhD**

Postdoctoral Fellow  
Department of Neurology  
Northwestern University  
303 E. Chicago Ave.  
Chicago, IL 60611  
*Drug development of a novel class of antidepressants*

**Rachel Hartley, PhD**

Postdoctoral Fellow  
Center for Addiction Research  
University of Texas Medical Branch  
301 University Blvd.  
Galveston, TX 77555  
*Modulation of the Serotonin 2C Receptor for the Treatment of Cocaine Addiction*

**Adam Hartman, MD**

Assistant Professor  
Neurology Department  
Johns Hopkins Medicine  
Meyer 2-147  
600 N. Wolfe St.  
Baltimore, MD 21287

*Metabolism-based therapy for seizures*

**Thomas Heinbockel, PhD**

Associate Professor  
Department of Anatomy  
Howard College of Medicine  
520 W. St., NW  
Washington, DC 20059

*Development of Novel Anxiolytic and Anticonvulsant Drugs*

**Yangzhong Huang, MD, PhD**

Senior Research Associate  
Department of Neurobiology  
Duke University Medical Center  
405 Bryan Research Dr.  
Durham, NC 27710

*Targeting TrkB Signaling for Prevention of Temporal Lobe Epilepsy*

**Dan Kaufmann, PhD**

Postdoctoral Research Associate  
Pharmacology and Toxicology Department  
University of Utah  
417 Wakara Way, Suite 3211  
Salt Lake City, UT 84108

*The Preclinical Evaluation Sec-Butyl Propylacetamide (SPD): A Novel Amide of Valproic Acid Analogue*

**Mei-Chuan Ko, PhD**

Professor  
Physiology and Pharmacology Department  
Wake Forest University School of Medicine  
Medical Center Blvd., 234 NRC  
Winston-Salem, NC 27157

*NOP-related Ligands as Analgesics*

**David Kokel, PhD**

Assistant in Medicine

CVRC

Massachusetts General Hospital, Harvard Medical School

149 13<sup>th</sup> St., 4<sup>th</sup> Floor

Charlestown, MA 02124

*Behavior based neuroactive drug discovery in the zebrafish*

**Jun-Xu Li, PhD**

Assistant Professor

Pharmacology and Toxicology Department

University at Buffalo, SUNY

102 Farber Hall

3435 Main St.

Buffalo, NY 14214

*Agmatine as a potential treatment for methamphetamine abuse*

**Patricia Maciel, PhD**

Associate Professor

Life and Health Sciences Research Institute

University of Minho School of Health Sciences

Campus de Gualtar

Braga, 4710-057 Portugal

*Development of therapeutic strategies for spinocerebellar ataxia type1*

**Karla-Sue Marriott, PhD**

Associate Professor

Chemistry & Forensic Science Department

Savannah State University

Drew Griffith 224

3219 College St.

Savannah, GA 31404

*Synthesis of Selective Neurotherapeutic Ligands*

**Cecilia Marzabadi, PhD**

Professor

Chemistry & Biochemistry Department

Seton Hall University

400 S. Orange Ave.

South Orange, NJ 07079

*A New Class of Carbohydrate-based Anticonvulsants*

**Martin Muller, MD**

Postdoctoral Associate

Department of Obstetrics, Gynecology & Reproductive Sciences

Yale University School of Medicine

PO Box 208063

333 Cedar St.

New Haven, CT 06520

*Synthetic PreImplantation Factor`s Role in Treatment of Encephalopathy of Prematurity*

**Tristano Pancini, PhD**

Postdoctoral Fellow

Vanderbilt Center for Neuroscience Drug Discovery

Vanderbilt University Medical Center

1205 Light Hall

Nashville, TX 37232

*Characterization of M4-PAMs in Huntington's Disease*

**Irfan Qureshi, MD**

Assistant Professor

Neurology & Medicine Department

Albert Einstein College of Medicine

1410 Pelham Parkway S., Suite 401

Bronx, NY 10461

*Developing Compounds that Modulate REST for Treatment of Ischemic Stroke*

**Kristen Rahn, PhD**

Postdoctoral Fellow

Department of Psychiatry

Johns Hopkins University School of Medicine

Pathology 627

600 N. Wolfe St.

Baltimore, MD 212187

*Improving Treatment of Pediatric Major Depressive Disorder*

**Rana Rais, PhD**

Postdoctoral Fellow

Brain Science Institute

Johns Hopkins University

855 N. Wolfe St.

Baltimore, MD 21205

*Delivery of 2-phosphonomethyl pentanedioic acid (2-PMPA) to the brain via intranasal route*

**Shivraj Sohur, MD, PhD**

Assistant in Neurology  
Neurology Department  
Massachusetts General Hospital  
15 Parkman St., 735 WACC  
Boston, MA 02114

*Using Developmental Cues to Identify Small Molecule Therapeutics for Parkinson's Disease*

**Naoki Suzuki, MD, PhD**

Postdoctoral Fellow  
Stem Cell & Regenerative Biology  
Harvard University  
Sherman Fairchild Biochemistry Building  
7 Diversity Ave.  
Cambridge, MA 02138

*Drug screening for ALS using human ES/iPS cells*

**Mary Torregrossa, PhD**

Assistant Professor  
Department of Psychiatry  
University of Pittsburgh  
450 Technology Dr., Room 228  
Pittsburgh, PA 15219

*Relapse Prevention for Addictive Disorders*

**Paul Trippier, PhD**

Assistant Professor  
Department of Pharmaceutical Sciences  
School of Pharmacy  
Texas Tech University Health Sciences Center  
1300 S. Coulter St.  
Amarillo, TX 79106

*Expanding the role of GSK3 inhibitors: Pediatric Neuromuscular Disorders*

**Kyle Wilcox, PhD**

Postdoctoral Fellow

Neurobiology Department

Northwestern University

4-160 Hogan

2205 Tech Dr.

Evanston, IL 60208

*HTS to Block ABO Binding to Nanodisc-Solubilized Synaptic Membrane Proteins*

**Ashkann Younai, PhD**

Postdoctoral Researcher

Department of Chemistry

Northwestern University

2145 Sheridan Rd.

Evanston, IL 60208

*Applying N-Heterocyclic Carbenes Towards the Synthesis of New Antipsychotic Drugs*

**Lecture 1: Target and Pathway Interrogation**

*Douglas Auld, PhD, Novartis Institutes for Biomedical Research*

This talk will cover key concepts and methods when attempting to study a target or pathway using low-molecular compound screening approaches. The talk will provide an overview of integrated lead finding, reverse and forward chemical genomic approaches, and definitions with a few examples of the types of assays used to develop a critical path in drug discovery. Complexities underlying cell-based (phenotypic) assays will be exemplified and strategies to generate hypothesis both pre- and post-HTS using annotated compound collections will also be covered.



## Lecture 2: William Janzen

### Biology Basics

Abstract: The transition from a target to a hit compound can take many paths. This lecture will discuss basic principles of drug and probe discovery and the techniques and terminology used in this segment of discovery. Because alternate approaches are covered in another lecture, we will focus on high throughput screening (HTS) approaches. HTS is capable of generating massive quantities of data but without a good understanding of assay cascade and mechanisms for minimizing and recognizing false positives, exciting compounds may be lost in the noise.

The assay is the most basic part of any hit discovery project. Whether you are applying HTS, computational analysis or co-factor analogs, you cannot measure differences without a valid cascade of assays to support hit progression. Assay development principles will be discussed, including detection technologies and logistics as well as the importance of assay validation.

### Hit to Lead to Candidate

Once a drug target has been identified and assays developed, *hits* (compounds with confirmed activity at the target) are obtained from many sources – often from high-throughput screening. Drug discovery scientists investigate the hits by obtaining or synthesizing related compounds and evaluating them in a battery of more and more stringent assays and filters. If potency, selectivity, and in vivo activity can be improved, a series of structurally related compounds (*leads*) emerge. Optimization usually requires iterative synthesis and testing of hundreds to thousands of molecules before a single molecule with all the desired properties is identified as a *candidate* for extensive safety testing to support human clinical trials. To facilitate the process of moving from hit to lead to candidate, a research operating plan containing relevant assays is developed. A research operating plan is like a funnel that uses high-throughput assays at the beginning to quickly winnow out compounds with poor potential for success. As compounds pass through these initial filters, more involved (expense and time) assays are used to further highlight strengths and weaknesses of compounds. Key aspects of the plan usually include a high-throughput biochemical assay and a cell-based functional assay that confirms the initial result in a more relevant cellular setting. Selectivity is also evaluated versus related targets and common “anti-targets” predictive of the overall safety of a compound. Pharmacokinetics and brain penetration potential are first explored using simplified in vitro assays such as microsome stability and transporter propensity. Select compounds are then checked for appropriate free exposure in the blood and brain before evaluating in biomarker and efficacy studies. When a compound is prepared and evaluated that pass all the criteria in the research operating plan, it is nominated as a candidate for extensive safety testing prior to evaluation in humans.

## **Lecture 4: Medicinal Chemistry**

Craig Lindsley, PhD  
Vanderbilt University Medical Center

This lecture will provide an overview of medicinal chemistry and the role of the CNS medicinal chemist. After the overview, we will dive into a real world case study, GlyT1 inhibitors, and walk through all of the issues and challenges in developing a nascent target from HTS to clinical candidate, as well as development of a biomarker strategy. Finally, we will discuss GPCRs, orthosteric vs. allosteric mechanisms to modulate their activity and issues/caveats in CNS drug discovery pertaining to receptor reserve, shallow SAR, 'molecular switches' and biomarkers.

## **Lecture 5: ALTERNATIVE APPROACHES TO LEAD GENERATION**

S.J. Enna, PhD

University of Kansas Medical Center

Historically, drug discovery was chiefly an empirical enterprise, with the shift to a more hypothesis-driven approach occurring in the 20<sup>th</sup> century. Whereas originally drug discovery was focused primarily on identifying therapeutically useful agents prior to defining their mechanisms of action, it is now more common to develop a target-selective compound before assessing its potential clinical utility. Too often this yields ligands that are useful as research tools, but worthless as therapeutics. Although the emphasis on target identification, or "targephilia", has yielded novel pharmaceuticals, it does not appear to have facilitated the drug discovery process overall, especially for compounds to treat central nervous system (CNS) disorders. In part, this is because the targephilic approach requires a keen understanding of the relationship between the target and organ system physiology, and the availability of in vivo and in vitro test systems that reliably predict human responses. The fact that the majority of CNS drugs have been identified empirically indicates the lack of knowledge about basic neurobiological processes and human behavior make drug discovery in this area less amenable to a target-based approach than for other types of therapeutics. Improving the success rate in CNS drug discovery requires a more pharmacometric-based strategy, with an emphasis on defining basic CNS function in intact animals and a more systematic in vivo behavioral analysis of novel chemical structures. Efforts should also be directed toward defining the sites of action of existing CNS drugs to aid in the design of second-generation agents and toward examining the CNS responses to drugs approved for other uses. Such a program requires a greater balance between, and integration of, pharmacometric and molecular techniques to maximize the contributions of both science and serendipity in drug discovery.

## Lecture 6: ADME: Absorption + Distribution + Metabolism + Excretion = Pharmacokinetics

Kennan Marsh, PhD  
AbbVie Inc.

Absorption, Distribution, Metabolism, Excretion (ADME) are the terms used to describe the behavior of a drug following administration to animals or man. These terms also highlight the barriers in the development of an efficacious drug. Together, the terms are integrated into the **pharmacokinetics** of a compound - the quantitation of the time course of a drug and its metabolites in the body. Using preclinical examples, this presentation will introduce the basic terms and concepts in pharmacokinetics, with a focus on understanding the integration and interdependencies of ADME characteristics. Pharmacokinetic considerations for compound screening and compound development activities will be discussed. The expectations from regulatory authorities (e.g. FDA, EMA) as related to ADME/PK characterization of new compounds for IND/CTA as well as NDA/MAA filings will be outlined.

It's all about dose.....Nonclinical Safety Assessment During Drug Development

Adaline C. Smith, PhD, DABT Senior Director, Toxicology, Ironwood Pharmaceuticals, Cambridge, MA

Nonclinical toxicology studies are critical during drug development because there is a scientific need and regulatory requirement to collect information which defines the toxicity profile and provides an evaluation of the relationship of dose and exposure to toxicity/safety of an investigational therapeutic in order to inform human risk before and during clinical development. Safety concerns (based on observed animal and human toxicities) are responsible for the majority of drug terminations and the evaluation of the toxicities in animals is useful in identifying and characterizing potential human toxicities. Toxicity assessments are initiated during drug discovery to identify key risks and provide an estimate of the nonclinical safety window before selection of a candidate molecule. Investigational New Drug (IND)-enabling toxicology studies are conducted after the selection of a candidate molecule under Good Laboratory Practice (GLP) regulations to inform the first-in-human and early clinical studies. Depending on the clinical development plan for a specific therapeutic and indication, additional toxicology studies are conducted to support the initiation of larger clinical trials and chronic dose administration as well as to evaluate risks related to potential reproductive and developmental toxicity and carcinogenicity. All the data from nonclinical toxicology studies that is collected before and during clinical development support a New Drug Application (NDA) submitted to regulatory authorities for the marketing of a new therapeutic. Nonclinical safety assessment is an integral component of drug development which provides information that defines potential human risks to inform safe clinical development and marketing of drugs.

## Lecture 9: IND Enabling Studies and Preparation of the IND

William Bracken, PhD

AbbVie

Preparing for submission of an IND to initiate human clinical trials involves three parallel streams of activities that interweave at various points during the development process: Efficacy, Safety and Quality. The objective of the submission is multifold: 1) demonstrate a plausible hypothesis supporting the proposed mechanism of pharmacological action, 2) demonstrate an understanding of safety concerns through the conduct of nonclinical studies that identify the adverse effect profile using both in vitro and in vivo study designs, establish a link between pharmacodynamics actions and drug concentrations (e.g., plasma drug concentrations) and adverse toxicologic effects and drug concentrations to understand the dose-related nature of the findings, and 3) demonstrate that a tightly controlled process for the drug form to be tested in humans has been developed to assure that a patient receives the same drug performance and attributes from batch to batch. Scientific evidence verifying each stream is developed and presented by a Sponsor to FDA or other regulatory agencies to support initiation of human clinical trials.

Ongoing efforts to globally harmonize the drug development processes has resulted in availability of the Common Technical Document (CTD) to support submission to regulatory agencies for both initiation of human clinical studies as well as the drug application supporting product registration. The presentation of information should be unambiguous and transparent, in order to facilitate review of the basic data and to help the reviewer become quickly oriented to the application contents. The CTD is organized in five modules: 1) Administrative Information specific to each region, 2) Summary documents, with specific sections for nonclinical, clinical and quality (manufacturing) components that highlight the main attributes of the investigational drug, 3) Quality, a section containing detailed information on drug substance and drug product manufacture as well as supporting data for process controls, 4) Nonclinical Study Reports contains individual reports for pharmacology, pharmacokinetic and toxicology studies, and 5) Clinical Study Reports contains reports and documentation of the human clinical trials. One can easily understand the value of a consistent approach to document preparation for an agency reviewer who is asked to review applications from multiple sponsors and multiple countries.

## **Lecture 11: Formulation and Route of Administration**

Janet Wolfe, PhD  
Wolfe Laboratories, Inc.

The formulation of an experimental therapeutics is an essential part of effective drug discovery and development. This module will give an overview of the benefits and limitations of various routes of administration and will then address formulation strategies that enable the drug discovery and early development process. Particular focus will be paid to methods to solubilize small molecules to maximize exposure via various routes of administration, thus allowing informed decision making on efficacy and safety.

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## **Lecture 12: Rigor in Translational Drug Discovery and Development**

Shai Silberberg, PhD  
NIH/NINDS

The quality of research depends on the rigor with which researchers conduct studies and control for potential biases. Recent publications and meetings have focused on the observation that published research results are often not reproducible. Although there are many possible causes for this problem, poor experimental design and inadequate reporting of research methodologies appear to be significant contributing factors. Evidence for this deduction will be presented, as well as actions taken by NIH and publishers to address the issues.



## **Lecture 14**

### **Funding Academic Drug Discovery**

Rebecca Farkas, PhD

The NIH supports drug discovery and development for nervous system disorders through a variety of programs. Some provide funding through grants or cooperative agreements to support specific stages of research and development, for particular disease areas. Others offer in-kind support from NIH drug discovery and development contracts or through collaborations with NIH-funded research centers or intramural labs. Examples of current programs will be presented, along with advice based on program directors' observations from study section reviews of hundreds of translational applications. Potential applicants are encouraged to contact program directors to discuss the best funding mechanism for their needs and strategies for developing a strong application.