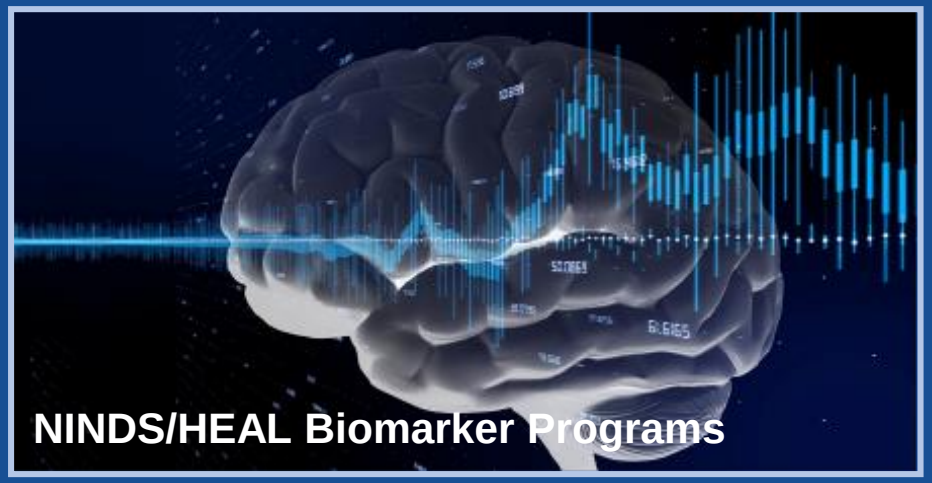
National Institute of Neurological Disorders and Stroke



New Biomarker Initiatives at NIH: Neurological Disorders and Pain

October 30, 2018

Mary Ann Pelleymounter, PhD
Program Director
mary.pelleymounter@nih.gov

About the Speaker

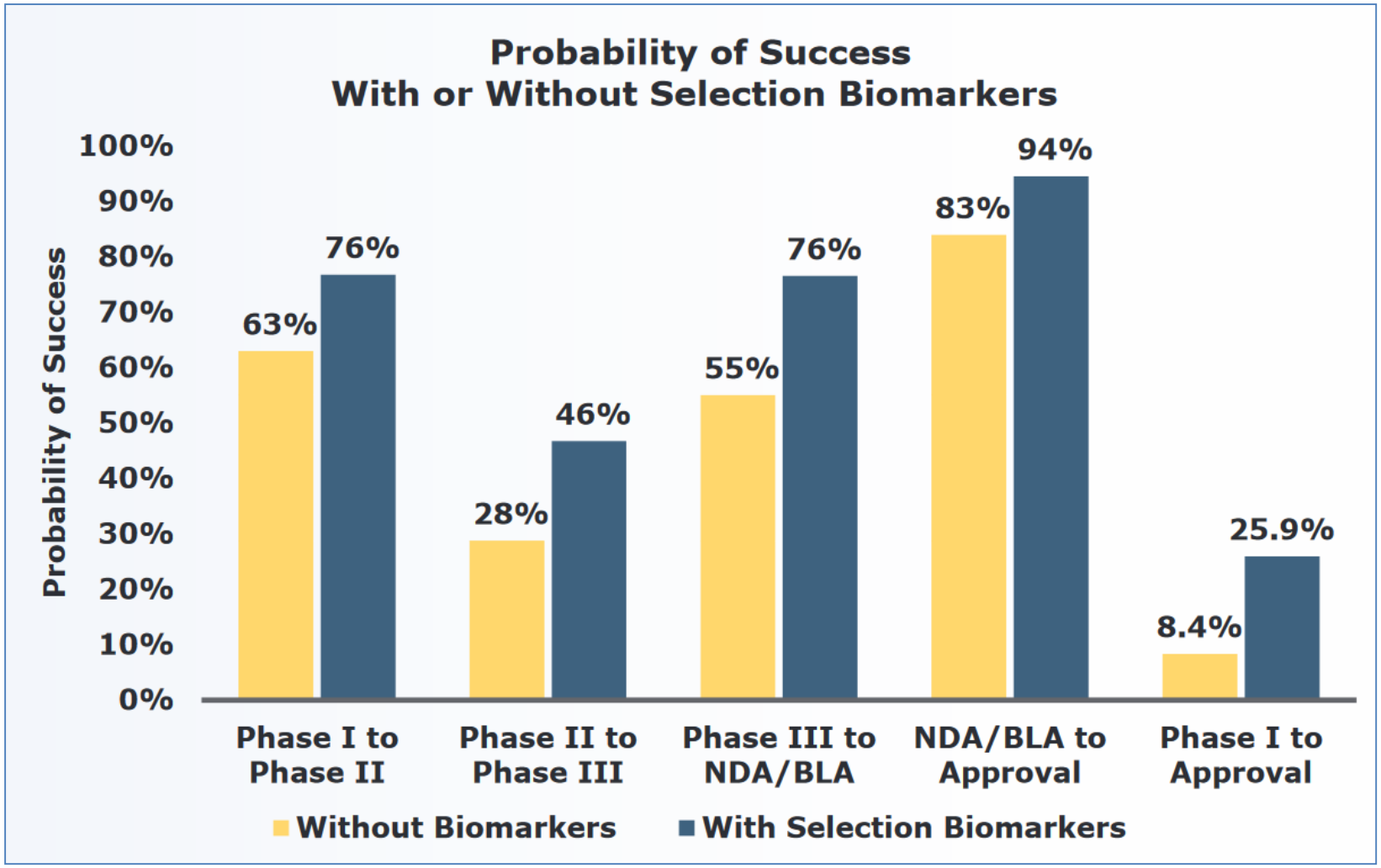
Dr. Pelleymounter is a Program Director in the Division of Translational Research at NINDS. She leads the new Biomarker Development Initiative at NINDS and is a scientific project manager for the Blueprint Neurotherapeutics program. She has over 25 years of experience in scientific research and over 20 years of experience in drug discovery and development. Mary Ann's scientific training is in the field of behavioral neuroscience with a focus on age-related cognitive dysfunction, neurodegeneration and neuropharmacology. Dr. Pelleymounter has over 60 published original research articles, reviews and book chapters and is the author of multiple published patents.

Mary Ann Pelleymounter, PhD
NINDS Program Director

Outline

- Importance of Validated Biomarkers
- Biomarker Development: Definitions and Process
- Neuroscience Biomarker Resources
- NINDS Biomarker Funding Opportunities
- Pain Biomarker Program: HEAL Initiative
- NIH Pain Biomarker Funding Opportunities
- Upcoming NIH Pain Biomarker Workshop

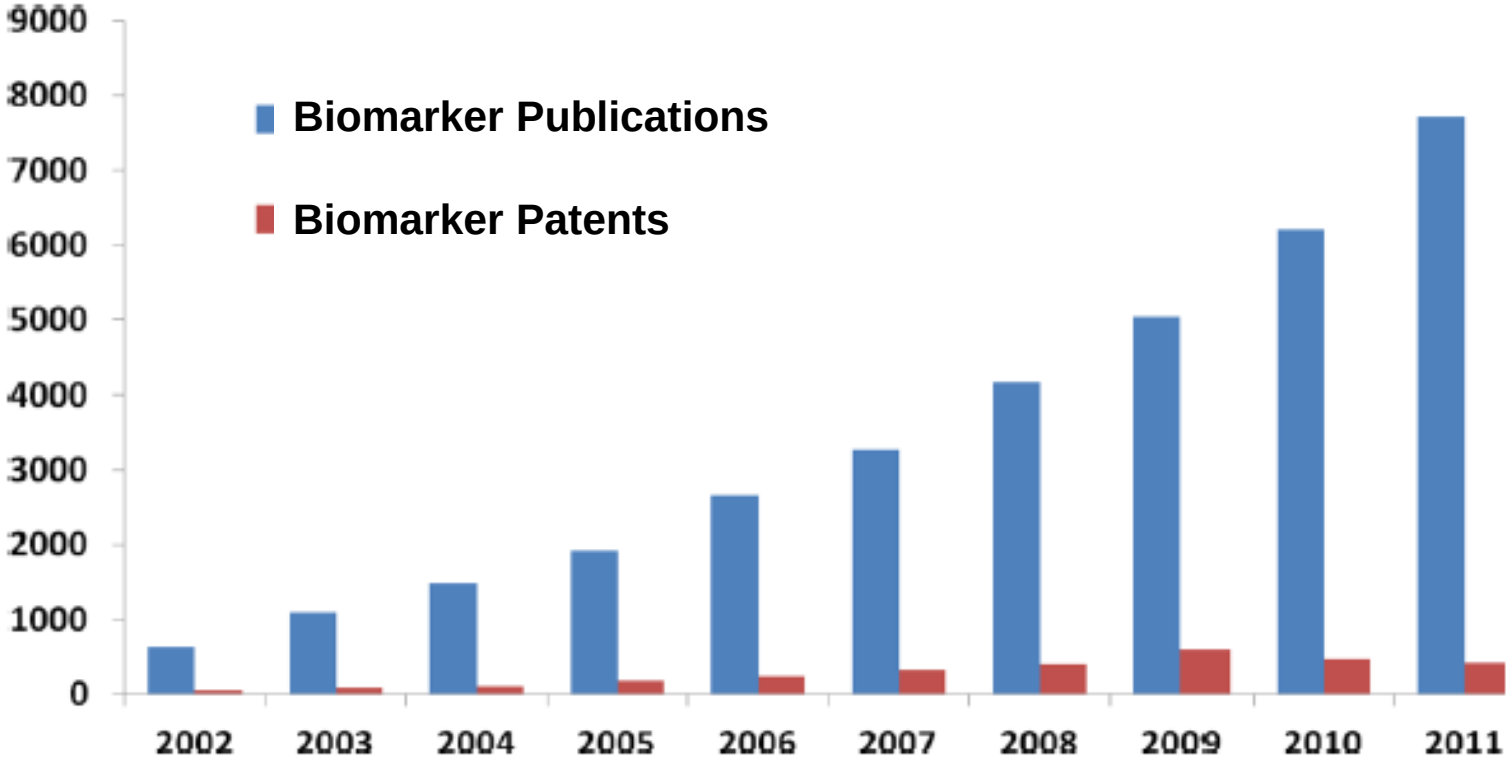
Biomarkers Significantly Improve the Probability of Successful Therapeutic Development



Thomas D.W., Burns J., Audette J., Carroll A, Dow-Hygelund C, Hay, M, Clinical Development Success Rates 2006-2015, Bio-Industry Analysis

National Institute of Neurological Disorders and Stroke

Few Biomarkers Progress from Discovery to Clinical Validation and Utility



Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Biomarkers Publikation	625	1087	1478	1920	2661	3270	4168	5033	6208	7720
Biomarker Patents	50	74	95	180	238	320	396	593	471	407

Drucker and Krapfenbauer, Pitfalls and limitations in translation from biomarker discovery To clinical utility in predictive and personalized medicine. The EPMA Journal 2013 4:7

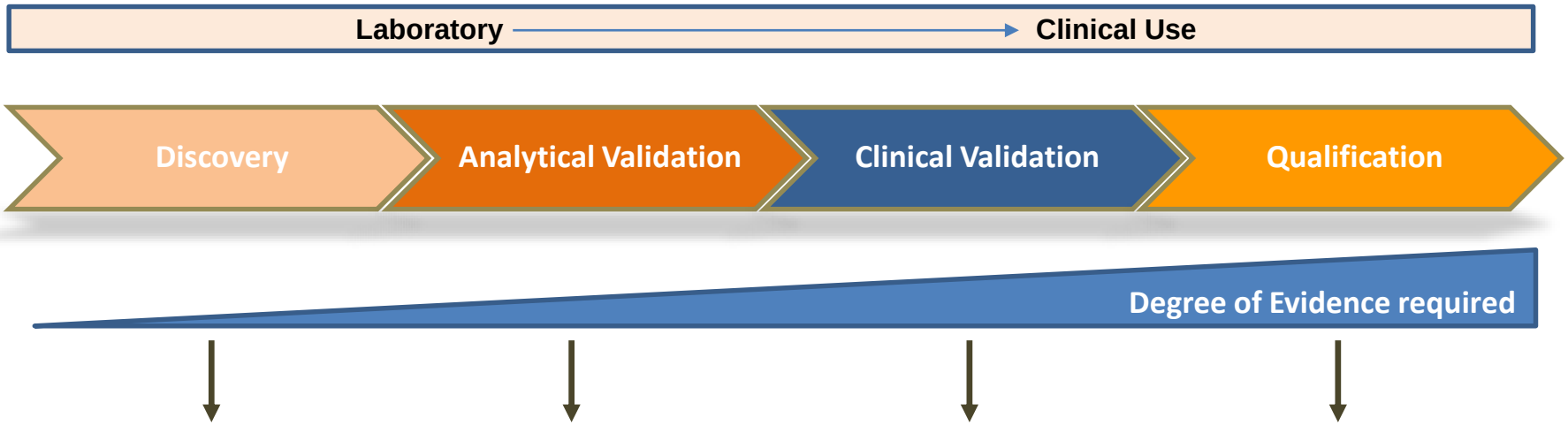
Advancing a Biomarker Candidate from Discovery Through Qualification

FDA-NIH Definitions

Biomarker: Indicator of a normal or pathological process or of a response to a therapeutic

Context of Use: Manner and purpose of use of a biomarker

Fit for Purpose: Refers to required degree of validation for intended use of biomarker



- ✓ Standardized sample source
- ✓ Bioinformatics
- ✓ Identification/POC
- ✓ Pilot Validation
- ✓ Detection Method

- ✓ Context of Use
- ✓ Establish acceptability of performance characteristics
- ✓ Precision, sensitivity, accuracy, dynamic range

- ✓ Large, prospective or retrospective clinical studies
- ✓ Context of Use
- ✓ Evaluate overall utility for clinical practice and drug development

- ✓ FDA review for qualification
- ✓ Within Context of Use, biomarker provides reliable application and allows specific interpretation

Analytical and Clinical Validation/Utility

Analytical Validation: Establishing that the performance characteristics of a measurement are acceptable in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol (which may include sample collection and standardization procedures).

The level of analytical rigor that is necessary depends upon the characteristics of the biomarker, the detection technology, the type of clinical question or its intended use as a biomarker (diagnostic, predictive, pharmacodynamic, etc).

Clinical Validation: Establishing that the biomarker acceptably identifies, measures or predicts the concept of interest.

Clinical Utility: The conclusion that a given use of a biomarker will lead to a net improvement in health outcome or provide useful information about diagnosis, treatment, management or prevention of a disease.

Use of the BEST (Biomarkers, EndpointS, and Other Tools Resource) standardized biomarker definitions is required
https://www.ncbi.nlm.nih.gov/books/NBK338448/

Neuroscience Biomarker Program

Goal: Facilitate the development of high quality biomarkers to improve the quality and efficiency of clinical research (Phase II and beyond)

Two Pillars:

- **Centralized NINDS "one-stop" web page** with links to all NINDS biomarker resources (including repositories) and public/private partnership opportunities
- **NINDS Funding opportunities** that support a rigorous, "fit for purpose" validation process.

Centralized NINDS "One-Stop" Resources Web Page

https://www.ninds.nih.gov/Current-Research/Focus-Tools-Topics/Biomarkers

Resources and Tools

Foundation for the National Institutes of Health Biomarkers Consortium
Brings together diverse partners around a common mission to develop promising biomarkers in order to help accelerate the delivery of successful new technologies, medicines and therapies for prevention, early detection, diagnosis and treatment of disease.

Consortiapedia
A searchable catalogue of nearly 500 profiles on research consortia. Includes information on mission, structure, data sharing, partners, ways to connect, and more.

Federal Interagency Traumatic Brain Injury Research (FITBIR)

NINDS Human Biomarkers Biospecimen and Data Repository (BioSEND)

NINDS Human Cell and Data Repository

FDA Draft Guidance for Industry: Enrichment Strategies for Clinical Trials
Provides draft guidance to industry on enrichment strategies that can be used in clinical trials intended to support effectiveness and safety claims in new drug applications (NDAs) and biologics license applications (BLAs).

Biomarkers, EndpointS, and other Tools (BEST) Resource Glossary
Clarifies terminology and uses of biomarkers and endpoints as they pertain to the progression from basic biomedical research to medical product development to clinical care. Developed by FDA and NIH to promote consistent use of biomarker terms and concepts, and thereby advance biomarker science.

NIH NeuroBioBank

Parkinson's Disease Data Management Resource (PDMR)

Funding Opportunities Supporting a "Fit for Purpose" Validation Process

Number	Title	Mechanism
PAR-18-550	Analytical Validation of a Candidate Biomarker for Neurological Disease*	U01
PAR-18-549	Analytical Validation of a Candidate Biomarker for Neurological Disease*	U44
PAR-18-664	Clinical Validation of a Candidate Biomarker for Neurological Disease*	U01
PAR-18-548	Clinical Validation of a Candidate Biomarker for Neurological Disease*	U44

Next application due dates **February 14, 2019; July 18, 2019*

- **Reviewed by NINDS Review Branch**

U01 = Research Project, Cooperative Agreements

U44 = Small Business Innovation SBIR Cooperative

All PARs are Clinical Trial Optional

U01 and U44 Cooperative Agreement Mechanisms

Extremely Clear, Quantitative and Definitive Milestones are Essential

Annual Go/No-Go Point at the end of each year

Transition occurs via Administrative Review

U01 and U44 Cooperative Agreement Mechanisms

Mechanism	Mechanism Name	Length	Budget
U01	Research Project, Cooperative Agreements	Up to 5 years	Not limited but must reflect the actual needs of the proposed project
U44	Small Business Innovation SBIR Cooperative Agreement	Phase I: Up to 2 years; Phase II: Up to 3 years	Phase I: Up to $700,000 per year; Phase II: Up to $1,500,000 per year. Must be reasonable and appropriate.

PAR-18-550 and PAR-18-549

Analytical Validation of a Candidate Biomarker for Neurological Disease

Goals

- To encourage rigorous analytical validation of candidate biomarker measures or endpoints in a manner that is consistent with FDA guidelines.
  - Evaluation of the assay, its performance characteristics, and the optimal conditions
- To facilitate the advancement of robust and reliable biomarkers to application in clinical trials and practice (Phase II clinical trials and beyond).

Entry Criteria

- Identified biomarker with a working hypothesis on context of use
- Developed method of detection, with further potential optimization
- Plans for management of pre-analytic variables
- Cogent biological rationale supporting the candidate biomarker
- Relevance to therapy development or clinical practice

PAR-18-550 and PAR-18-549

Examples of Appropriate Biomarker Analytical Validation Studies

- Determination of the accuracy, precision, sensitivity, dynamic range, specificity, etc. for the method of biomarker detection
- Harmonization of analytical performance if the assay is to be performed in multiple laboratories
- Establishment of appropriate quality control and improvement procedures
- The goal for analytical validation should be that the biomarker measurement meets FDA analytical performance criteria https://www.fda.gov/downloads/drugs/guidances/ucm368107.pdf within the scope of the intended Context of Use.

PAR-18-550 and PAR-18-549

Examples of Out-of-Scope Biomarker Analytical Validation Studies

- Natural history studies aimed at understanding disease pathophysiology, genetic, or epigenetic mechanisms
- Biomarker identification
- Initial development of the biomarker detection method (although it is recognized that optimization of that detection method will occur during the validation process)
- Therapeutic target identification
- Preclinical animal studies
- Development of candidate therapeutics
- Studies focused on clinical validation of a candidate biomarker

PAR-18-664 and PAR-18-548

Clinical Validation of a Candidate Biomarker for Neurological Disease

Goals

- To encourage rigorous clinical validation of a candidate biomarker using retrospective and/or prospective methods in a manner that is consistent with the purpose of the biomarker
- To facilitate the advancement of robust and reliable biomarkers to application in clinical trials and practice (Phase II clinical trials and beyond).

Entry Criteria

- Identified biomarker with a working hypothesis on context of use
- Analytical validation for the candidate biomarker should be completed and consistent with FDA standards
- Plans for management of pre-analytic variables
- Preliminary validation data
- Cogent biological rationale supporting the candidate biomarker
- Relevance to therapy development or clinical practice

PAR-18-664 and PAR-18-548

Examples of Appropriate Clinical Validation Studies

- Demonstration of association of the result of the biomarker assay with a clinical endpoint (e.g., survival, response, disease presence or absence) in samples or data from patients that have been exposed to a uniform intervention or that have or will develop a disease or disorder
- Definition of the sensitivity and specificity of the assay result within the context of the defined clinical endpoint and clinical population
- Estimation of the prevalence of the marker within subjects or patients for the intended clinical context
- Retrospective, well controlled, multi-site clinical studies using meta-analysis or multiple independent studies
- Prospective focused and randomized multi-site clinical studies
- Studies to characterize patient cohorts with biomarkers that will be used to stratify patients or determine inclusion/exclusion criteria in clinical trials
- Intervention studies where pharmacodynamic, predictive, monitoring, or safety biomarker validation is the focus of the study
- Non-intervention studies where diagnostic, prognostic and risk/stratification biomarker validation is the focus of the study

PAR-18-664 and PAR-18-548

Examples of Out-of-Scope Clinical Validation Studies

- Natural history studies aimed at exploring disease pathophysiology, genetic or epigenetic mechanisms
- Applications that propose any animal studies
- Studies of biomarker identification or technology development
- Biomarker analytical validation as the sole intent (it is recognized that optimization of the method of detection may continue throughout the clinical validation process)
- Applications that propose only to create or maintain patient registries
- Clinical testing of candidate therapeutics
- Clinical intervention studies other than those necessary to validate biomarkers
- Applications that request support for infrastructure to establish new clinical trial networks are beyond the scope of this FOA.

HEAL (Helping to End Addiction Long Term) Pain Biomarker Program

The Unmet Medical Need for Non-Addictive Pain Therapeutics

- >25 million Americans suffer from chronic pain
- Over-reliance on opioid treatments due to lack of alternatives

Objective Biomarkers and Endpoints Can Facilitate Discovery of New Non-Addictive Treatments for Pain

- Define pathophysiologic subsets of pain
- Evaluate target engagement of a therapeutic
- Predict analgesic efficacy of new therapeutics

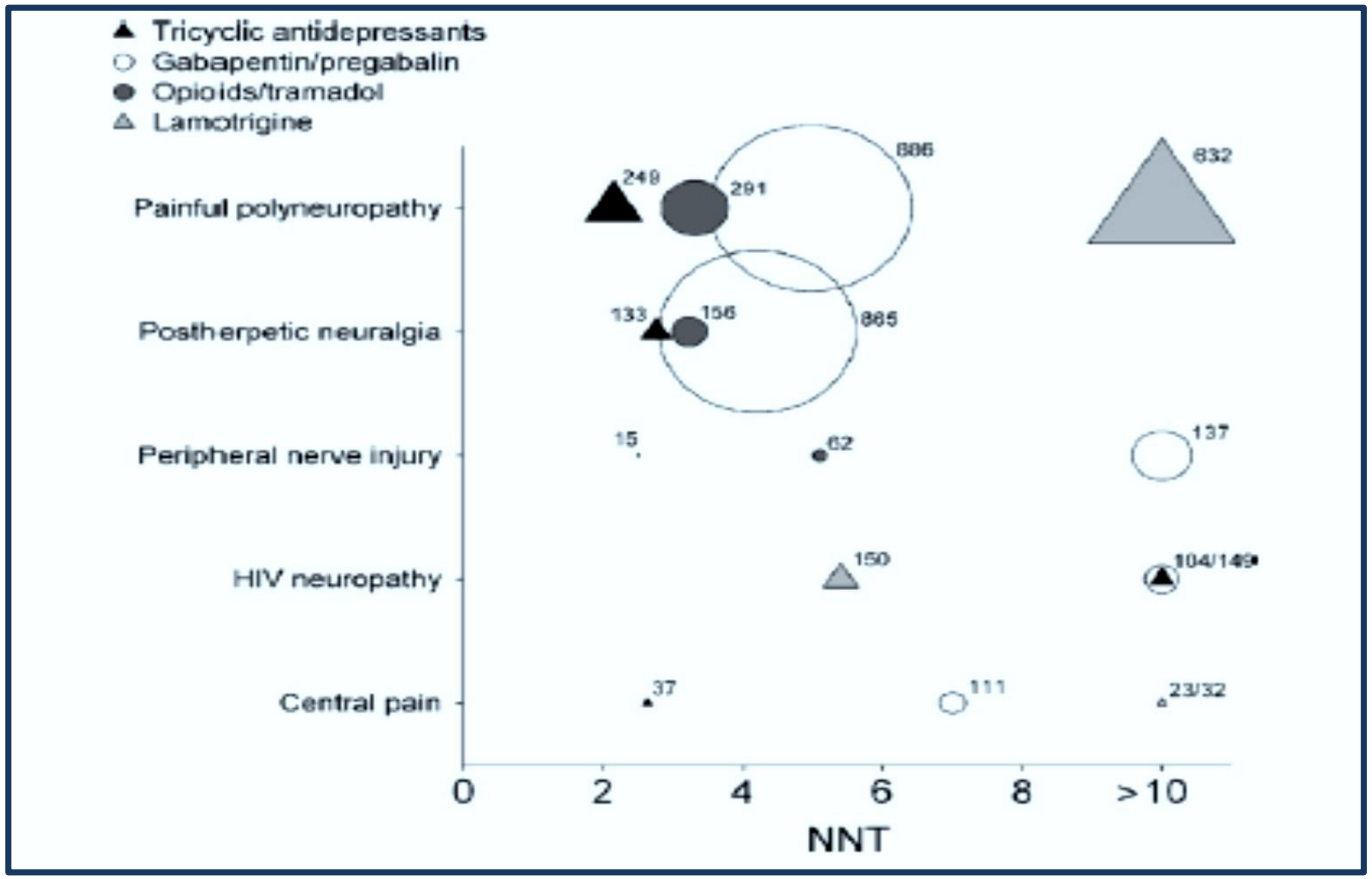
HEAL (Helping to End Addiction Long-term)

- An aggressive, trans-agency effort to speed scientific solutions to stem the national opioid public health crisis.
- Set-aside budget-for the biomarker program alone intend to issue 8-10 awards in 2019
- **Grantees from *for-profit* applicant organizations must provide a 50% match and/or in-kind contribution**

https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative

The Unmet Need for Effective Pain Treatment

Efficacy for Different Drug Classes in Specific Types of Pain

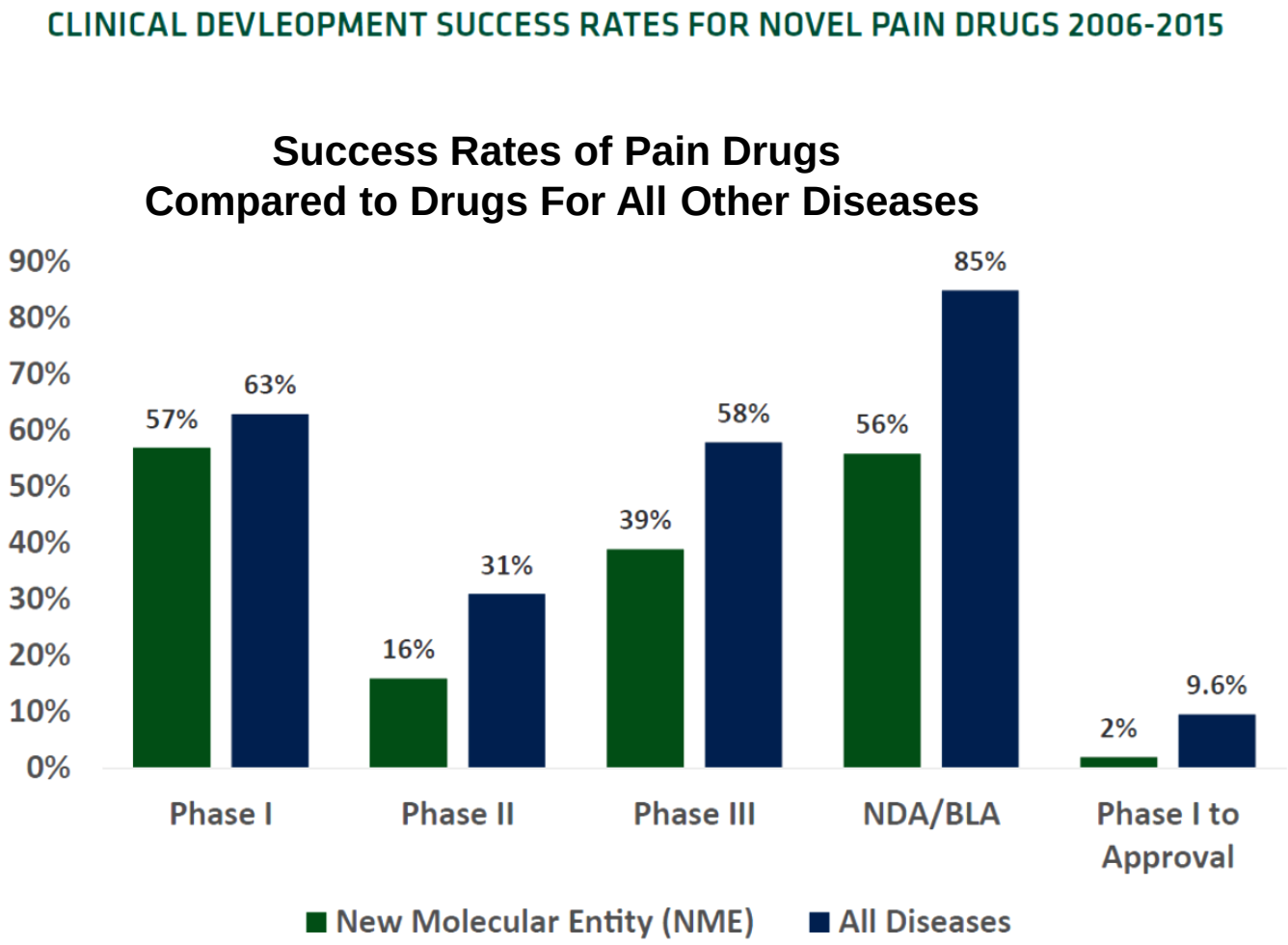


*NNT=Number needed to treat; 1 or 2 is good (2=risk of unfavorable outcome (<50% relief) is reduced by 50%)

National Institute of Neurological Disorders and Stroke

Finnerup, N.B., et al., Pain, (150, 2010) 573-581

Drug Development Success Rates for Pain Therapeutics Are Lower Than Other Disease Indications



National Institute of Neurological Disorders and Stroke

Thomas, D and Wessel, C., Pain and Addiction Therapeutics, Biotechnology Innovation Organization, February, 2018

Resources: Biomarkers and Endpoints for Pain

❖ Funding Opportunities

*Discovery of Biomarkers, Biomarker Signatures, and Endpoints for Pain RFA-NS-18-041	Analytical and Clinical Validation of a Candidate Biomarker For Pain RFA-NS-18-046
Identification and initial biological, analytical and clinical validation of pain biomarkers, biomarker signatures, and/or endpoints.	*Advanced analytical and clinical validation of pain biomarkers, biomarker signatures, and/or endpoints using retrospective and/or prospective methods*

Phased Grant Mechanisms:
R61/R33

❖ ***Upcoming Receipt Dates:***
November 27, 2018; March 7, 2019;
November 25, 2019; March 12, 2020

❖ **Review: NIH Center for Scientific Review**

❖ **Workshop: "Discovery and Validation of Biomarkers to Facilitate the Development of Non-Addictive Therapeutics for Pain"** ***November 14-15, Washington, D.C.***

*R61 and R33 Phased Innovation Award Mechanisms

Mechanism	Mechanism Name	Length	Budget
R61	Phase I Exploratory/Developmental Grant	1-3 years	Not limited but must reflect the actual needs of the proposed project
R33	Phase II Exploratory/Developmental Grant	1-2 years	Not limited but must reflect the actual needs of the proposed project

*Total project duration no more than 5 years

RFA-NS-18-041

Discovery of Biomarkers, Biomarker Signatures, and Endpoints for Pain

NINDS, NCI, NEI, NHLBI, NIA, NIAAA, NIAMS, NIBIB, NICHD, NIDCR, NIDDK, NIDA, NINR, NLM, NCATS, NCCIH, OBSSR, ORWH

Goal

- To promote the discovery of strong candidate biomarkers and endpoints for pain that can be used to facilitate the development of non-opioid pain therapeutics from discovery through Phase II clinical trials.

Entry Criteria

- Cogent biological rationale supporting the candidate biomarker
- Relevance for pain therapeutic development

RFA-NS-18-041

Examples of Activities That Are Responsive to RFA-NS-18-041

- Identification and initial validation of a potential pain biomarker
- Identification and procurement of sample sources necessary for biomarker discovery and assurance of source standardization and annotation
- Identification and validation of objective pain endpoints
- Comprehensive set of biomarker discovery studies designed to identify a set of mechanistic markers associated with diverse pain conditions, including identification of combined biomarkers that form a “signature” for the selected pain condition
- Bioinformatics and/or statistical approaches to support biomarker identification
- Analysis and resolution of pre-analytical variables included in the detection technology or biomarker measurement technology
- Proof of concept studies using human tissue, biofluids or imaging samples to confirm biomarker identification obtained using animal tissue sources
- Preliminary clinical validation studies to confirm biomarker identification

RFA-NS-18-041

Examples of Activities That Are Not Responsive to RFA-NS-18-041

- Natural history studies aimed at understanding disease pathophysiology, genetic, or epigenetic mechanisms *in the absence* of biomarker identification, development of detection technology and early validation
- Biomarker identification or validation based only on animal data without confirmation using human tissue sources or preliminary clinical validation
- Use of non-standardized sample sources
- Large, prospective design clinical validation studies
- *Therapeutic target* validation and development
- Preclinical animal studies without a transition to studies involving human samples or data
- Development of candidate therapeutics
- Biomarker discovery outside non-addictive therapeutic options to pain conditions

RFA-NS-18-046

Analytical and/or Clinical Validation of a Candidate Biomarker for Pain

NINDS, NCI, NEI, NHLBI, NIA, NIAAA, NIAMS, NICHD, NIDCR, NIDDK, NIDA, NINR, NLM, NCCIH, OBSSR, ORWH

Goal

- To promote the validation of strong candidate biomarkers and endpoints for pain that can be used to facilitate the development of non-opioid pain therapeutics from discovery through Phase II clinical trials.

Entry Criteria

- Biomarker, biomarker signature or endpoint must be identified with a working hypothesis regarding Context of Use
- Method of detection should be developed
- Supporting data for the above should be provided
- Cogent biological rationale and evidence for unmet need
- Relevance for therapeutic development
- Focus of biomarker, biomarker signature or endpoint should be on specific pain condition

RFA-NS-18-046

Examples of Activities That Are Responsive to RFA-NS-18-046

- Analytical validation of detection methods where the biomarker is likely to be used as a tool in the diagnosis and treatment of pain
- Analytical and clinical validation of tissue/biofluid, imaging, physiological or behavioral biomarkers of pain conditions
- Analytical and clinical validation of biomarkers involving clinical intervention such as pharmacodynamic/response biomarkers, predictive biomarkers, safety biomarkers, or monitoring biomarkers
- Analytical and clinical validation of biomarkers that do not involve clinical intervention such as diagnostic, prognostic or susceptibility/risk biomarkers
- Rigorous evaluation of the sensitivity and specificity of the biomarker, biomarker signature or endpoint
- Retrospective or prospective well controlled, multi-site clinical studies

RFA-NS-18-046

Examples of Activities That Are Not Responsive to RFA-NS-18-046

- Natural history studies aimed only at exploring disease pathophysiology, genetic or epigenetic mechanisms rather than focused on biomarker, biomarker signature or endpoint development
- Studies on biomarkers that are not clinically relevant to pain
- Applications that propose animal studies
- Applications that solely focus on creating or maintaining patient registries
- Development or clinical testing of candidate therapeutics
- Applications that request support for infrastructure to establish new clinical trial networks

NIH Biomarker Workshop: Pain Biomarker, Biomarker Signature and Endpoint Development

"Discovery and Validation of Biomarkers to Develop Non-Addictive Therapeutics for Pain"

Marriott Wardman-Park, Washington, DC

November 14-15, 2018

Purpose of the Workshop

- To inform the community about current regulatory standards and guidelines for the development of biomarkers and endpoints
- To evaluate the state of the science in pain biomarker development
- To explore potential scientific and collaborative approaches that could facilitate the discovery and validation of robust biomarkers and endpoints that would provide the tools necessary for the diagnosis and treatment of pain conditions

National Institute of Neurological Disorders and Stroke

Link to Pain Biomarker and Endpoint Workshop:
https://meetings.ninds.nih.gov/Home/Index/20748

Questions?

Please contact us with any questions or for Pre-Application Consultation:

Mary Ann Pelleymounter, PhD
Program Director
mary.pelleymounter@nih.gov

Website:
https://www.ninds.nih.gov/Current-Research/Focus-Tools-Topics/Biomarkers

Links to Funding Opportunities:

Analytical Validation of a Candidate Biomarker for Neurological Disease
PAR-18-549: U44 SBIR
PAR-18-550: U01

Clinical Validation of a Candidate Biomarker for Neurological Disease
PAR-18-548: U44
PAR-18-664: U01

Discovery of Biomarkers, Biomarker Signatures and Endpoints for Pain
RFA-NS-18-041: R61/R33

Analytical and/or Clinical Validation of a Candidate Biomarker for Pain
RFA-NS-18-046: R61/R33