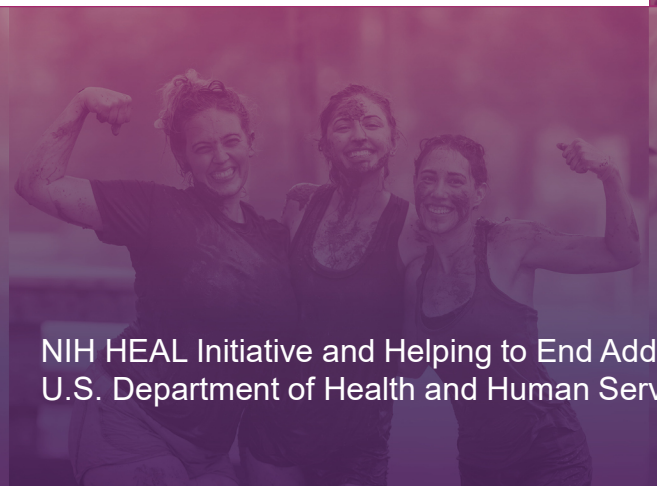


NIH
HEAL
INITIATIVE

Helping to End Addiction Long-term

July 27, 2020

Francis Collins
Director, NIH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Helping to End Addiction Long-term

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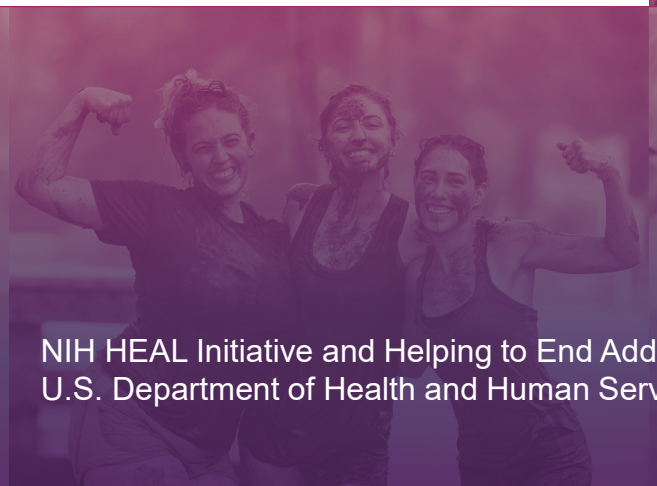
Rebecca Baker,
Director, HEAL Initiative, Office of the Director, NIH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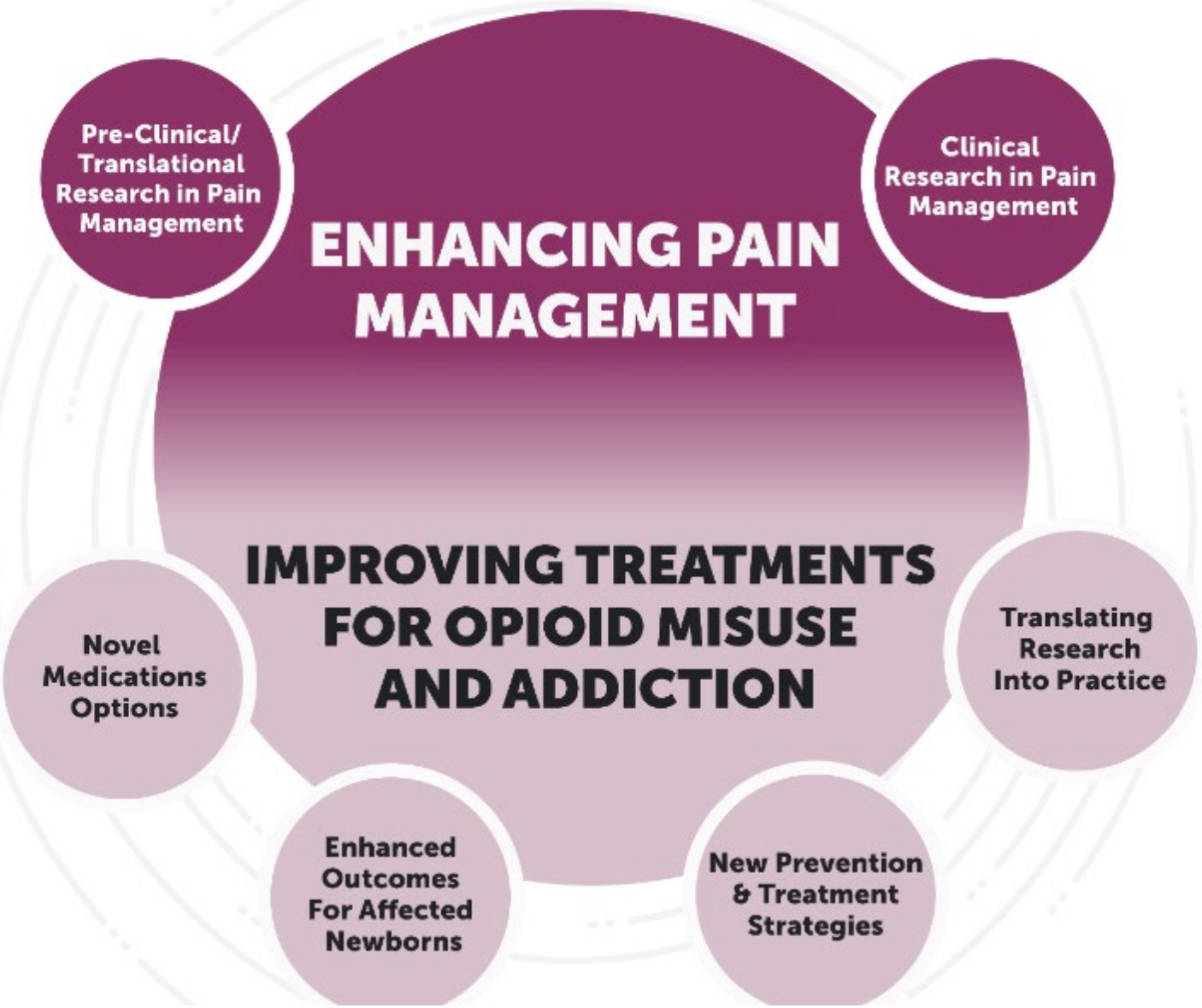
HEAL Mission: scientific solutions to the opioids crisis

- $500 million/year Sustained Research Investment
- 40+ Funding Opportunity Announcements
- Awards across 41 States
- 400+ Investigators

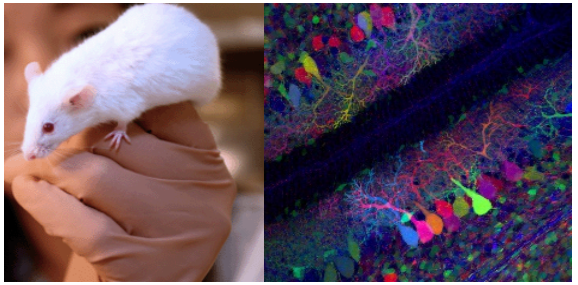
FY 2019
$945 million+ research awards

NIH HEAL INITIATIVE RESEARCH OVERVIEW



Pre-Clinical and Translational Research in Pain

- Discovery and validation of novel targets for safe and effective pain therapeutics
- Translating discoveries into effective devices for pain treatment
- Engineering preclinical screening platforms + novel drug development
- Biomarkers, signatures and endp

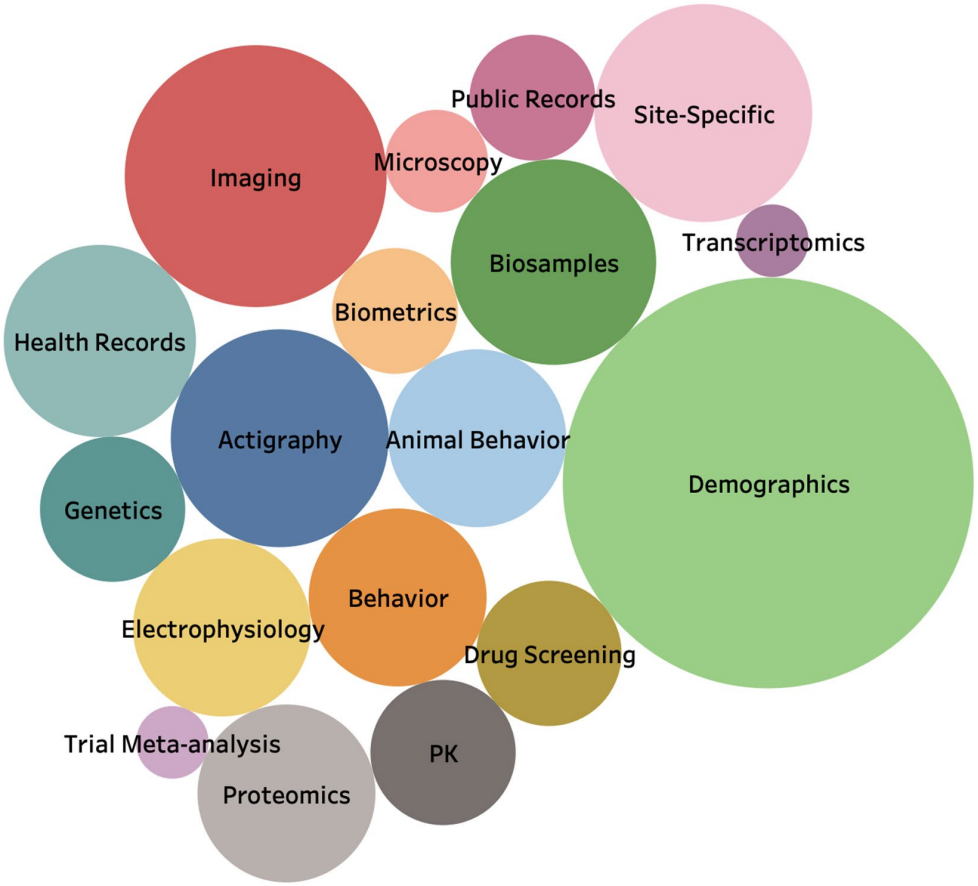


Clinical Research in Pain Management

- Novel phase 2 clinical trials network: (EPPIC Net)
- Back Pain Research Consortium (BACPAC)
- Integrated approach to pain and opioid use in hemodialysis patients (HOPE)
- Pain Management Effectiveness Research Network (ERN)
- Pragmatic and Implementation Studies for the Management of Pain (PRISM)

Data Sharing and Harmonization

- Therapeutics Development
- Basic Science of Pain and Opioid Use Disorder
- Clinical Trials: Phase 2 and Effectiveness Trials
- Clinical Research: Implementation and Sustainability



Addressing Gaps in Research: FY20 Investments

Understanding the Relationship Between Pain and Addition

Targeted Clinical Trials of Palliative Pain Management in the Context of Opioid Use Disorder ($1M)

Pain Management in the Setting of Opioid Use/OUD ($2.75M)

Workshop: Interventions for Managing Comorbid Chronic Pain & OUD/Physical Dependence ($75K)

Addressing Opioid Use Disorder and Co-occurring Mental Health Conditions

Social Network Analyses to Reduce American Indian and Alaska Native Opioid Use Disorder and Related Risks for Suicide and Mental Health Disorders ($2.6M)

Research to Understand and Manage Common Co-Occurring Conditions and Suicide Risk in People Affected by the Opioid Crisis ($8M)

Reducing Stigma of Addiction and Pain

Strategies to Reduce Stigma in Pain Management and OUD and Addiction Treatment ($3.75M)

Workshop: Addressing Social and Economic Determinants of Opioid-Related Health Disparities- Expert Panel Workshop and Planning Meeting

Research Networks for the Study of Recovery Support Services for Persons Treated with Medications for Opioid Use Disorder ($6M)

Understanding Diversity of Care Received in Across Health Settings

Best Management of Specific Pain Conditions in Primary Care, Hospital, DENTAL or Emergency Settings ($28.3M)

Workshop: Navigating Pediatric to Adult Health Care: Lost in Health Care Transition

Increasing Diversity Among HEAL Investigators

Enhance the Workforce Diversity to Grow the Next Generation of Investigators in HEAL Areas of Research ($5M)

Training Supplement for Heal Network Clinical Trials ($2M)

Goals for Today's Meeting

- Review HEAL preclinical pain portfolio.
- Critique realignment of HEAL therapy development program.
  - Identify potential gaps or weaknesses
  - Recommend refinements to optimize successful project intake and program outcomes
  - Identify optimal metrics and benchmark targets for success at appropriate stages
  - Recommend oversight approaches to evaluate, monitor, and criteria to progress or re-invest to ensure success of the program



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HEAL Partnership Committee
July 27, 2020

Overview of HEAL Clinical Pain Research

July 27, 2020

Linda Porter, Director OPPP



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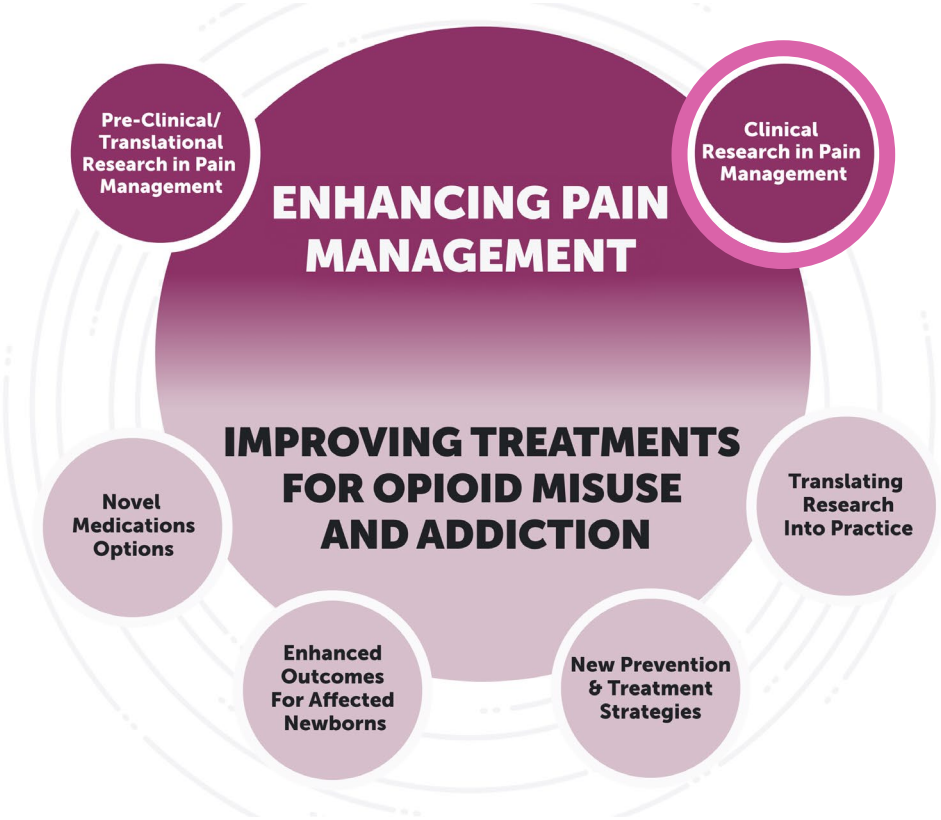
HEAL Initiative Research Focus Areas



HEAL Pain Clinical Programs

EPPIC Net: Early Phase Pain Investigation Pain Network

engage partners & patients to test novel drugs & devices

BACPAC: Back Pain Consortium

probe mechanisms of back pain to develop & test integrated precision ca

ERN: Comparative Effectiveness Pain Management Network

inform patients & providers on best practices for pain management

PRISM: Pragmatic and Implementation Studies for the Management of Pain

integrate interventions with demonstrated efficacy into health care systems

HOPE: Integrated Approach to Pain and Opioid Use in Hemodialysis Patients

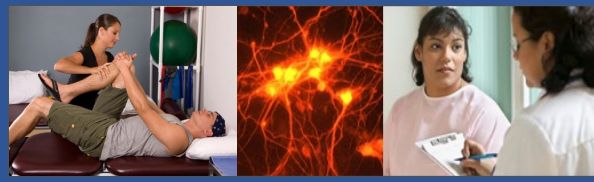
tailored interventions for pain for hemodialysis patients

BIOMARKERS: Discovery of Biomarkers, Biomarker Signatures, Endpoints for Pain

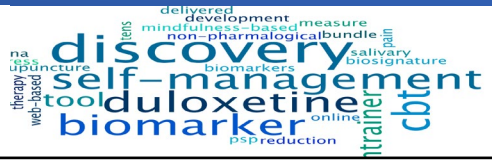
discovery of biomarkers, signatures and objective endpoints

DEVICES: Translational and Clinical Devices to Treat Pain

enhance targeting and reduce invasiveness of therapeutic devices

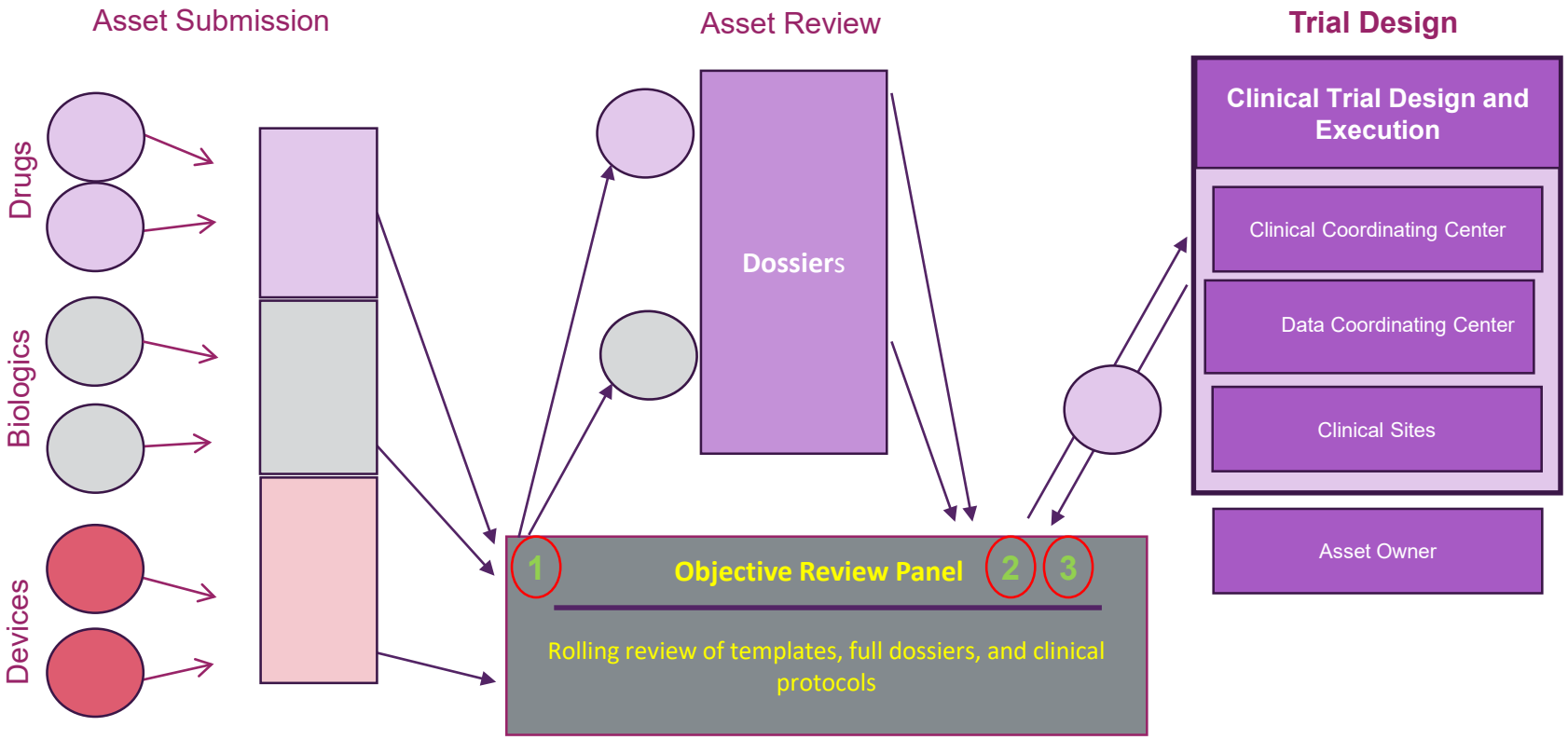


HEAL Clinical Research Features



Comparative Effectiveness Research	Perioperative pain	mHealth psychological intervention
	Chronic Overlapping Conditions	e-Pain guide
	Musculoskeletal pain	e-Pain Trainer & duloxetine, coached CBT & ketamine
	Chronic pain	e- coached telehealth
	Hip/Knee OA	Pain Trainer, nerve ligation,
	Cancer pain: GI & Lung	e-Pain-Trainer, duloxetine
	Post-caesarian pain	IOPP, shared decision making
	Kidney dialysis pain	Buprenorphine, CBT, acupuncture
Implementation Research	Low back pain	Acupuncture, Mindfulness, Chiropractic and Physical Therapy
	Fibromyalgia	Physical Therapy andTENS
	Perioperative pain	EHR Clinical decision support
	Chronic pain	Pain Tracker (self-management, decision support
BACPAC	Low back pain	Negative Affect CBT Virtual Reality
Biomarker Research	Musculoskeletal pain	Prognostic and predictive biomarkers
	Sickle cell disease pain	Prognostic biomarkers
	Acute and chronic pain	Diagnostic biomarker
	TMD	Mechanistic biomarkers
	Chronic neck pain, Whiplash	Prognostic biomarkers, predictive biomarkers

EPPIC-Net Protocol Development and Review



Supplements to HEAL or HEAL Associated Awards

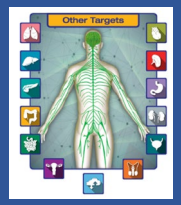
New Additions to HEAL

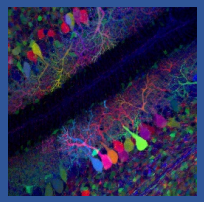
- **Stigma in Pain Management and Opioid Use Disorder and Treatment**
- **For Managing Comorbid Chronic Pain and Opioid Use Disorder**
- **For Diversity in Pain Research**
- **For Training in pain clinical research settings**

HEAL Pain Pre-Clinical Programs

Discovery & validation of novel targets for safe & effective pain treatment
Accelerate discovery and development of non-addictive treatments for pain
Engineering preclinical screening platforms + novel drug development
Translating discoveries into effective devices for pain treatment
Biomarkers, signatures and endpoints for pain









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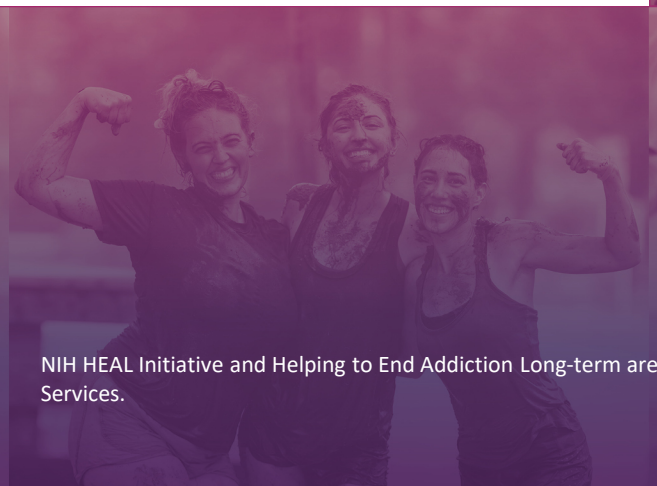
NCATS HEAL Research Collaborations

Christine Colvis, M.D.
Director, Drug Development Partnership Programs
National Center for Advancing Translational Sciences

July 27, 2020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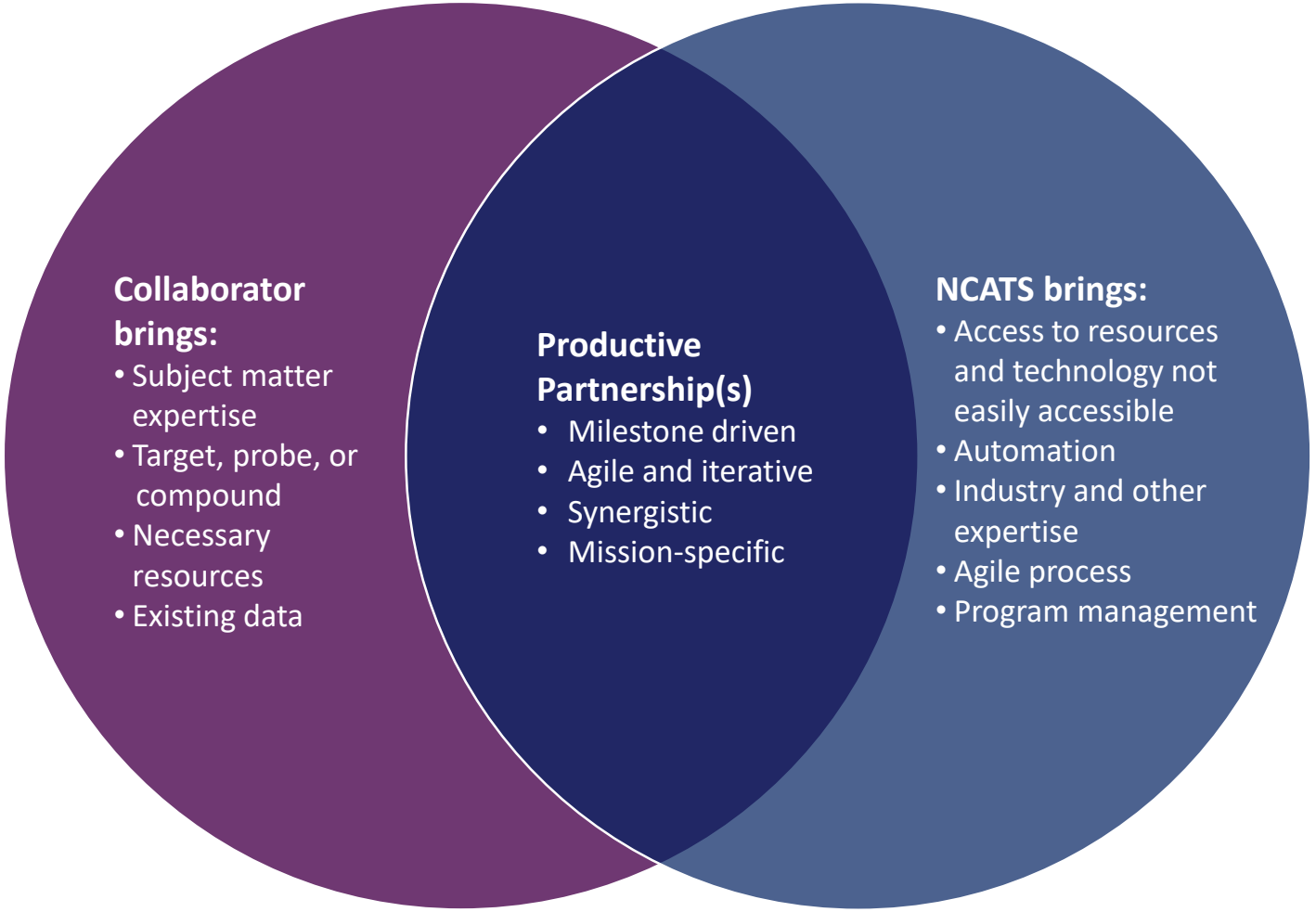
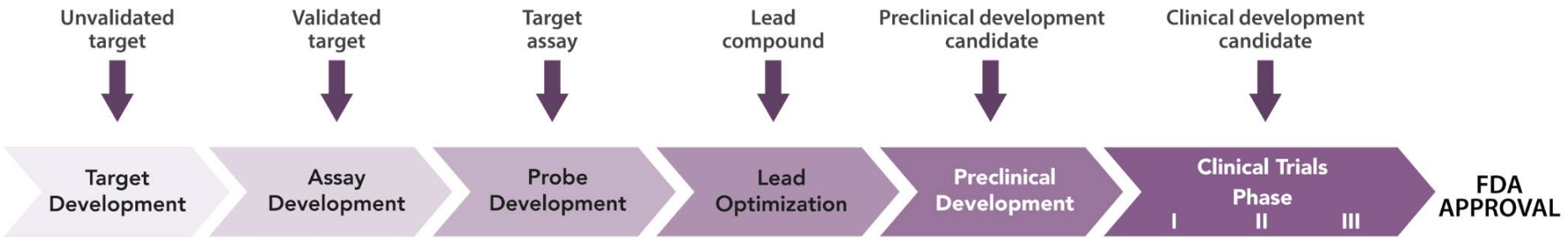
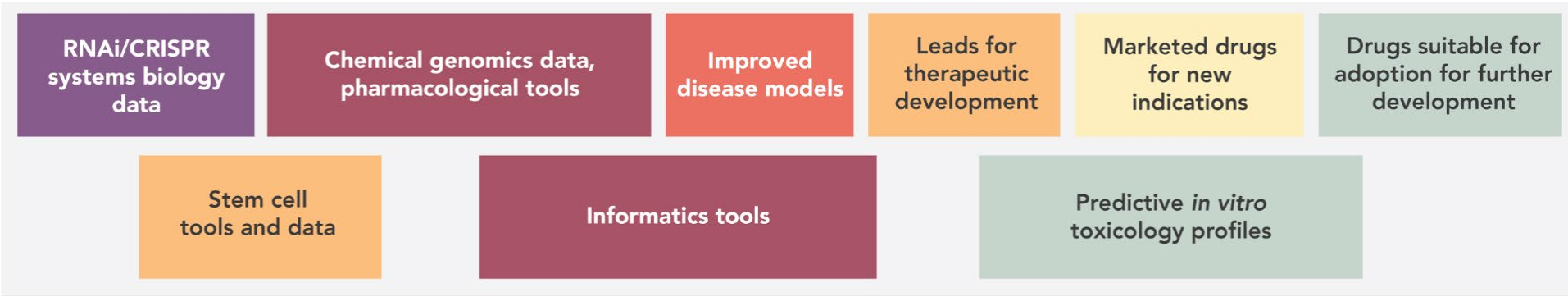
NCATS Collaborative Model



Collaborator Entry Points



Deliverables





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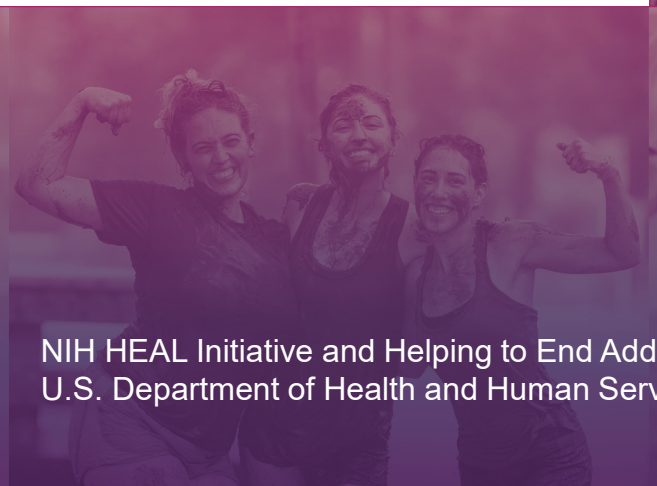
HEAL Analgesic Development Preclinical & Translational Programs

Michael Oshinsky (NINDS)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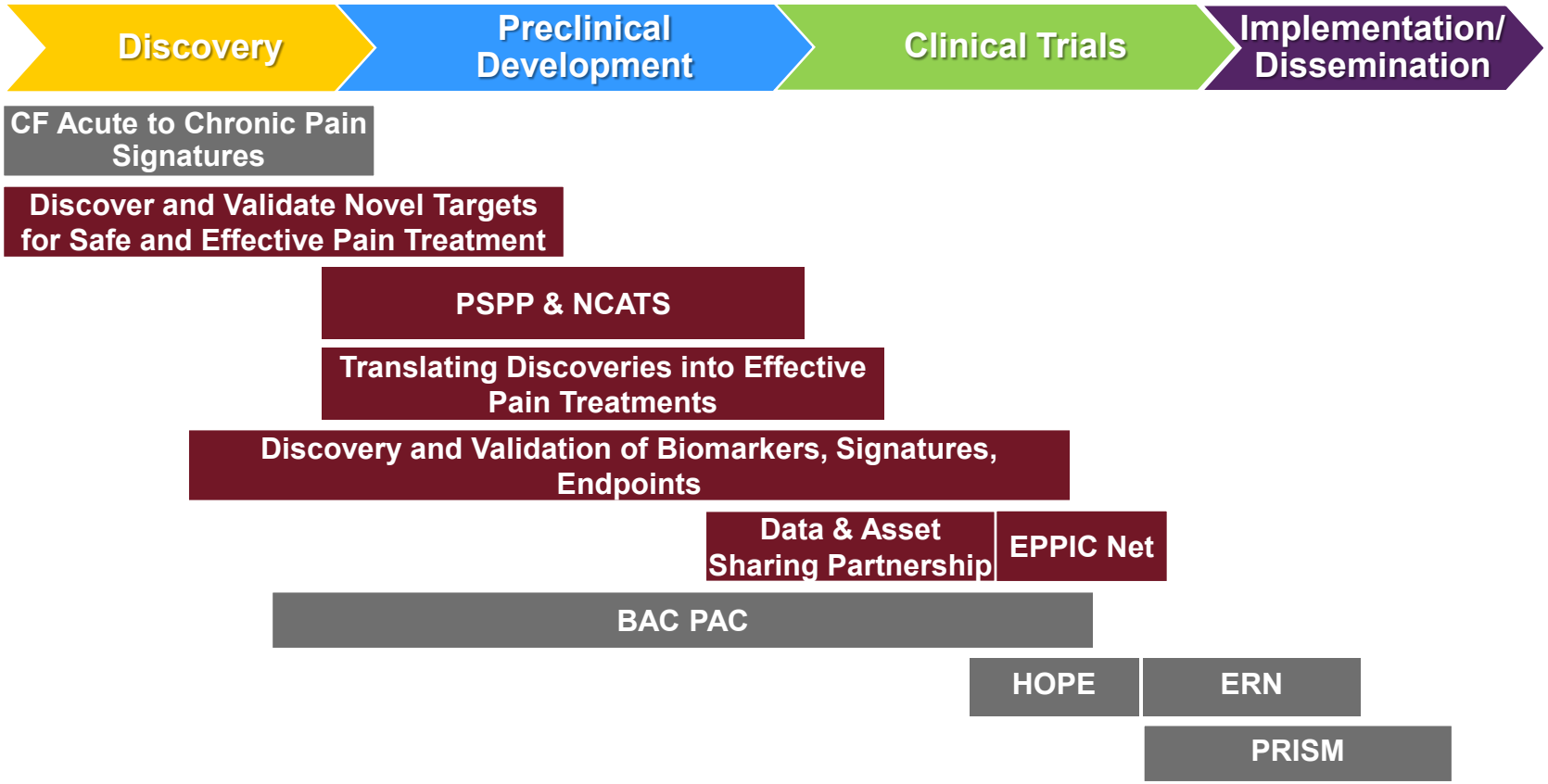
HEAL Programs for Enhancing Pain Management



HEAL: Discover and Validate Novel Targets for Safe and Effective Pain Treatment

To promote the basic science discovery and validation of "targets" for the treatment of pain that can be used to develop therapeutics that little to no abuse/addiction liability

GOALS

- Designed to validate novel targets for:
  - small molecules
  - natural products
  - Biologics
  - devices
- Encourage collaboration from other fields
- Device target validation:
  - Discovery of new sites for stimulation or electrophysiological signatures

Type of Validation

- Animal model systems development (i.e. knockouts)
- Multidisciplinary tools(i.e. siRNA, electrophys.)
- Multisite validation
  - Reproducibility
- Use of pharmacodynamic and predictive biomarkers

HEAL: Preclinical Screening Platform for Pain (PSPP)

Preclinical Development Strategy: Screen, Profile, and Validate

PSPP GOALS:

Screen

- In vitro opioid activity
- In vitro abuse liability
- Pharmacokinetic studies

Profile

- In vivo abuse liability
- In vivo efficacy

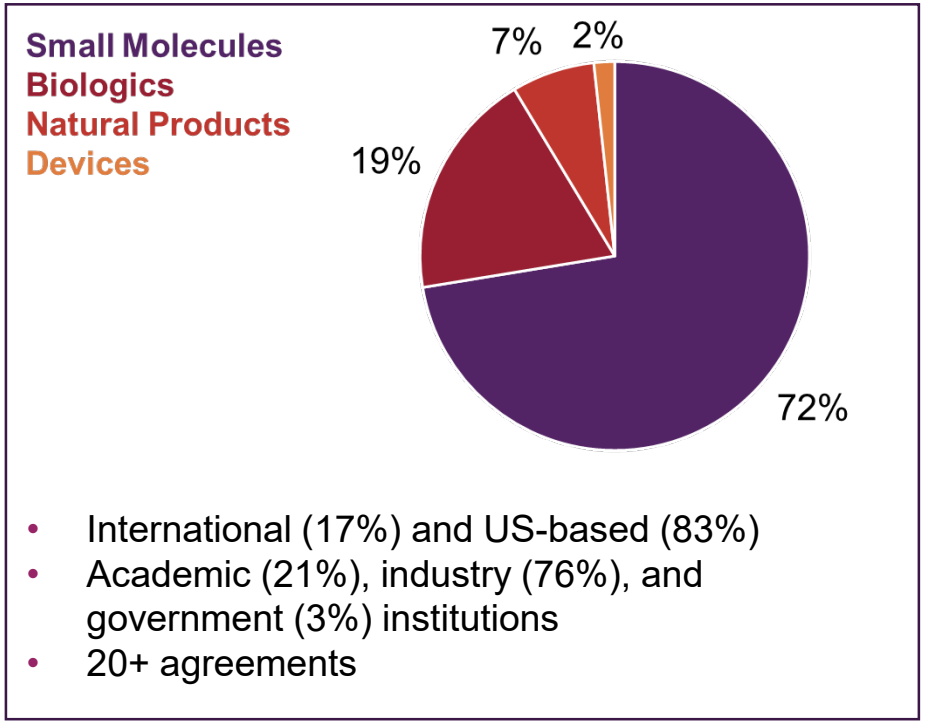
Validate

- Validate new endpoints
- Validate new models

Contract Facilities

- PsychoGenics, Inc., Paramus, NJ
- RTI International, Research Triangle Park, NC

PSPP is open to academic or industry asset owners worldwide at no cost to the participant



- International (17%) and US-based (83%)
- Academic (21%), industry (76%), and government (3%) institutions
- 20+ agreements

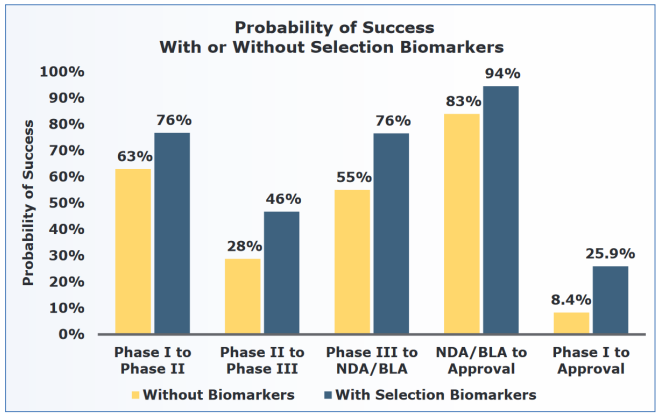
HEAL Initiative PSPP: https://heal.nih.gov/research/preclinical-translational/screening-platform

PSPP Public Facing Database: http://pspp.ninds.nih.gov

HEAL: Biomarker Program

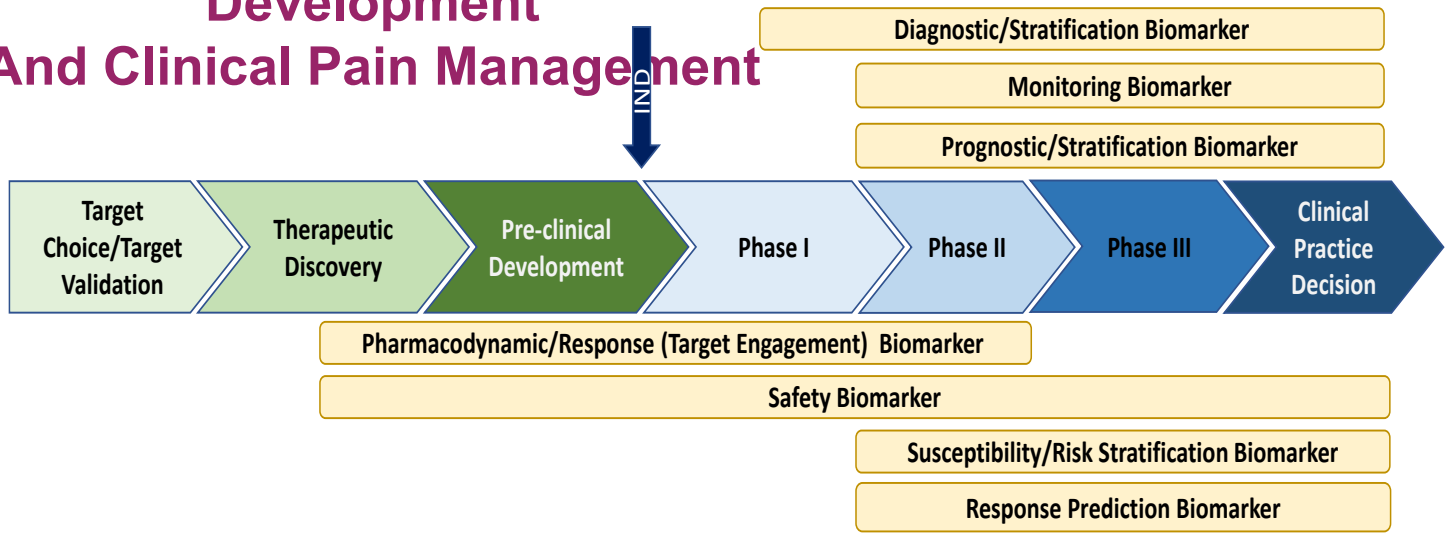
Supporting Biomarker Discovery and Validation to Facilitate Clinical Trial Design and Clinical Pain Management Decisions

Patient Stratification Biomarkers Improve the Probability of Success in Drug Development



Thomas, D. W. *et al.* Clinical development success rates 2006–2015. *San Diego: Biomedtracker/Washington, DC: BIO/Bend: Amplion* (2016).

Biomarkers Have Specific Roles in Drug Development And Clinical Pain Management



84 Applications
8 Awards (4th Cycle)

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HEAL: Optimization of Non-addictive Therapies [Small Molecules and Biologics] to Treat Pain Program

Award Format:

- **5 Year Research Grants Have 2 Phases**
- **Driven by Go/No Go Milestones**

- GOAL: **Preclinical optimization and development of safe, effective, and non-addictive small molecule and biologic therapeutics to treat pain.**

- SCOPE: **Optimization and early development activities, IND-enabling studies, and assembly of Investigational New Drug (IND) application.**

➢ **6 funded grants**: 2 biologics and 4 small molecules

Limited Access to Contract Resources:

- BPN PK and Tox Contract (both small molecule and biologics)
- Ad hoc access to BPN and CREATE Subject Matter Expert Consultants (Optimization and Development)
- NCATS intramural scientists and programs

Non-HEAL Translational Programs to Bridge Gaps

- **Academics and Small Biotechs:**
  - Have excellent ideas with good scientific premise
  - Can provide disease biology expertise

  But often lack:
  - Resources to advance their ideas
  - Complete preliminary data packages
  - Screening assays and chemical starting points
  - Models for future testing
- **NIH can:**
  - Provide specialized drug discovery and development planning and expertise
  - Provide access to drug discovery infrastructure and testing to advance to clinic
  - Perserve investigators IP
  - Combine the strengths of NIH and industry expertise for drug discovery

IGNITE and BPN are Models to Bridge the Gaps to Pain Therapeutics Development

IGNITE

BPN

Innovation Grants to Nurture Initial Translational Efforts

- End goal is to meet BPN entry criteria
- Milestone-driven grant

NIH National Institute of Neurological Disorders and Stroke

Blueprint Neurotherapeutics Program

- Provides resources (CROs, consultants) in addition to grant support
- Milestone-driven cooperative agreement

NIH **Blueprint** for Neuroscience Research

Key Attributes of IGNITE and BPN

Program Attributes
Emphasize deliverables
Milestone-driven
Address risk(s) and expect attrition
Provide funding and resources

Innovation Grants to Nurture Initial Translational Efforts (IGNITE)

Three types of grants to bridge the gap between basic science and the BPN entry criteria:

1. Assay development and compound screening, also includes early hit optimization

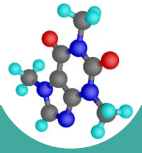
2. Rigorous in vivo efficacy studies, also includes PK/PD, early ADME, tox; supports small molecules and biologics

3. Development of clinically relevant, carefully validated animal models, ex vivo models and PD markers

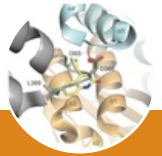
BPN: Small Molecule Drug Discovery and Development for Neuroscience Indications

- Projects can enter at either the
  - **Discovery stage:** additional medicinal chemistry is required to identify preclinical candidate
  - **Development stage:** no additional med-chem required (candidate(s) are identified)
- The goal in all cases is to advance to IND-enabling toxicology studies and phase I clinical testing
- Program does not allow for simultaneous back-up generation and development (i.e. no med-chem during development; only one candidate for GLP tox studies)
- Expanding to include biologics

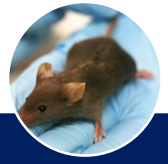
BPN Network: Infrastructure, Expertise, and Grants



Hit to Lead



Lead Optimization



Pre-clinical Development

Early Clinical Development

Lead Development Team*

Principal Investigator
Industry-seasoned consultants
NIH staff

NIH Grant

Bioactivity/ Efficacy Studies

NIH Contracts

Medicinal Chemistry
AMRI

PK/Tox

SOUTHERN RESEARCH INSTITUTE

Data Management

CDD COLLABORATIVE DRUG DISCOVERY

Manufacturing & Formulation

MRIGlobal

AMRI

Clinical Trials

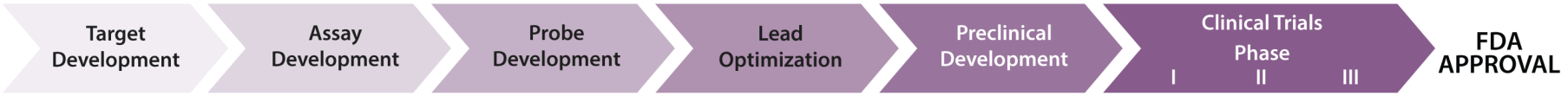
Duke

PPD

* Contract resources are tailor-made to support PI teams

Michael.Oshinsky@nih.gov

Appendix of HEAL Preclinical Pain Research Programs



Snapshot of NCATS DPI HEAL platform and pain project portfolio

iPSC-Derived Cells for Pain & Reward Pathways

- Disseminating Validated iPSC-derived Cell Types for Target ID and Drug Screening
- Developing iPSC-derived Schwann cells for Disease Modeling and Treating Pain
- Developing iPSC-derived Satellite Glial Cells for Drug Development
- Developing iPSC-derived Aβ Sensory Neurons for Chemogenetic Pain Treatment
- Testing a Reversible Gene Editing Method for Analgesia using iPSC-derived Sensory Neurons
- New iPSC lines from Phelan-McDermid Syndrome Patients to Identify Novel Pain Mechanisms
- Modeling and Analysis of Diabetic Polyneuropathy by using Patient-derived iPSC Lines
- Manufacturing and Functional Characterization of iPSC-derived Nociceptors and Astrocytes
- Comprehensive Molecular Characterization of Primary Human DRG Tissues by Deep Sequencing

3D Biofabricated Tissue Models

- Human iPSC-derived dorsal horn model
- Macromolecular Crowding
- Blood Brain Barrier Model
- Multiwell Format Neurovascular Unit
- Innervated 3D Skin

Development of Pharmacological Probes for Novel Targets

- 5-HT7R Agonist
- PIEZO2 Antagonist
- RXFP3 Antagonist
- Substance P Antibody Development
- SUMOylation Blocker of CRMP2
- GCPII Inhibitor
- AC1 Inhibitor

Development of Investigational New Drugs for Clinical Testing

- Sickle Cell Mini-Pig Pain Model
- BoNT-Based Analgesic
- Endosome Targeting NK1R and CLR Antagonist
- MRGX2 NAM
- MET-IN delivered LENK

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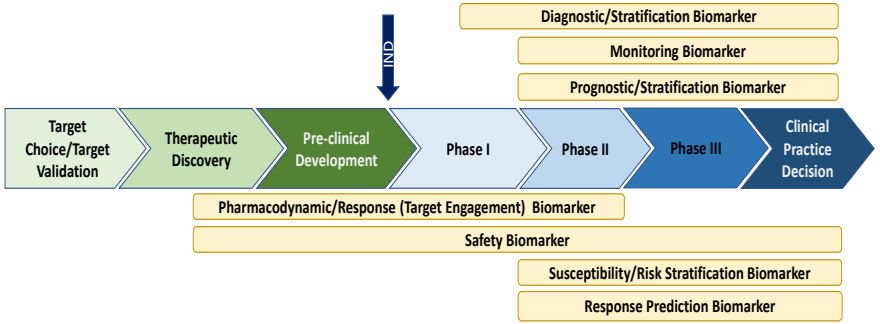
Discover and Validate Novel Targets for Safe and Effective Pain Treatment

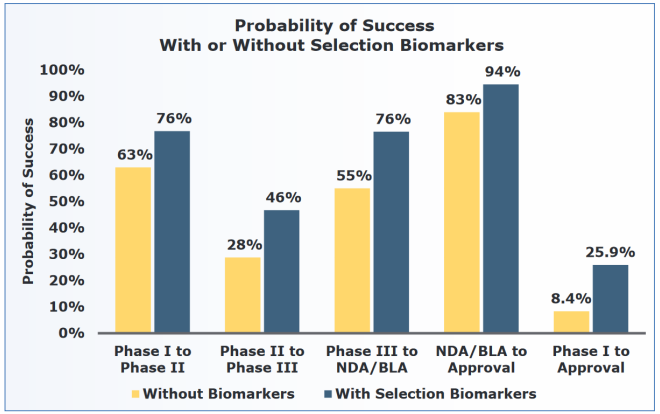
Type of Target	Taget Name
Transcription Factor	Dnmt3a (a specific DNA Methyltransferase)
Transcription Factor	Nrf2 (Nuclear factor erythroid 2-related factor 2)
Transcription Factor	lncRNA V1 and V2 (long non-encoding RNAs)
Peptide Receptor	AMY1 (Amylin receptor)
Peptide Receptor	TNFSF14 (TNF superfamily 14) and LTβR (Lymphotoxin β toxin receptor)
Peptide	CCL2
Peptide	TLQP-62 receptor (VGF peptide)
Peptide	CGRP(calcitonin gene-related peptide) in pancreatic tissue
Membrane Protein	AKAP(A-Kinase Anchoring Proteins) and TRP channels
Membrane Protein	ApoA-I binding protein and TLR4 dimerization
Membrane Protein	TIMP3 (Tissue-inhibited metalloproteinase 3)
Membrane Protein	MAGI1 protein trafficking of NAV1.8 (Membrane Associated Guanylate Kinase, WW And PDZ Domain Containing 1)
Membrane Protein	TSP4/Ca-alpha2-delta-1 (extracellular matrix protein thrombospondin-4)
Ion Channel	TRESK (TWIK-related spinal cord K+ channel)
Cell Group	Sympathetic innervation of DRG
Cell Group	CeA-GA neurons (Central Amygdala general anesthesia neurons)
Cell Group	monosynaptic circuit (TG-PB(L))
2nd Messenger System	KOR-Gi-GIRK signaling pathway
2nd Messenger System	EPAC1(exchange proteins activated by cAMP)
2nd Messenger System	MrgprD signaling pathway(Mass-related G protein-coupled receptor D)
2nd Messenger System	GPR160
2nd Messenger System	P2X4-macrophage-TGFβ (transforming growth factor β) pathway

HEAL Biomarker Program: *Supporting Biomarker Discovery and Validation to Facilitate Clinical Trial Design and Clinical Pain Management Decisions*

Biomarkers Have Specific Roles In Drug Development And Clinical Pain Management



Patient Stratification Biomarkers Improve the Probability of Success in Drug Development



Thomas, D. W. *et al.* Clinical development success rates 2006–2015. *San Diego: Biomedtracker/Washington, DC: BIO/Bend: Amplion* (2016).

Type	Biomarker Use	Project Title
Prognostic	Patient stratification in a clinical trial	Discovery of Biomarker Signatures Prognostic for Neuropathic Pain after Acute Spinal Cord Injury
Prognostic	Patient stratification in a clinical trial	Biomarker Signature to Predict the Persistence of Post-Traumatic Headache
Prognostic	Patient stratification in a clinical trial	The Inflammatory Index as a Biomarker for Pain in Patients with Sickle Cell Disease
Prognostic	Treatment Decision in clinical practice	Validation of a novel cortical biomarker signature for pain
Prognostic	Treatment Decision in clinical practice	Discovery and analytical validation of Inflammatory bio-signatures of the human pain experience
Diagnostic	Treatment Decision in clinical practice	Discovery of the Biomarker Signature for Neuropathic Corneal Pain
Prognostic	Treatment Decision in clinical practice	SPRINT: Signature for Pain Recovery IN Teens

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HEAL: Optimization of Non-addictive Therapies [Small Molecules and Biologics] to Treat Pain Program

- The scope of this program includes optimization and early development activities, IND-enabling studies, and assembly of Investigational New Drug (IND) application.
- This is a milestone-driven phased cooperative agreement program involving participation of NIH program staff in the development of the project plan and monitoring of research progress.

Type of Target	Project Title
Ion Channel ◆	Optimization of non-addictive biologics to target sodium channels involved in pain signaling
Ion Channel ◆	Novel HCN1-selective small molecule inhibitors for the treatment of neuropathic pain
2nd Messenger System	Development of MRGPRX1 positive allosteric modulators as non-addictive therapies for neuropathic pain
Ion Channel	Novel mGlu5 negative allosteric modulators as first-in-class non-addictive analgesic therapeutics
2nd Messenger System	Development and Optimization of MNK Inhibitors for the Treatment of Neuropathic Pain
Ion Channel	Selective Kv7.2/3 activators for the treatment of neuropathic pain
Ion Channel	Modeling temporomandibular joint disorders pain: role of transient receptor potential ion channels

Funding:

- **5 Year Research Grants: 2 Phases**
- **Driven by Go/No Go Milestones**

Supports preclinical optimization and development of safe, effective, and non-addictive small molecule and biologic therapeutics to treat pain.

Funding novel small molecules and biologics and innovative approaches, including computational modeling approaches to improve the molecules ability to target neuropathic peripheral pain, including affecting unique targets

Limited access to contract resources:

- BPN PK and Tox Contract (both small molecule and biologics)
- Ad hoc access to BPN and CREATE Subject Matter Expert Consultants (Optimization and Development)



NIH
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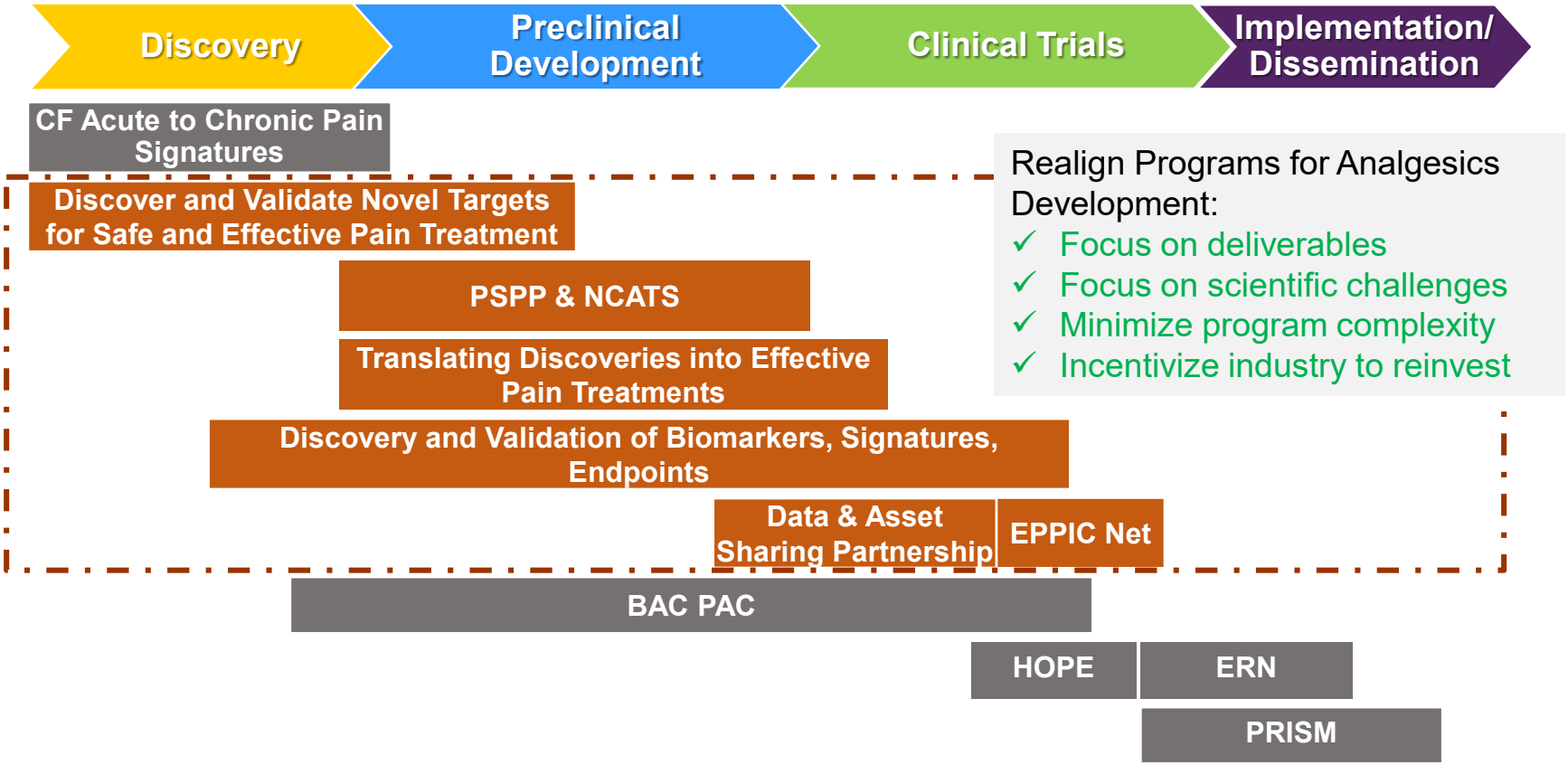
Framework for Re-alignment of the Pain Therapeutic Development Program

July 27, 2020

Amir Tamiz

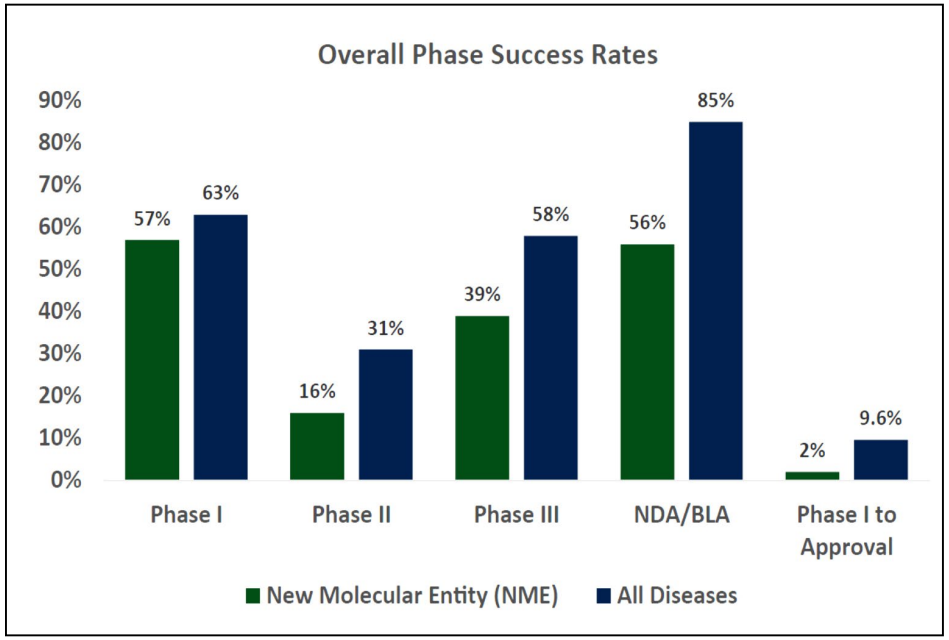
#NIHhealInitiative

HEAL Programs for Enhancing Pain Management



Scientific Challenges – Analgesics Development

Success Rates of Pain Drugs Compared to Drugs For All Other Diseases



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

Specific Challenges:

1. Complexity of biology/pharmacology
2. Lack of validated targets
3. Lack of translatable pain measures
4. Lack of predictable preclinical models
5. Rigorous proof of concept studies
6. Robust therapeutic tools
7. Early indication for safety and efficacy
8. Lack of resources and expertise at academic centers

Proposed HEAL Analgesic Development Program

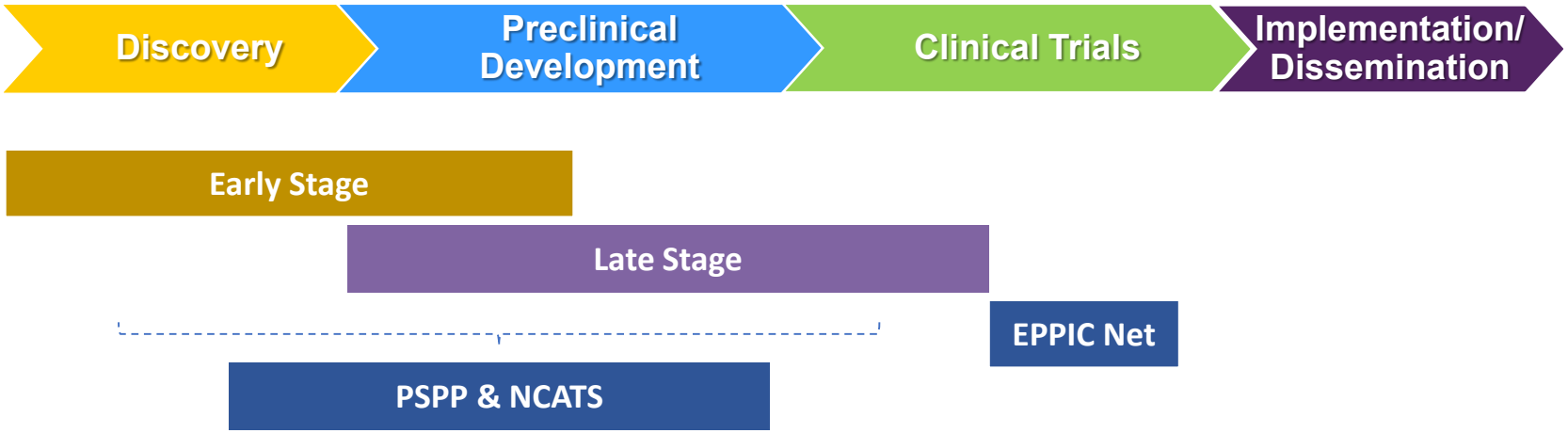
Goal

Accelerate development of novel, non-opioid, non-addictive analgesics

Five-year Benchmarks

- ✓ At least 5 promising projects with appropriate assay(s), model(s), and tools - ready for preclinical lead optimization.
- ✓ At least 3 novel analgesics with an IND and human safety data – ready for clinical efficacy studies through EPPIC-Net or equivalent phase II trial.

Proposed HEAL Analgesic Development Program



Realign Programs for Analgesics Development:

- ✓ Focus on deliverables
- ✓ Focus on scientific challenges
- ✓ Minimize program complexity
- ✓ Incentivize industry to reinvest

Grants | Grants & Contracts | Grants, Contracts & Intramural Resources

Program Attributes

Enhanced monitoring & evaluation for program progression

- External panel of consultants
- Implementation, selection of models, assays, tools, nomination of candidate & program progress

Enhanced coordination

- Assist early stage projects to come into the program: planning awards
- Facilitate project advancement through development phases
- Coordinate with clinical input to advance project
- Facilitate industry partnership for early adoption
- Assure mission relevance and overall diversity

Enhanced Participation

- Assist early stage projects to come into the program: planning awards

Proposed HEAL Analgesic Development Program: *Early Stage*

Planning

- Construct preliminary data for targets, assays, and models
- Validate initial findings to reduce risk
- Build teams to transition into Early stage

Early Stage*

- Validate promising target(s)
- Develop assays and conduct screening
- Perform rigorous efficacy studies including PK/PD/ADME
- Validate end points and models
- Collaborate with PSPP and NCATS

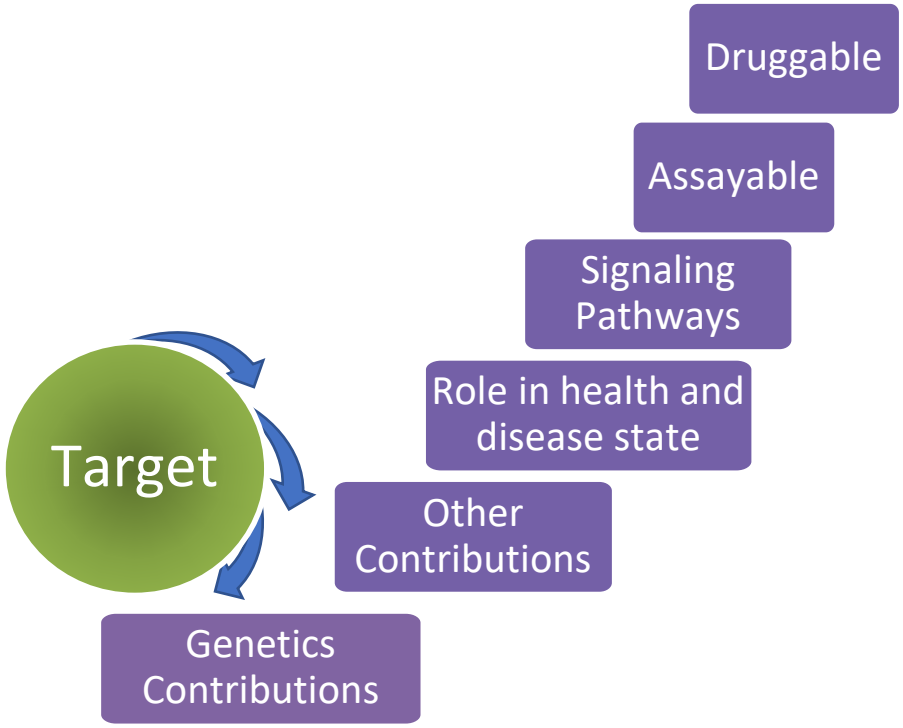
End Goals and Milestones:

- ✓ Identify assays
- ✓ Validate models and testing tools
- ✓ Identify tools ready for optimization
- ✓ Identify a development path forward
- ✓ Seek partnerships
- ✓ Ready for Late Stage

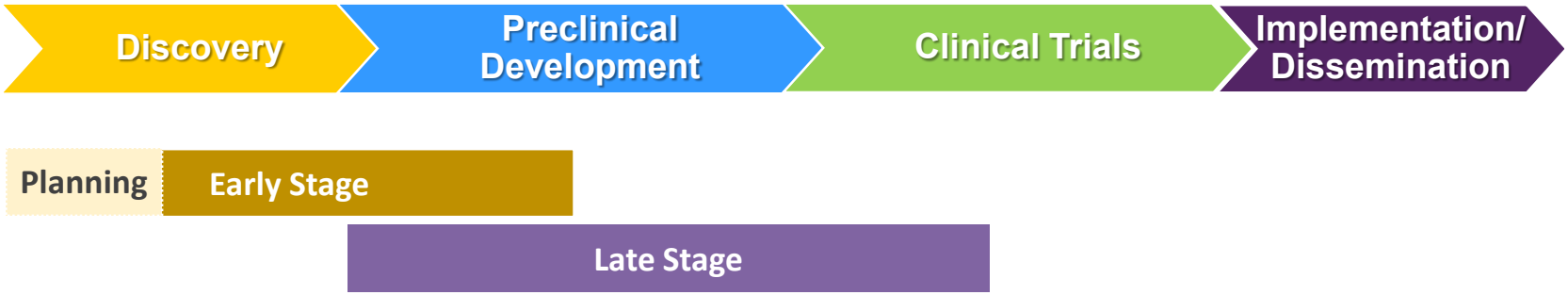
*Projects can go directly into Early Stage

Early Stage: Build Confidence and Ready for Preclinical Lead Optimization

- ✓ Study signaling pathway
- ✓ Identify multiple mechanisms that modulate the target
- ✓ Demonstrate target effects on the pathophysiology
- ✓ Demonstrate modulation of target effects the pathophysiology
- ✓ Develop and validate assays and tools specific for analgesic development



Proposed HEAL Analgesic Development Program: *Late Stage*



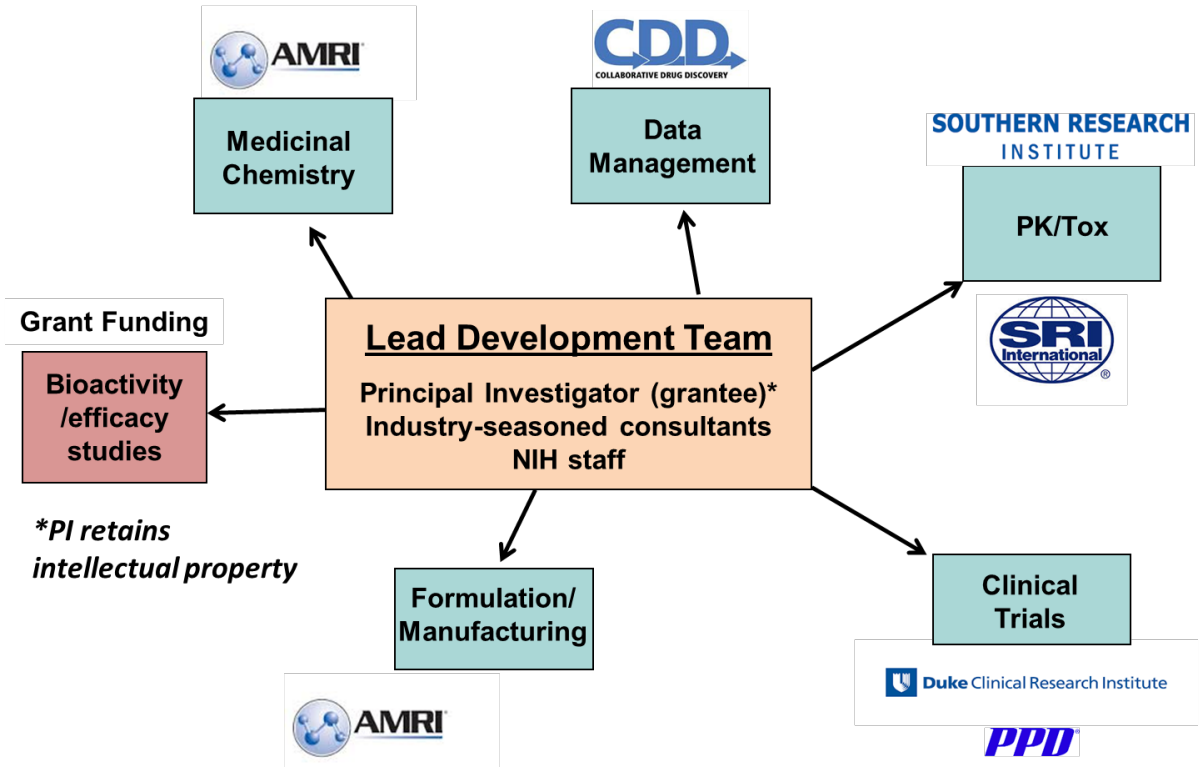
Late Stage

- Confirm assays and studies necessary to initiate optimization or IND-enabling studies
- Conduct lead optimization to identify a development candidate
- Conduct IND-enabling studies and Phase I trials
- Collaborate with expert scientific consultants, CROs, PSPP, and NCATS

End Goals and Milestones:

- ✓ Identify clinical candidate
- ✓ File IND
- ✓ Complete phase I trial(s)
- ✓ Identify companion biomarker
- ✓ Seek partnerships
- ✓ Ready for phase II clinical trial

Late Stage: Provide Resources Not Readily Available in Academia



* Contract resources are tailor-made to support PI teams

Late Stage: Focus on Markers to Support Target Validation and Product Development

- ✓ Evidence that the test agent has interacted with the intended molecular target
- ✓ *Direct* or *indirect* biological consequence of target engagement by the drug regardless of desired clinical outcome

- PD/response (target engagement) biomarkers
- Stratification biomarkers
- Safety biomarkers

- PD/response (target engagement) biomarkers
- Safety biomarkers

- ✓ Correlated with drug exposure (PK/PD), can facilitate hypothesis testing
- ✓ Predict efficacy and can be used as surrogate markers of efficacy

Late Stage: Consult with FDA

- ✓ Discuss projects related to the prevention, treatment or diagnosis of acute or chronic pain
- ✓ Seek opportunities to collaborate in order to improve efficiency of the submission and review process for clinical investigators.
- ✓ Discus policy issues and guidance of interest
- ✓ Participate in NIH/NINDS sponsored conferences and workshops
- ✓ Help NINDS guide grantees by providing NINDS with relevant reference documents to investigational product review process and marketing approval processes

https://www.fda.gov/about-fda/domestic-mous/mou-225-19-027