The Search for an Ideal Analgesic

The NIH Pain Consortium and Translational Medicine Program

Linda L. Porter, Ph.D.

no conflicts
The NIH Pain Consortium
1996-2012
Pain Consortium Members

National Cancer Institute
National Institute on Aging
National Institute on Alcohol Abuse and Alcoholism
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Biomedical Imaging and Bioengineering
National Institute of Child Health and Human Development
National Institute on Deafness and Other Communication Disorders
National Institute of Dental and Craniofacial Research
National Institute of Diabetes and Digestive and Kidney Disorders
National Institute on Drug Abuse
National Institute of General Medical Sciences
National Institute of Mental Health
National Institute of Neurological Disorders and Stroke
National Institute of Nursing Research
National Heart Lung and Blood Institute
National Center for Research Resources
National Center for Complementary and Alternative Medicine
John E. Fogarty International Center
Warren Grant Magnuson Clinical Center
  Office of Behavioral and Social Sciences Research
  Office of Technology Transfer
  Office of Research on Womens Health
  Office of Rare Diseases
The NIH Pain Consortium

Co-Chairs of the Consortium

Dr. Josephine Briggs, Director, NCCAM
Dr. Patricia A. Grady, Director, NINR
Dr. Story Landis, Director, NINDS
Dr. Martha Somerman, Director, NIDCR
Dr. Nora Volkow, Director, NIDA
The NIH Pain Consortium

Goals of the Consortium

- develop a comprehensive/long term pain research agenda across NIH
- identify key opportunities in pain research
- pursue the pain research agenda through public–private partnerships
- increase visibility for NIH pain research
NIH Funding for Chronic Pain Research

<table>
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<th>Year</th>
<th>$ millions</th>
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<tr>
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NIH Pain Research Portfolio

- Basic Research, 33%
- Clinical Research, 37%
- Translational Research, 11%
- Comparative Effectiveness Research, 4%
- Epidemiology, 6%
- Health Disparities, 5%
- Training, 4%

2008-2010 Source: NIH RePORT report.nih.gov
The NIH Pain Consortium Activities

Initiatives

- Blueprint
- Common Fund
- Pain Consortium ICs

Website

painconsortium.NIH.gov

Annual Pain Consortium Symposium

Workshops

Portfolio Analysis

Advocacy, Reporting, Training, Interagency Activities, Online publications
Pain Consortium Initiatives

NCCAM Intramural Partnerships on Mechanistic Research on Central Processing of Pain
Preliminary Clinical Studies in Preparation for Large Interventional Trials of CAM Therapies
Biology of Manual Therapies

Fostering the Development of Interdisciplinary Team Science for the Study of Interstitial Cystitis/Painful Bladder Syndrome
Vulvodynia - Systematic Epidemiologic, Etiologic or Therapeutic Studies
Neurobiology of Migraine
Mechanisms, Measurement, and Management of Pain in Aging: from Molecular to Clinical
Mechanisms, Models, Measurement, & Management in Pain Research
Mechanistic Studies of Pain and Alcohol Dependence
Biomechanisms of Peripheral Nerve Damage by Anti-Cancer Therapy
NIDCR Institutional Career Development Award for Enhancing Research Capacity in TMJD and Orofacial Pain
NINR Pain Methodologies Boot Camp
Leveraging Existing Data or Longitudinal Studies to Evaluate Safety and Effectiveness of Pharmacological Management of Chronic Pain in Older Adults
Collaborative Research on the Transition From Acute to Chronic Pain: New Models and Measures in Clinical and Preclinical Pain Research
Pain Consortium
Highlighted Initiatives

The NIH Blueprint Grand Challenge on Pain

NIH Pain Consortium
Centers of Excellence in Pain Education

Common Data Elements for Headache Research
The 7th Annual Pain Consortium Symposium on Advances in Pain Research

Advancing Pain Therapies
May 29 and 30, 2012
Further information and registration: http://www.cvent.com/d/2cq0dk

The FDA Workshop
Assessment of Analgesic Treatment of Chronic Pain – A Scientific Workshop
May 30 and 31, 2012
Further information and registration
http://www.fda.gov/Drugs/NewsEvents/ucm283979.htm

Videocast.nih.gov
Secretary DHHS engage the IOM for activities

- increase the recognition of pain as a significant public health problem, evaluate the adequacy of assessment, diagnosis, treatment, and management of pain, identify barriers to appropriate pain care, establish an agenda for public and private sectors to reduce barriers and improve the state of pain care research, education, and clinical

  NIH sponsored IOM report “Relieving Pain in America”

- The Pain Consortium be required to make recommendations on pain research initiatives that could be supported by the Common Fund
  - annual effort

- Secretary DHHS to establish an interagency pain research coordinating committee
  - first meeting in March 2012

- Director NIH is encouraged to continue and expand, through the Pain Consortium, an aggressive program of basic and clinical research on the causes of and potential treatments for pain
2011 IOM Report Recommendations for NIH

• Increase support for interdisciplinary research in pain
• Increase the conduct of longitudinal research in pain
• Increase the training of pain researchers
• Designate a lead institute at the NIH responsible for moving pain research forward, and increase the support for and scope of the Pain Consortium
2011 IOM Report
Recommendations for NIH

- Improve the process for developing new agents for pain control
  - NIH Symposium/FDA Workshop 2012
  - Drug development, translational research programs
  - NCCATS
Interagency Pain Research Coordinating Committee

“federal advisory committee created by the DHHS to enhance pain research efforts and promote collaboration across the government, with the ultimate goals of advancing fundamental understanding of pain and improving pain-related treatment strategies”

• Develop a summary of advances in pain care research supported or conducted by the Federal agencies relevant to the diagnosis, prevention, and treatment of pain and diseases and disorders associated with pain.

• Identify critical gaps in basic and clinical research on the symptoms and causes of pain.

• Make recommendations to ensure that the activities of the NIH and other Federal agencies are free of unnecessary duplication of effort.

• Make recommendations on how best to disseminate information on pain care.

• Make recommendations on how to expand partnerships between public entities and private entities to expand collaborative, cross-cutting research.
NIH Translational Research Programs

• Common Fund Resources
• Blueprint Resources
• NCATS
• Institute and Center Programs
  • Intramural
  • Extramural
Small molecules are extremely important to explore molecular, cellular, and in vivo function and for treating diseases. Most medicines marketed today are from this class.

A key challenge is to identify small molecules effective at modulating a biological process or disease state. Researchers must systematically screen tens of thousands of small molecules to find a match between a chemical and its target through high-throughput screening. The capacity for HTS exists in the pharmaceutical and biotechnology sectors for drug development, but similar resources have not been available in the public sector.

The program offers access to large-scale screening capacity necessary to identify small molecules that can be optimized as chemical probes to study the functions in health and disease and facilitate the development of new drugs, by providing early stage chemical compounds to researchers in the public and private sectors for validation of new drug targets.

The Molecular Libraries Program has three components
Molecular Libraries Probe Production Centers Network

- A consortium of small molecule screening centers to produce innovative chemical tools for use in biological research.
- Performs HTS on assays provided by the research community, against a large library of small molecules maintained in a central repository.
- Performs optimization chemistry required to produce useful \textit{in vitro} chemical probes (research tools for the targets or phenotypes studied in the assays) from the “hits” identified in the initial screening.
- A \textbf{collection of 350,000 chemically diverse small molecules} some with known biological activities and others with potential to modulate novel biological functions. The collection will be expanded.
Molecular Libraries Network Members

- Broad Institute Comprehensive Screening Center
- Sanford Burnham Center for Chemical Genomics
- NIH Chemical Genomics Center NCATS intramural
- The Scripps Research Institute Molecular Screening Center
- Johns Hopkins Ion Channel Center
- University of New Mexico Center for Molecular Discovery
- Southern Research Specialized Biocontainment Screening Center
- Kansas Specialized Chemistry Center
- Vanderbilt Specialized Chemistry Center for Accelerated Probe Development
Common Fund Molecular Libraries and Imaging

Pub Chem

- Data from the Molecular Libraries Network are placed into PubChem and are available to researchers in public and private sectors for studying biology and disease.

- PubChem. A comprehensive database of chemical structures and their biological activities developed by the National Center for Biotechnology Information at NIH. PubChem houses both compound information from the scientific literature as well as screening and probe data from the MLPCN.
the ultimate goal of the Molecular Libraries Program is unachievable with current technologies. Therefore, the Molecular Libraries Program is devoted to technology development in the following three areas:

- **Chemical Diversity.** supports the development of new and diverse chemical libraries for screening in the MLPCN centers, as well as new methods for producing, isolating, characterizing, and modifying natural products.

- **Assay diversity.** supports the development of an evolving stream of novel and outstanding assays that can be automated and used for screening small molecules within the Molecular Libraries Probe Production Centers Network. The aim of this effort is to enable the design of pharmacologic tools to explore cellular and physiological function.

- **Instrumentation.** This area supported the development of new methods for high-throughput measurement of novel biological assays.
Access to the MLSPN

Access

• Investigators who have a HTS-ready assay, a potentially HTS-compatible assay, or a validated screening hit, are a PI of an existing assay grant, or want to submit compounds to the Molecular Libraries Small Molecule Repository, can apply through appropriate FOAs.

Benefits for an assay provider

• Obtain a small molecule probe with characteristics specified in your proposal, which includes the primary HTS screen and follow-up cheminformatics/informatics and medicinal chemistry.
• free or minimal costs to the assay provider.
• access to one of the largest screening collections, including a collection of known bioactives, a range of novel chemical classes sourced from the academic community, and a diverse set of commercially available compounds.
NIH Blueprint Neurotherapeutics Grand Challenge: Discovering Novel Drugs for Disorders of the Nervous System

• Most nervous system disorders lack effective treatment
• Researchers often lack resources to develop novel therapeutics strategies to where they can attract industry interest

• Pharmaceutical companies hesitate to invest in neurotherapeutics development because there are few validated targets or strategies, a long record of failure, and often small populations

The Blueprint Neurotherapeutics Network

A program to bridge the gap in drug development between academic and industry research. The Network offers neuroscience researchers a "virtual pharma" to develop compounds from chemical optimization through Phase I clinical testing
The Blueprint Neurotherapeutics Network

• **Who:** Researchers in possession of assays and small molecule compounds that show promise for treating nervous system and psychiatric disorders, but are not yet suitable for clinical testing

• **What:** A unique opportunity for investigators working with small molecule compounds to access to a robust ‘virtual pharma’ network to discover neurotherapeutic drugs.

• **Awardees** become collaborative participants in the network.

• **How:** Funding (U01) to conduct biological testing of compound analogs in disease assays and models in the investigator’s laboratory.

• No-cost drug discovery services; medicinal chemistry optimization, IND-directed pharmacology and toxicology, and Phase I clinical testing.
Blueprint Neurotherapeutics Network

- Goal: phase I clinical success
- Target: nervous system indication
- Approach: “Virtual pharma” structure

**Lead Development Team**

- Principal investigator
  - Industry-Seasoned Consultants
  - NIH staff

**Bioactivity/Efficacy Studies**

**Medicinal Chemistry**

**PK/Tox**

**GMP/Formulation**

**Phase I Trials**

**U01s**

**NIH Contracts**

- Free access to drug development services + funding for biology
- For novices and experts seeking additional capacity
- PI retains control of IP

RFA-NS-13-003
Receipt Date: 10/8/12
The NCI experimental therapeutics program NExT: A Unique Partnership with the NCI to Facilitate Oncology Drug Discovery and Development

• The NExT Program, a new drug discovery and development pipeline, is a partnership to bring new cancer treatments to patients. Researchers in academia, government, and industry are eligible.

• Drug discovery and development projects enter an NCI pipeline focused on unmet needs in therapeutics that are not adequately addressed by the private sector.

• The NCI is committed to moving high-priority discovery and development projects through to proof-of-concept clinical trials.

• Entry into NExT can occur at any stage of the drug discovery or development pipeline
Stage for entries

- Completion of drug development
- Exploratory screen development and optimization
- Preclinical development for an agent with a specific molecular target
- A different formulation of your agent for it to be clinically useful
- Pharmaceutical-grade investigational drug to conduct clinical studies
- A pharmacodynamic assay or imaging technique to determine if your agent is modulating its target
- Proof-of-concept or first-in-human studies
- Other resources to support drug discovery and development
IC specific translational research programs

- NINDS cooperative program in translational research
- supports preclinical development and testing of new therapies for neurological disorders.
- supports preclinical optimization and testing of the leads through IND or IDE application.
- does not support early-stage therapeutic discovery activities such as screening.
- does not support clinical stages
All NIH Institutes: Small Business program

- SBA eligible biotech companies
- (RULES ARE CHANGING!)

- All levels of drug/device discovery and development (R41,42,43,44)

- Provides cooperative agreement funding (U44) to small businesses for the preclinical development and testing of novel therapeutics and devices, in preparation for an IND/IDE.
  - XT-101: A Novel and Potent Non-Opioid Treatment for Neuropathic Pain
NCATS

Division of Pre-Clinical Innovation

Bridging Interventional Development Gaps
Molecular Libraries Probe Production Center

Office of the Director

Designing a Tissue Chip for Drug Screening
Rescuing and Repurposing Drugs
NCATS BrIDGS

- Bridging Interventional Development Gaps provides resources for development of new therapeutic agents.
- Applicants receive no-cost access to NIH contractors who conduct preclinical studies: synthesis, formulation, pharmacokinetic and toxicology services to support IND.
- BrIDGs can support key steps or most of the development tasks needed to file an IND.
- NIH staff and principal investigators plan the studies. Contractors perform approved tasks. Development proceeds sequentially. One segment of the project (toxicology) may depend on completion of preceding segments (formulation).
- BrIDGs has lead to 12 successful INDs.
- any disease or disorder may be submitted, but therapeutic agents should have demonstrated activity in vivo effects.
Designing a Tissue Chip for Drug Screening

The current process for developing new drugs to treat and prevent disease is time and resource costly.

To streamline this process, NCATS is developing 3-D tissue chips to predict the performance of a candidate drug, vaccine or biologic agent quickly and inexpensively. These bio-engineered human tissue models, are being designed to detect signals of safety and effectiveness early in the translational pipeline.

Researchers can test candidate drugs in the tissue chips for signs of toxicity and determine which compounds are binding to their intended targets and exhibiting the desired activity. These chips might allow researchers to eliminate toxic and/or ineffective drugs early in the development process.

Tissue chips would be cellular and organ microsystems with a multicellular architecture representing the characteristics and functions of the tissue of origin. They could remain viable for several weeks when kept at the pH and temperature levels normally found in the human body.
Rescuing and Repurposing Drugs

- Small molecules and biologics whose development was abandoned before FDA approval
- Small molecules and biologics approved for human use in other diseases.

NCATS Pharmaceutical Collection

- NCATS is enhancing repurposing activities to organize available data on drugs and investigational compounds through the NCATS Pharmaceutical Collection, a publicly accessible database of small molecule compounds that have been approved and registered for human clinical trials.

NCATS and Eli Lilly: NCATS’ Pharmaceutical Collection of 3,800 approved and investigational medicines will be screened using Lilly’s Phenotypic Drug Discovery panel. The biological profiles of molecules may enable biomedical researchers to better predict treatment outcomes, improve drug development, and lead to more specific and effective approaches. All data generated through this effort will be deposited into PubChem.
**Pharmaceutical Collection** is a comprehensive, publicly accessible collection of approved and investigational drugs for high-throughput screening that provides a valuable resource for both validating new models of disease and better understanding the molecular basis of disease pathology and intervention. The NPC already has generated several useful probes for studying a diverse cross section of biology, including novel targets and pathways.

- **NCATS** currently possesses 3,800 molecules as part of its screening collection, which was sourced from traditional chemical suppliers, specialty collections, pharmacies and custom synthesis.