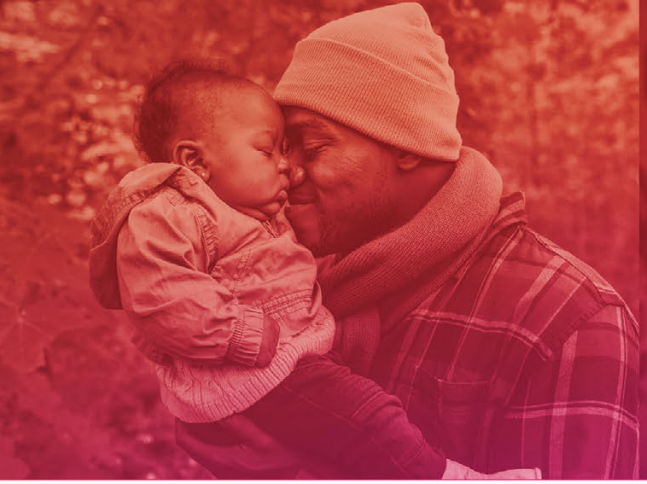

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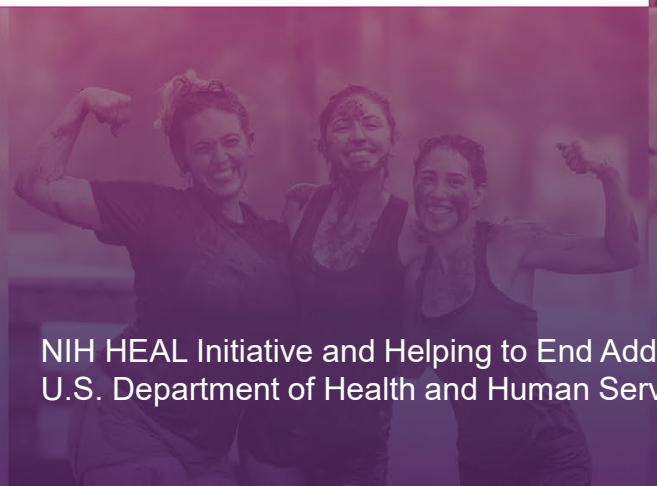
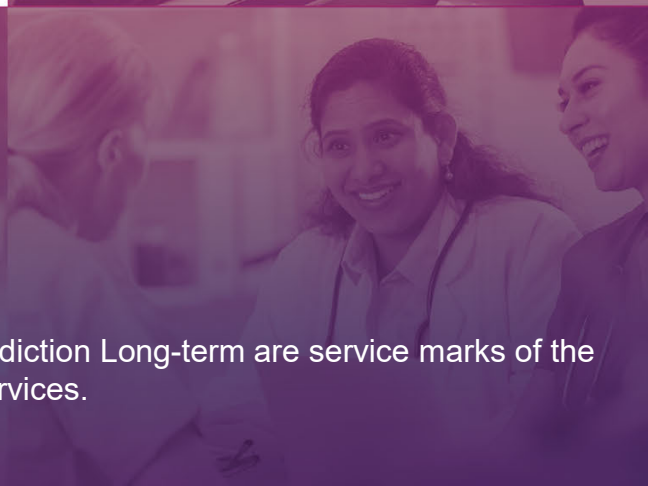
NIH HEAL Multi-Disciplinary Working Group

August 31, 2020

National Institutes of Health
HEAL Initiative

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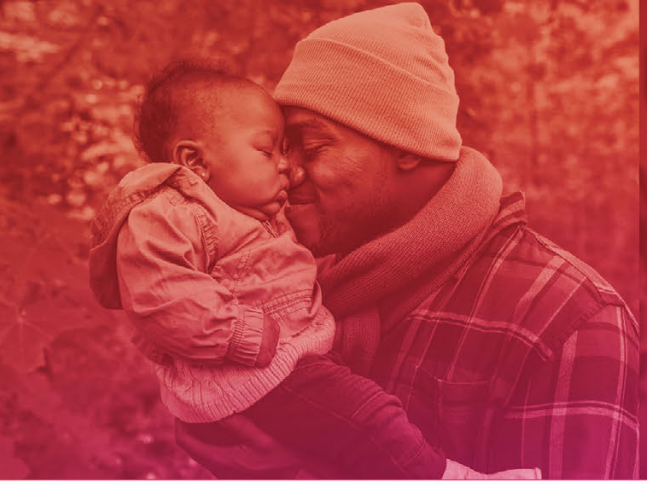
Welcome and Introductions



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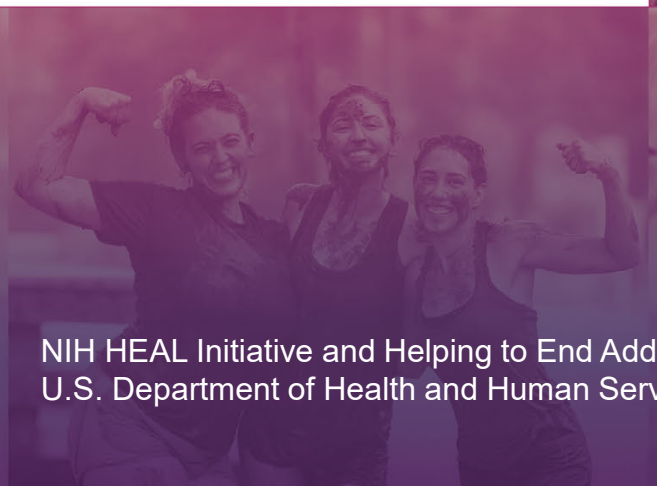
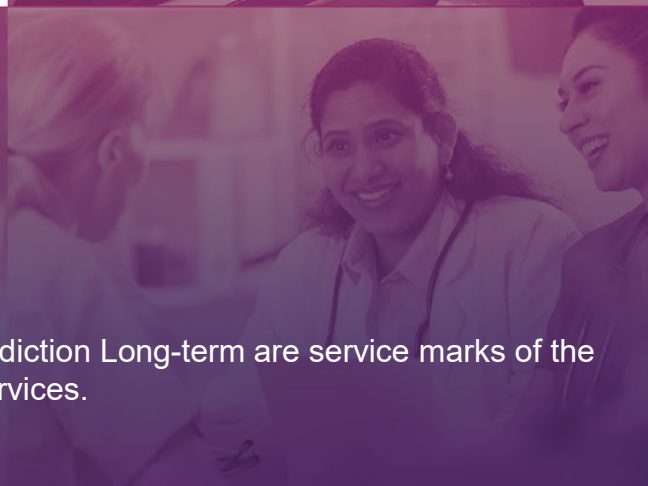
Overview of Current Portfolio

August 31, 2020

Rebecca Baker, Director, NIH HEAL Initiative

National Institutes of Health
HEAL Initiative

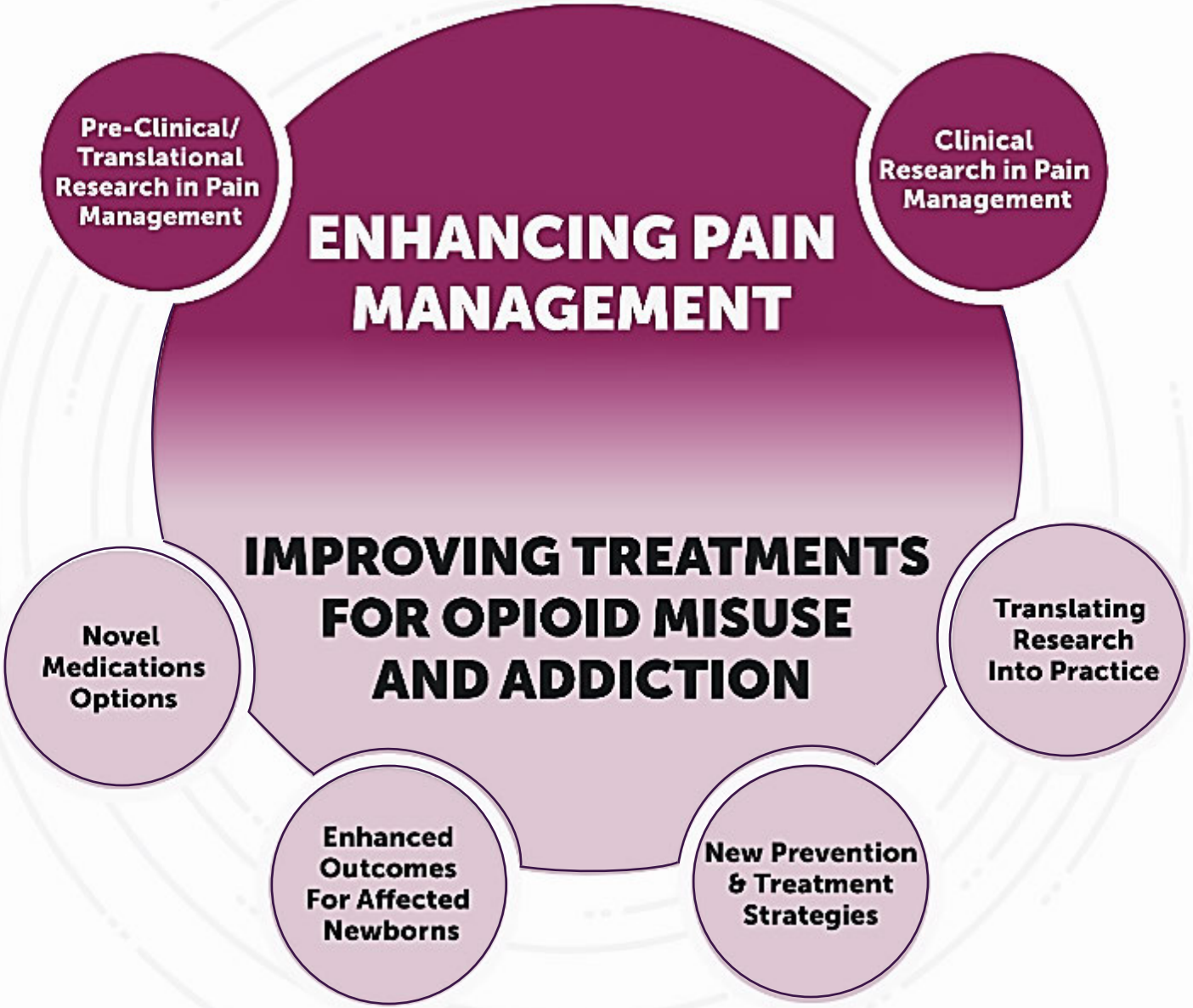
By the Numbers: $500 million/year Sustained Research Investment

25+ HEAL Research Programs

- 20 NIH ICs collaborating on studies
- Trans-NIH governance structure
- Partnerships across government, communities, and the private sector

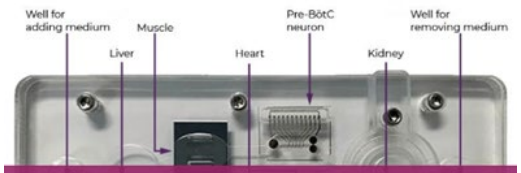
Prevention – Basic & Translational Research – Clinical Trials – Implementation Science

NIH HEAL INITIATIVE RESEARCH OVERIVEW



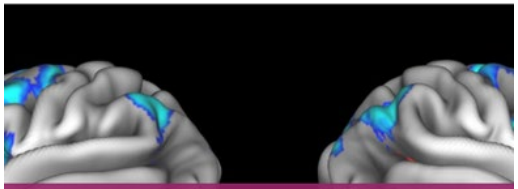
Research Spotlights

Help for Babies Born Dependent on Opioids
Infant/Child Outcomes



"Human-on-a-Chip" Models Effects of Opioid Overdose
Pain – Preclinical/Translational Research

The Search for New, More Targeted Pain Treatments
From surgery and drugs to cell-based therapies, researchers will test innovative, non-addictive approaches for treating pain.



Can Exposures Before Birth Predict Health Later in Life?
Infant/Child Outcomes

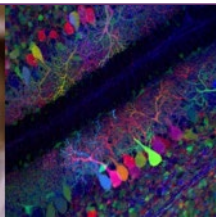
Is Lack of Sleep a Risk Factor for Relapse?
Preventing/Treating OUD

Next-gen Device Could Relieve Phantom Limb Pain
Pain – Preclinical/Translational Research

Staying on the Road to Recovery
Preventing/Treating OUD

Pre-Clinical and Translational Research in Pain Management

- Discovery and validation of novel targets for safe and effective pain treatment
  - 3 publications in basic and translational research area
- Translating discoveries into effective devices for pain treatment
- Optimizing non-addictive therapies to treat pain
  - Fast tracked FDA decision for new pain candidate
- Engineering preclinical screening platforms
- Biomarkers, signatures and endpoints for pain



Clinical Research in Pain Management

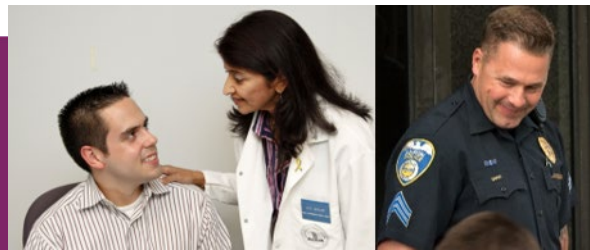
- Early Phase Pain Investigation Pain Network
- Back Pain Consortium Research Program
  - Dynamic back pain model
  - Predictive models for individualized responses to multimodal interventions
- Pain Management Effectiveness Research Network
- Pragmatic and Implementation Studies for the Management of Pain (PRISM)
  - Partner with CMS on effectiveness of acupuncture for low back pain
- Integrated Approach to Pain and Opioid Use in Hemodialysis Patients

New Prevention & Treatment Strategies for Opioid Use Disorder

- Preventing OUD among at risk adolescents
  - 9 projects focused on vulnerable populations (e.g. homeless youth and American Indian/Alaskan Natives)
- Optimizing care for people with OUD and common mental disorders
- Managing opioid misuse and low severity OUD
- Understanding the role of sleep dysfunction
- Determining the optimal length of medication treatment

Translation of Research into Practice for Effective Treatments for OUD

- Integrating multiple evidence-based interventions: HEALing Communities Study
- Enhancing the NIDA Clinical Trials Network to address opioids
- Promoting innovation in the criminal justice system (JCOIN)
  - 13 research studies across 21 states; >40K justice-involved youth
  - COVID-19 guidelines developed and distributed
- Understanding the role of behavioral health interventions (BRIM)



Novel Medication Options for Opioid Addiction and Overdose

- Increase effective medication options:
  - Enhanced formulations; addressing craving and withdrawal; novel targets for addiction and overdose
  - 8 HEAL-funding projects obtained IND
- Immune-based therapies for heroin and fentanyl
  - Consortium established

Enhanced Outcomes for Affected Newborns

- Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome: ACT NOW Study
  - Completed site selection across 20 states.
    - Clinical trials to begin early September 2020
    - Longitudinal Study launched Aug 5
- Understanding the long-term consequences of early opioid exposure: HEALthy BCD Study

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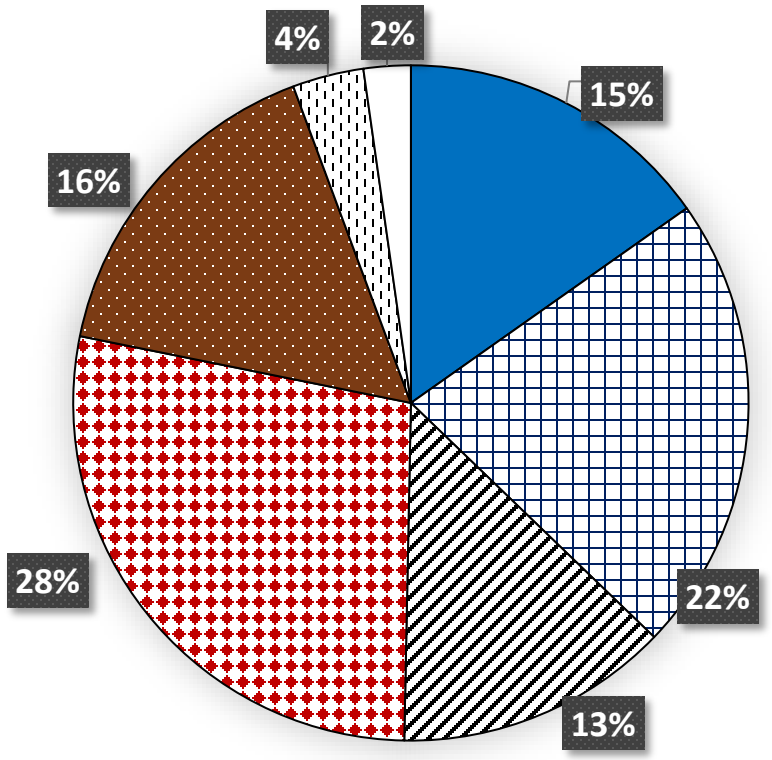
Investment in Pain and Addiction Research

5-year Budget Summary

Existing HEAL Investment by Research Focus Area (FY2019 Obligations)



- Preclinical and Translational Research in Pain Management
- Clinical Research in Pain Management
- New Strategies to Prevent and Treat Opioid Addiction
- Translation of Research to Practice for the Treatment of Opioid Addiction
- Novel Medication Options for Opioid Use Disorder and Overdose
- Enhanced Outcomes for Infants and Children Exposed to Opioids
- Research Support

Total= $945,569,913

Addressing Gaps in Research: Selected Examples of FY20 Investments

Understanding the Relationship Between Pain and Opioid Use Disorder

- Pain Management in the Setting of Opioid Use
- Strategies to Reduce Stigma in Pain Management and Addiction Treatment
- **Workshop:** Interventions for Managing Comorbid Chronic Pain & OUD

Addressing OUD and Co-occurring Mental Health Conditions

- Social Network Analyses to Reduce AI/AN OUD and Related Risk for Suicide
- Research to Manage Common Co-occurring Conditions
- Research Networks for the Study of Recovery Support Services for Persons Treated with Medications for OUD

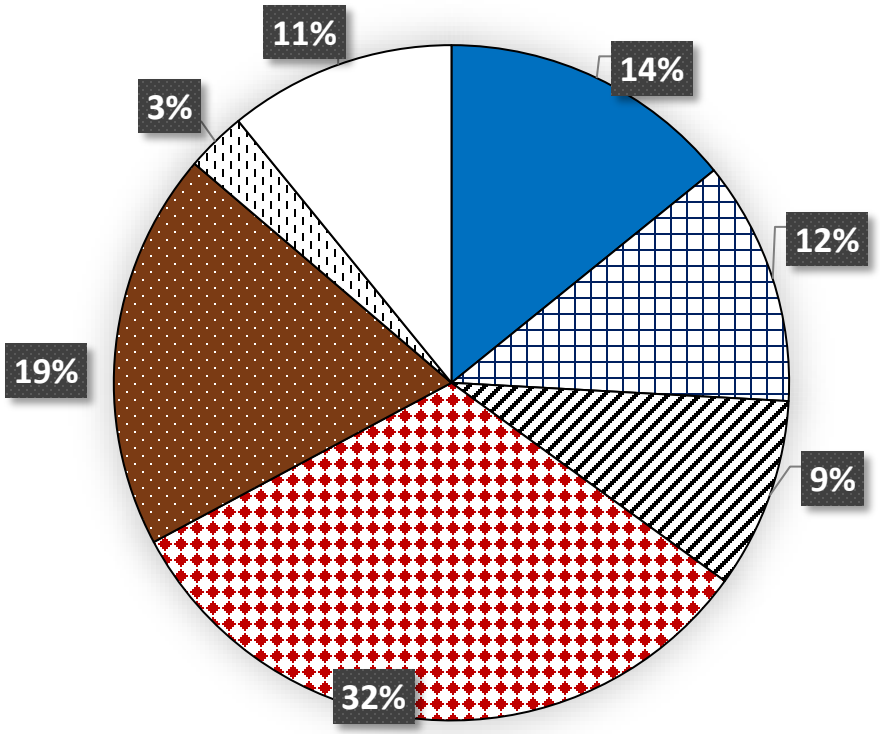
Understanding Diversity of Care Received Across Health Settings

- Best Management of Specific Pain Conditions in Primary Care, Hospital, Dental, or Emergency Settings
- **Workshop:** Navigating Pediatric to Adult Health Care Transition

Increasing Diversity Among HEAL Investigators

- Enhance Workforce Diversity
- Training Supplements for HEAL Network Clinical Trials
- **Workshop**: Research Priorities for Addressing Social and Economic Determinants of Opioid Related Health Disparities

Planned FY20 Obligation by HEAL Research Focus Area



Total: $532 million

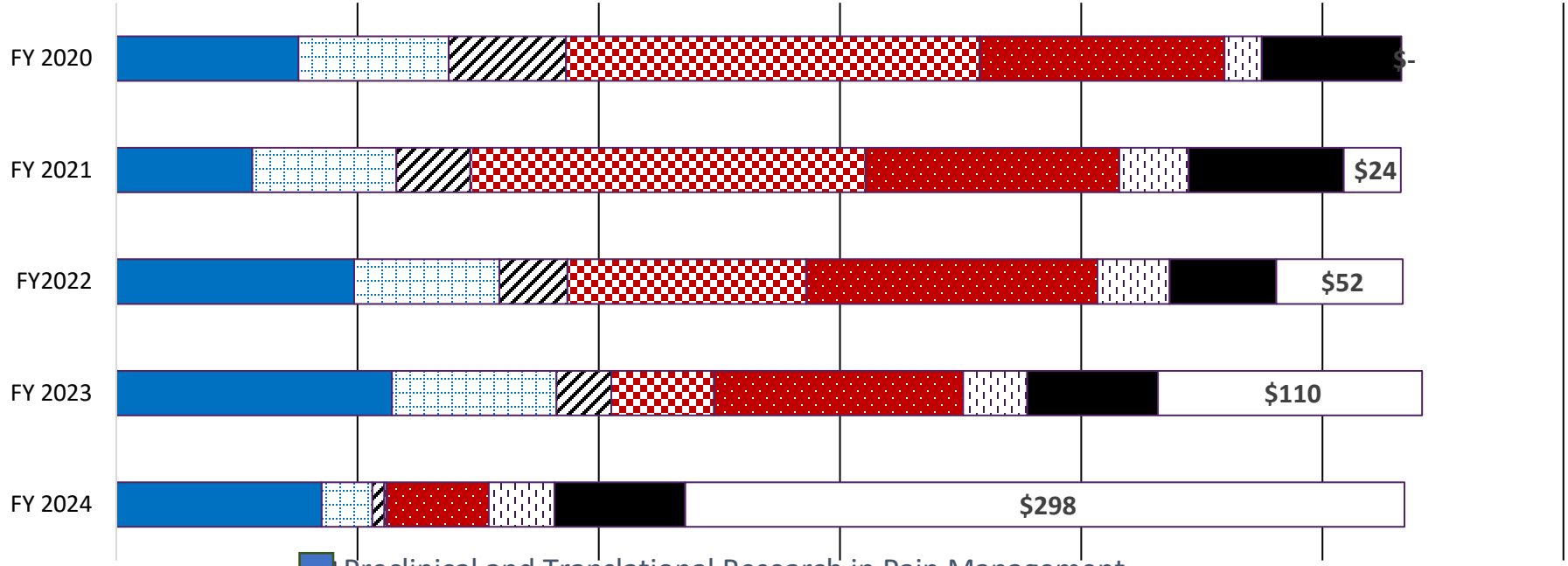
- Preclinical and Translational Research in Pain Management
- Clinical Research in Pain Management
- New Strategies to Prevent and Treat Opioid Addiction
- Translation of Research to Practice for the Treatment of Opioid Addiction
- Novel Medication Options for Opioid Use Disorder and Overdose
- Enhanced Outcomes for Infants and Children Exposed to Opioids
- Research Support

HEAL Concepts Moving Forward in FY2021

- ***Concept 1:** A Coordinated Suite of Funding Opportunities Supporting Early-Phase Therapeutic Development for Pain
- **Concept 3:** HEAL Studies to Enhance Phenotyping of Study Participants with Chronic Overlapping Pain Conditions
- **Concept 4:** Managing comorbid chronic pain and OUD

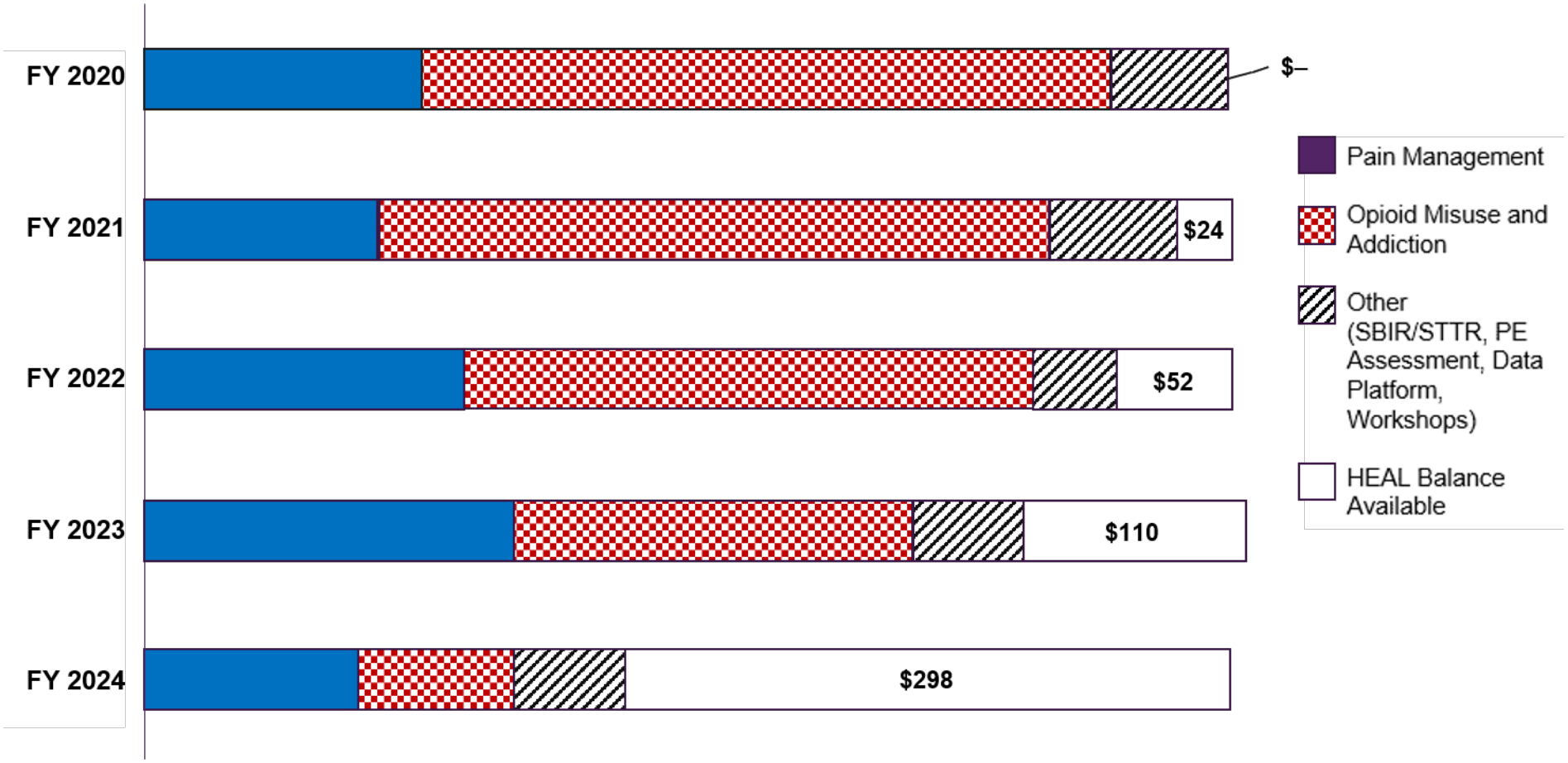
- **Concept 6:** Optimizing multi-component service delivery interventions for people with opioid use disorder, co-occurring conditions, and/or suicide risk
- **Concept 8:** HEALthy Brain and Child Development Study
- **Concept 9:** Comparative-effectiveness trial for the pharmacological treatment of neonatal opioid withdrawal syndrome
- **Concept 10:** Fast-track the discovery and development of medications to treat opioid use disorders

HEAL Initiative Budget: Future Funding Framework



Available funds to be divided evenly between pain and addiction focused research

HEAL Initiative Budget: Future Funding Framework



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Future Opportunities

FY 2020 HEAL Workshops

Interventions for Managing Comorbid Chronic Pain & OUD/Physical Dependence	June 1-2, 2020
Towards the Use of Buprenorphine in Infants: Scientific and Practical Considerations	August 24-25, 2020
Research Priorities for Addressing Social and Economic Determinants of Opioid-Related Health Disparities- Expert Panel Workshop and Planning Meeting	September 9, 2020
Workshop on the structural and dynamic imaging of myofascial tissues: potential impact on musculoskeletal pain research	September 16-17, 2020
Navigating pediatric to adult health care: Lost in health care transition	September 30-October 1, 2020
Developing meaningful endpoints for pain clinical trials	October 8 & October 15, 2020
Target Validation for Non-Addictive Therapeutics Development for Pain - Strategic Approaches and Best Practices	October 21, 2020

MDWG Topics of Interest

- Impact of COVID 19
- Ongoing budget outlook
- Special Populations
- Individuals with OUD and Mental Health Conditions
- Older Adolescents and Young Adults
- Justice Involved Individuals
- Infants and Children with NOWS

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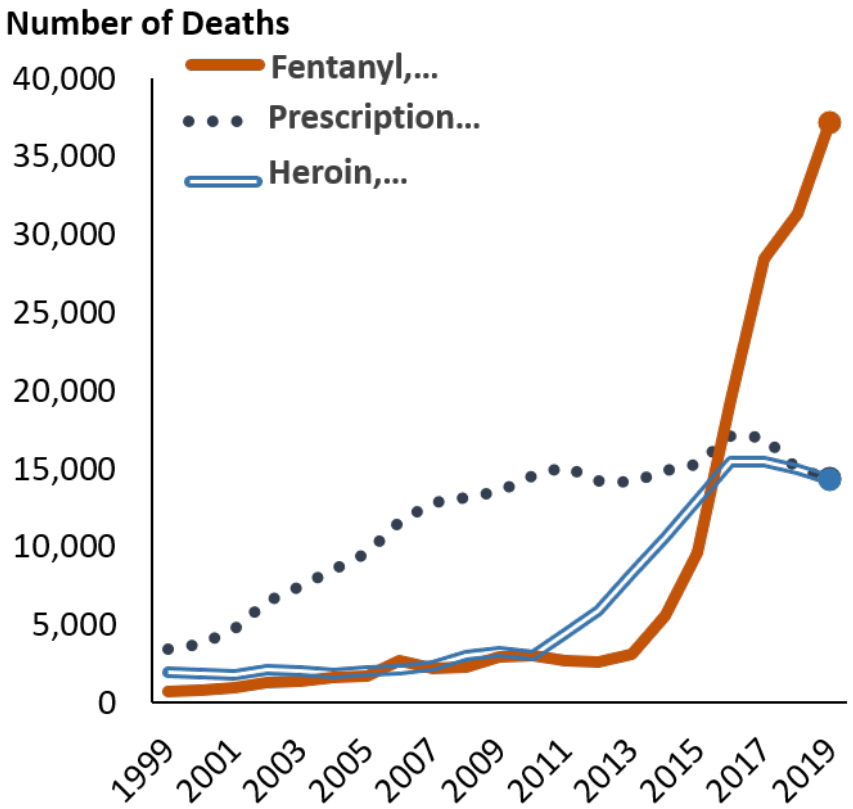
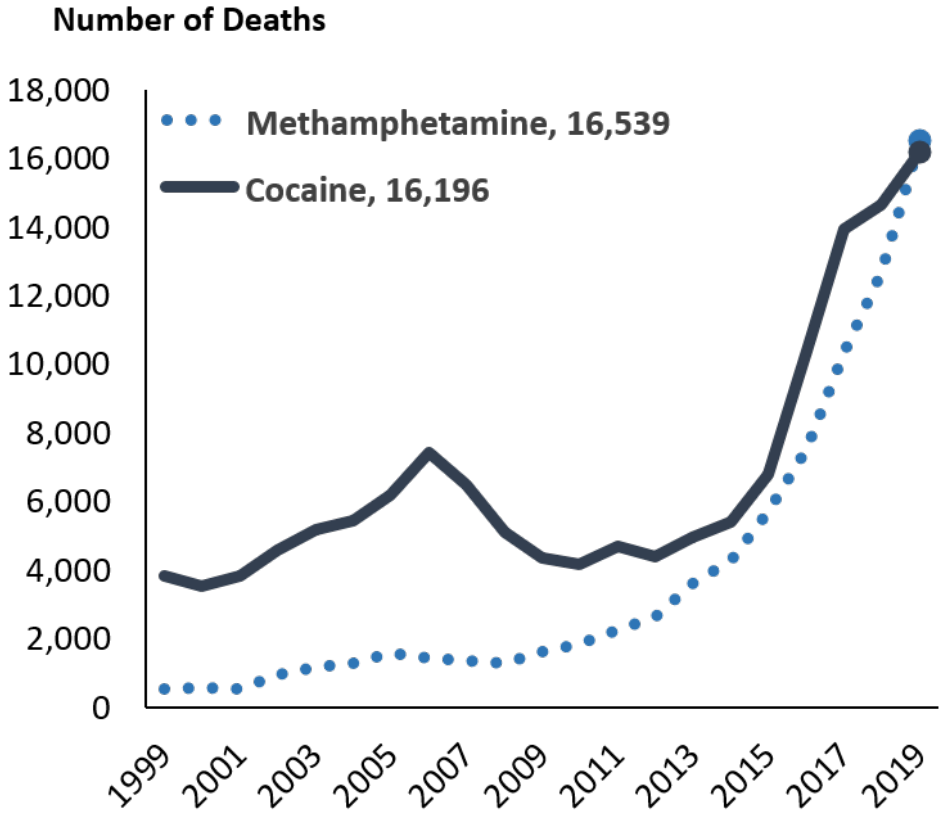
Emerging Issues in the Opioid Crisis: Collision of COVID-19 on Opioid Overdose and Treatment

Nora D. Volkow, M.D., Director, National Institute on Drug Abuse

Overdose Deaths in 2019 Increased by 4.6%





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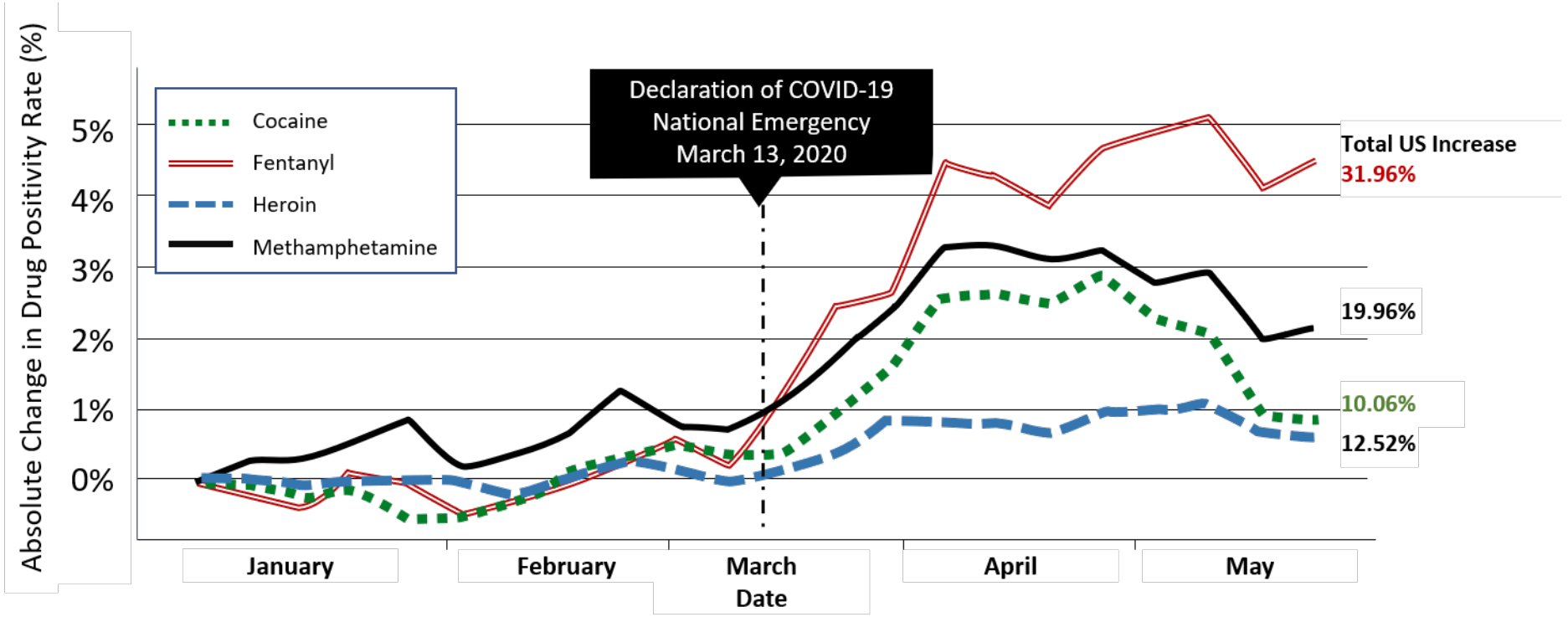
Drug Use Increase During COVID



Total Study Population Change in Unadjusted Positivity Rate for Cocaine, Fentanyl, Heroin and Methamphetamine

Millennium Health Signals Report™ **COVID-19 Special Edition**: Significant Changes in Drug Use During the Pandemic Volume 2.1 | Published July 2020

Overdoses Grew Dramatically During COVID Pandemic

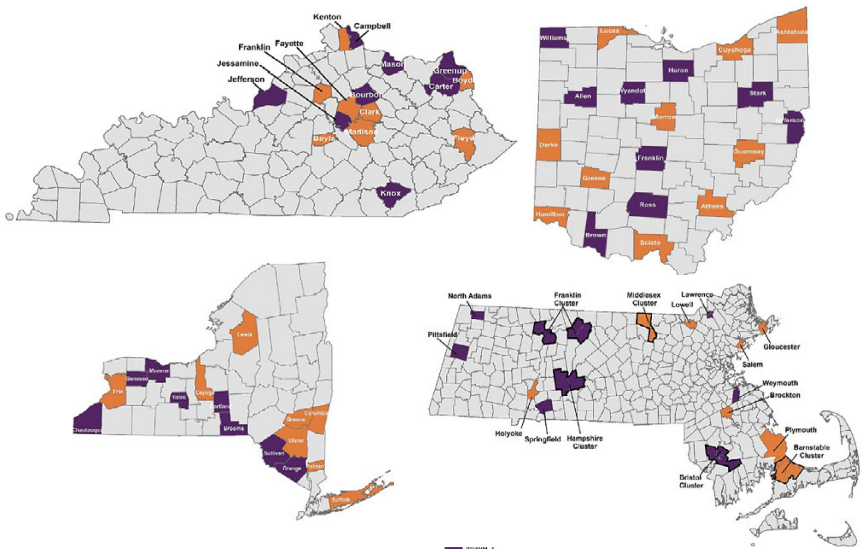
Overdoses increased up to 42% per month during the pandemic, as compared to the same months in 2019.

Note: Percent growth references the 1,201 agencies reporting to ODMAP by January

Source: ODMAP OVERDOSE DETECTION MAPPING APPLICATION PROGRAM

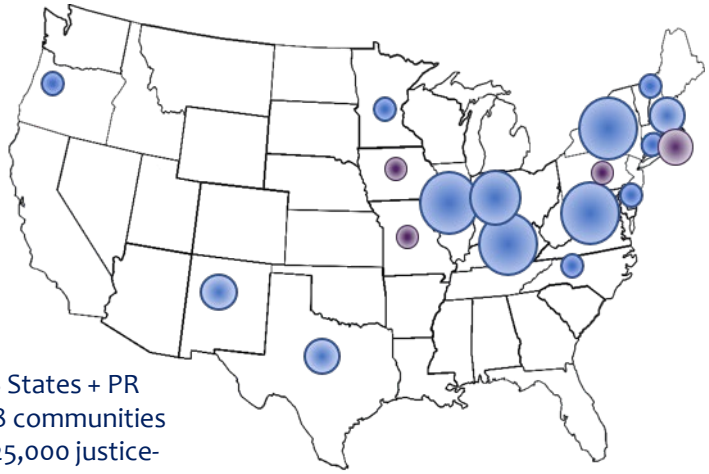
ALYSSA FOWERS/THE WASHINGTON POST

HEALing Communities Study



- Has the rate of overdoses changed?
- Impact on treatment initiation and retention
- Impact on drug access in the community
- Challenges to providers and first responders
- Challenges to those with SUD

Justice Community Opioid Innovation Network



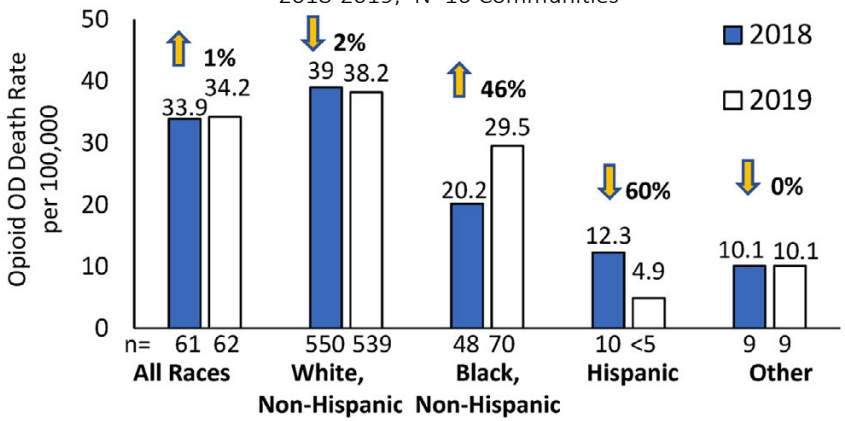
18 States + PR
88 communities
>25,000 justice-involved persons

- Compiled >120 guidelines/resources for justice systems responding to COVID-19
- Advisory group to provide real-time information to NIDA COVID-19 impact in justice settings

Overdose Deaths in HEALing Communities States

Kentucky Opioid Overdose Deaths by Race/Ethnicity:

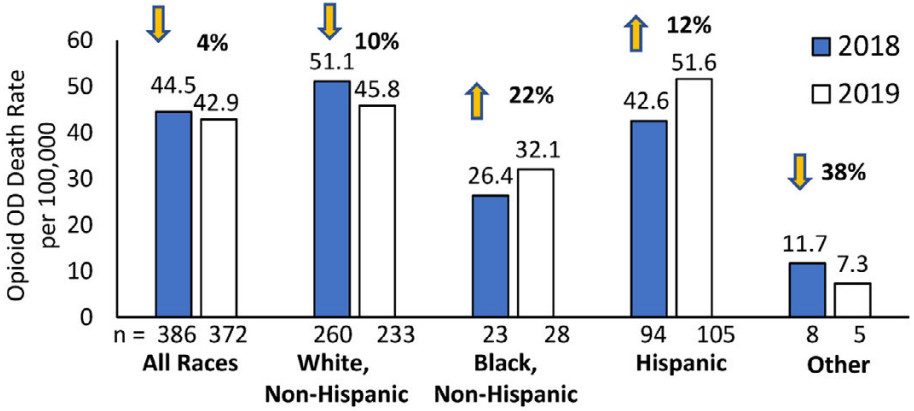
2018-2019, N=16 Communities



Source: KY Drug Overdose Fatality Surveillance System. Data as of July 3rd, 2020. Counts less than 5 suppressed by state data reporting policy. Produced by the Kentucky Injury Prevention and Research Center, University of Kentucky.

Massachusetts Opioid Overdose Deaths by Race/Ethnicity:

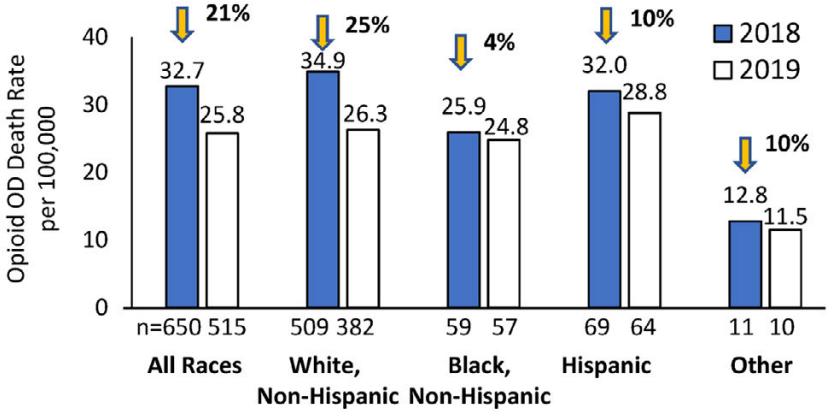
2018-2019, N=16 Communities



Source: MA Registry of Vital Records and Statistics

New York Opioid Overdose Deaths by Race/Ethnicity:

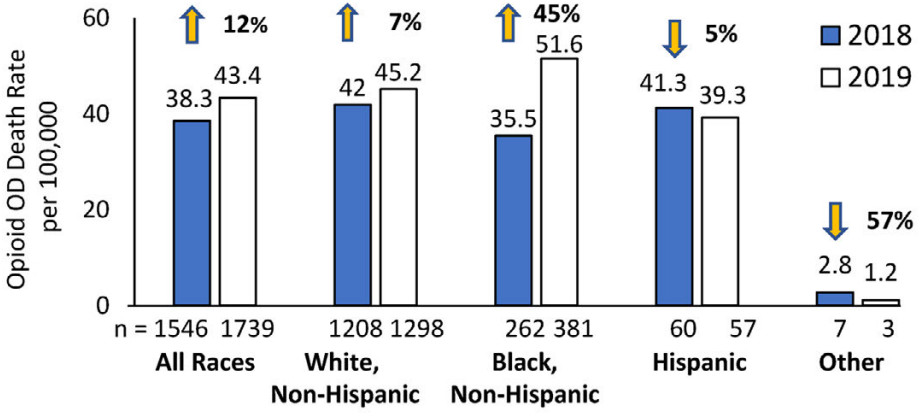
2018-2019, N=16 Communities



Data and analysis provided by New York State Department of Health
July 27, 2020

Ohio Opioid Overdose Deaths by Race/Ethnicity:

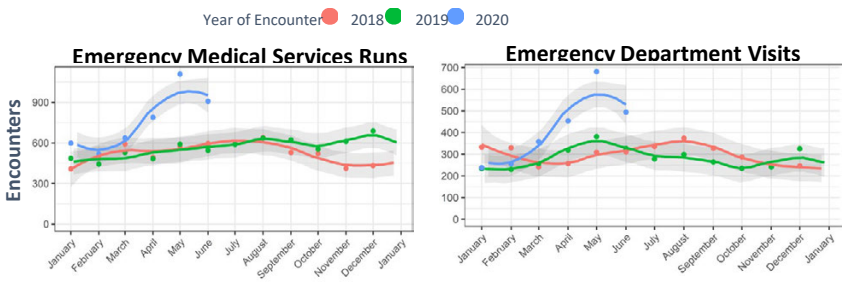
2018-2019, N=16 Communities



Source: OH Vital Records and Statistics (excludes small number of decedents missing race/ethnicity)

Overdose Encounters in HEALing Communities States

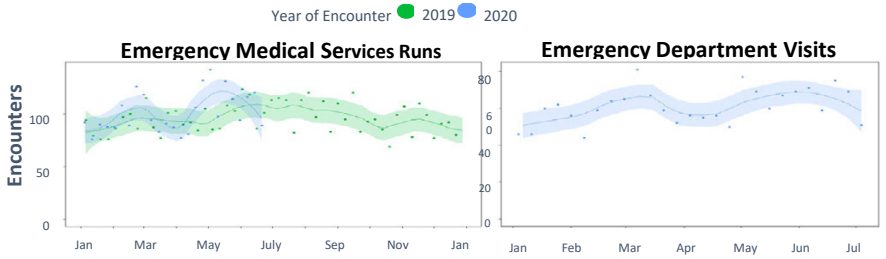
Kentucky HCS Opioid Overdose-related Encounters:
2018-2020, N=16 Communities



Data Sources: Kentucky Board of Emergency Medical Services data and Syndromic surveillance of emergency department visits

Solid lines represent LOESS Regression of Opioid Overdose Encounters. Points represent raw counts of records.

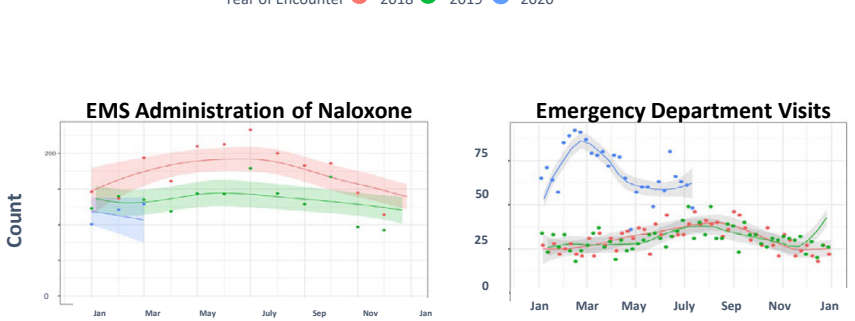
Massachusetts HCS Opioid Overdose-related Encounters:
2019-2020, N=16 Communities



Data Sources: MA Department of Public Health; MA Ambulance Trip Information System and Syndromic Surveillance data

Solid lines represent LOESS Regression of Opioid Overdose Encounters. Points represent raw counts of records.

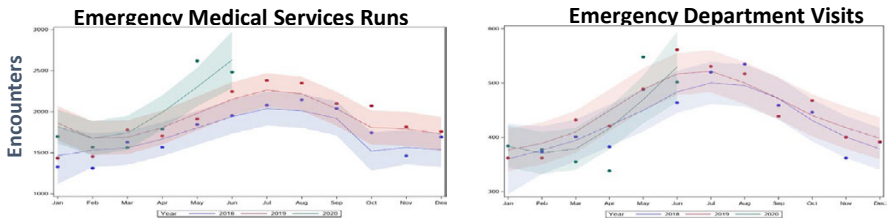
New York HCS Opioid Overdose-related Encounters:
2018-2020, N=16 Communities



Data Sources: New York State Bureau of Emergency Medical Services and Trauma Systems and Syndromic Surveillance of emergency department visits

Solid lines represent LOESS Regression of Opioid Overdose Encounters Points represent raw counts of records.

Ohio HCS Opioid Overdose-related Encounters:
2018-2020, N=19 Communities



Data Sources: Ohio syndromic surveillance of emergency department visits

Solid lines represent LOESS Regression of Opioid Overdose\ Encounters. Points represent raw counts of records.

[An accessible description of the graphs on this slide is available on the final slide in this presentation.]

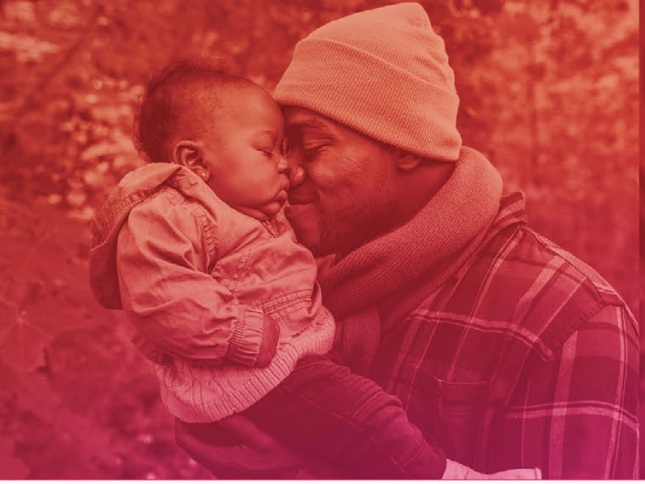
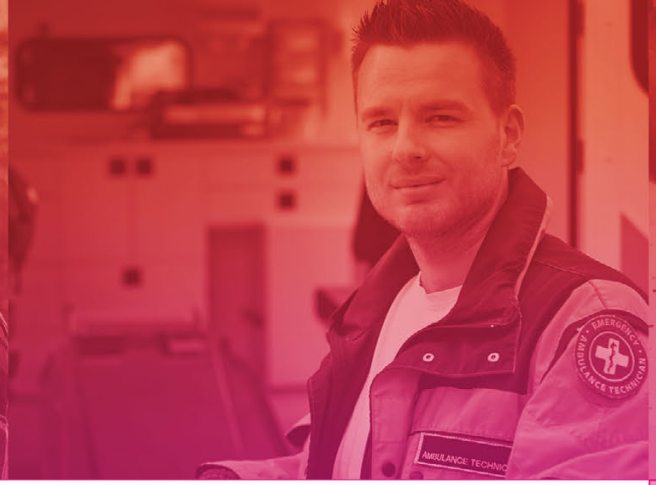
COVID & The Justice System

- People in jails & prisons are particularly vulnerable to COVID
- Some of the largest outbreaks in U.S. have been in jails or prisons
  - As of August 4th: > 86,000 cases
  - Outbreaks in jails and prisons can spread to the community
- Testing has been limited in prisons and jails (when available infection rates tend to be high; up to 98%).
- Rapid push to reduce incarcerated populations reduced census in jail & prison
  - Limited the ability to connect to community support services (housing, mental health, MOUD)
- Prisoners have limited access to MH and SUD services
  - Telehealth services are being adopted in some jails/prisons

Sources: https://www.nytimes.com/2020/06/16/us/coronavirus-inmates-prisons-jails.html; https://www.vera.org/publications/covid19-jail-population-decline https://www.themarshallproject.org/2020/05/01/a-state-by-state-look-at-coronavirus-in-prisons; https://www.vera.org/projects/covid-19-criminal-justice-responses/covid-19-data; https://www.themarshallproject.org/2020/07/16/prison-populations-drop-by-100-000-during-pandemic; https://www.themarshallproject.org/2020/06/01/what-covid-19-prison-outbreaks-could-teach-us-about-herd-immunity

Discussion

- How can collaboratives such as the JCOIN and HEALing Communities Study be assets during changing landscape of COVID?
- How can the HEAL Initiative best respond to the changing landscape of drug use during COVID?
- How are other aspects of HEAL affected by COVID and related aspects of the pandemic?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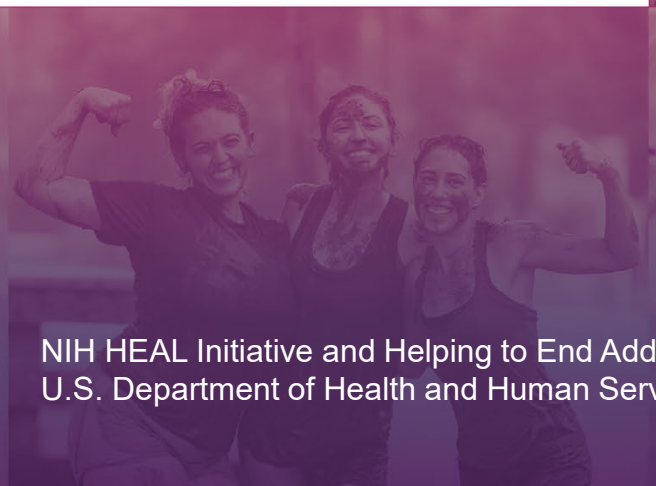
Realignment of the Analgesic Development Program

Walter Koroshetz, MD
Director, NINDS

HEAL Multidisciplinary Working Group; Aug. 31, 2020



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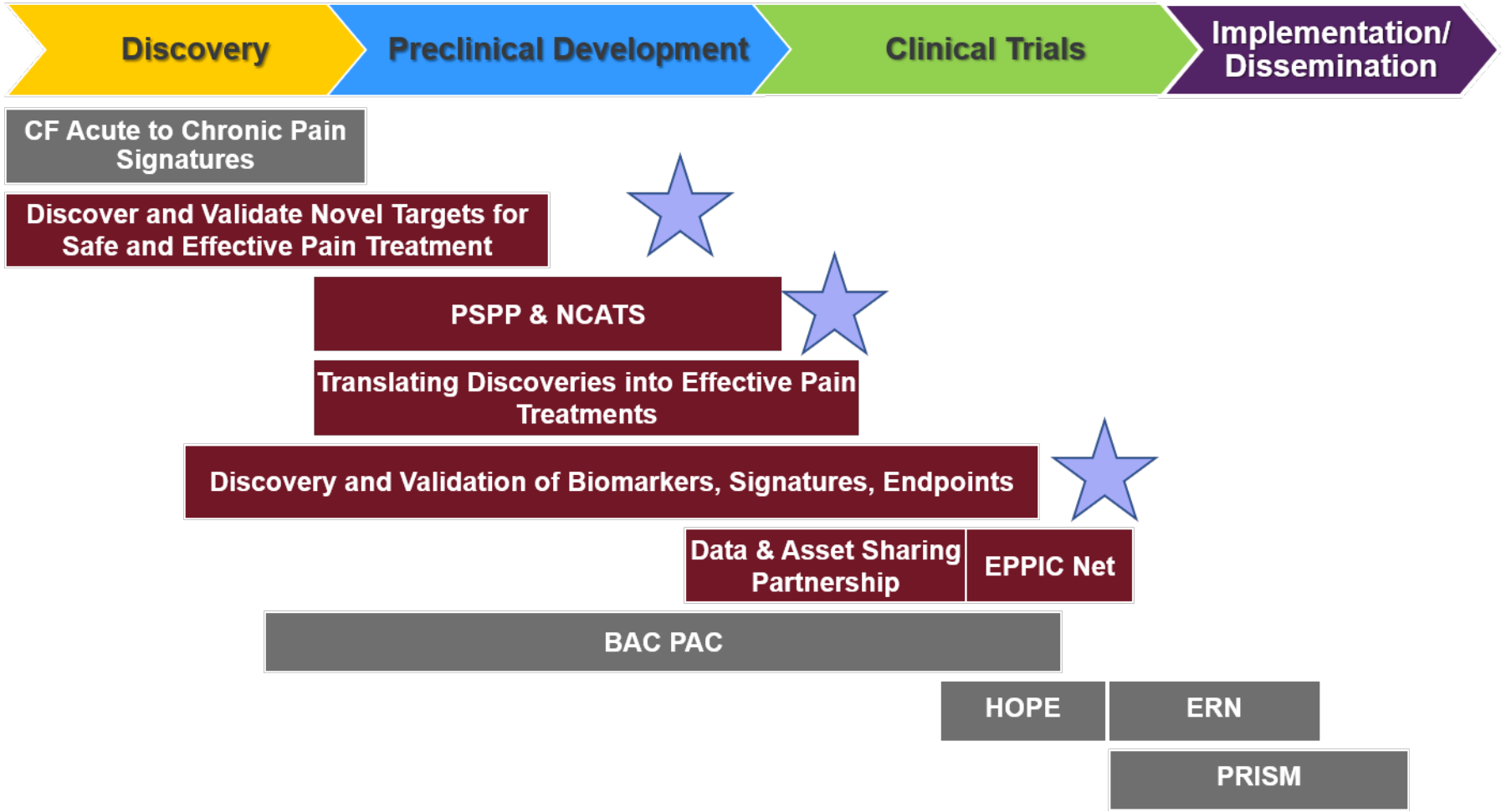
Bridging Gaps in the analgesic development pipeline

- **Academics and Small Biotechs:**
  - Excellent ideas with good scientific premise
  - 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
- **Realigned HEAL program will:**
  - Provide specialized drug discovery and development planning and expertise
  - Provide access to drug discovery infrastructure and testing to advance to clinic
  - Preserve investigators' IP
  - Combine the strengths of NIH and industry expertise for drug discovery

Current HEAL Programs for Enhancing Pain Management



Current HEAL Programs:

Discover and Validate Novel Targets for Safe and Effective Pain Treatment

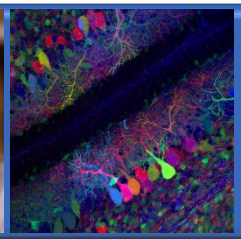
Previously identified targets

Basic biology target discovery projects

- *novel targets for small molecules, natural products, biologics, devices*
- *discovery of new stimulation or circuit*
- *CNS or PNS*

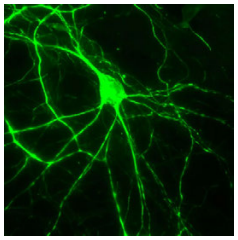
Pain target validation

- *In vitro/ex vivo assays*
- *Animal model development*
- *validation; robustness; reproducibility, pharmacodynamic and predictive biomarkers*

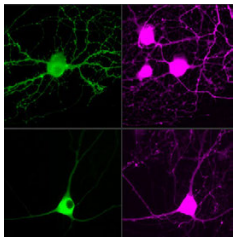


Enhancing Pain Management

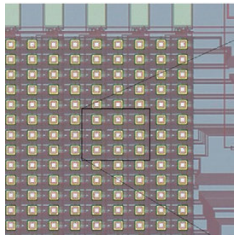
Current HEAL Programs:
Human Cell-based Screening Platforms



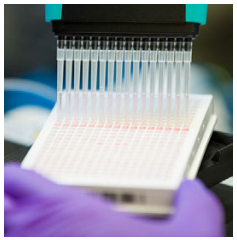
Access to human cell types



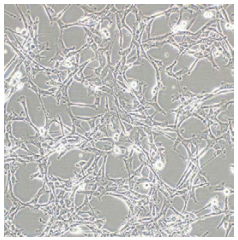
Advanced imaging technologies for functional cell characterization



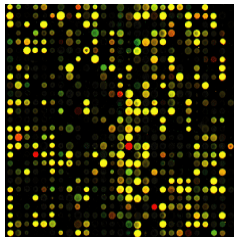
Electrophysiology methods



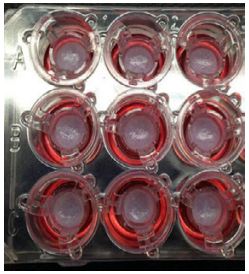
Measurement of signaling pathways, metabolism



Longitudinal tracking of cell behavior



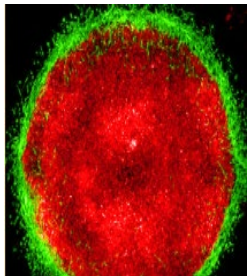
Combined single-cell transcriptomic & proteomic analyses



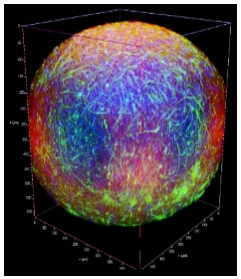
Tissue engineering technologies

Automated production of iPS cell-derived cells

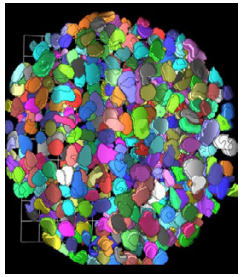
3D bioprinters



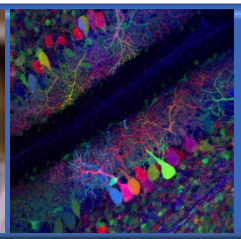
Spatially defined and physiologically relevant tissue models



Validation of 3D organoid cultures



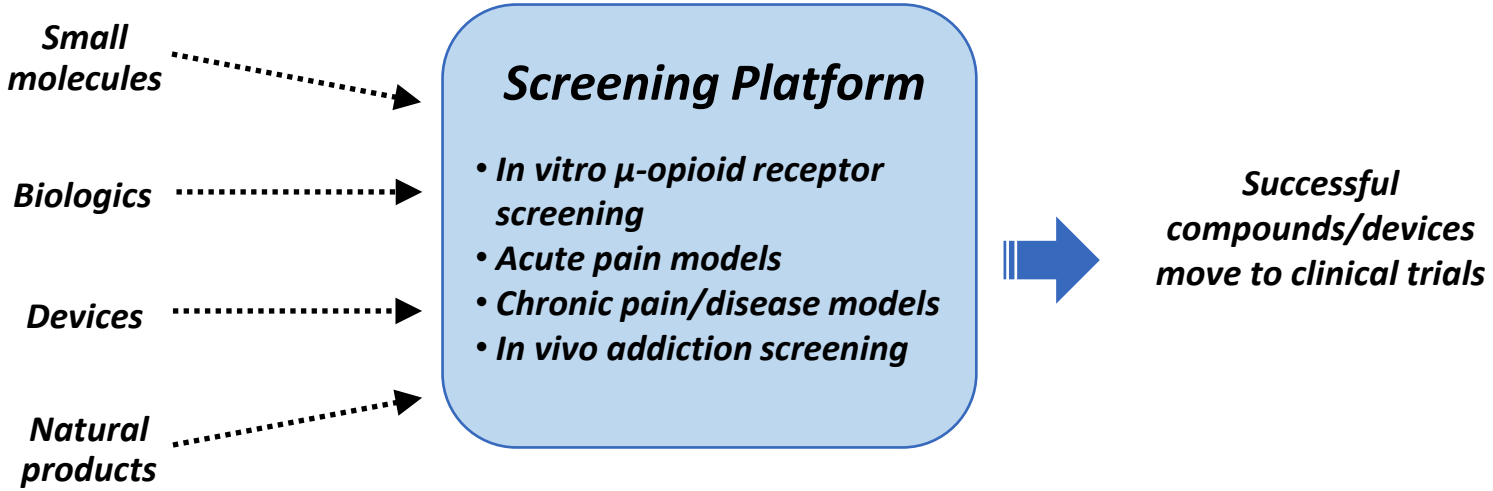
Assays using 3D tissue models

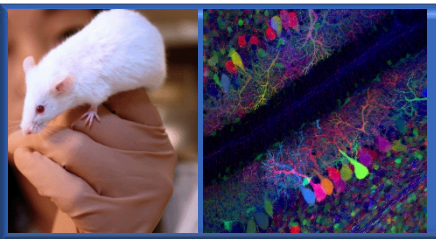


Enhancing Pain Management

Current HEAL Programs:
Preclinical Screening Platform for Pain (PSPP)

- Promote testing and characterization of non-addictive treatments
- Incentivize academia & industry to accelerate discovery of non-addictive, effective therapies
- Develop or refine animal models of pain conditions
- Generate high quality data to support partnerships, translational programs





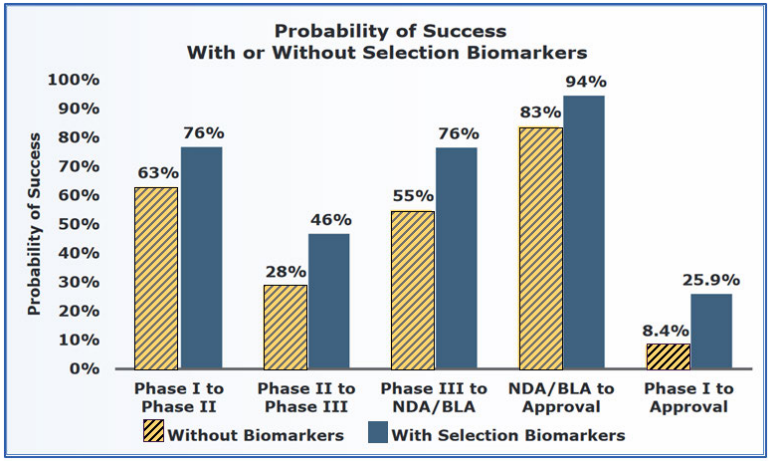
Enhancing Pain Management

Current HEAL Programs: *Biomarker Program*

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

Discovery of Biomarkers, Biomarker Signatures, and Endpoints for Pain

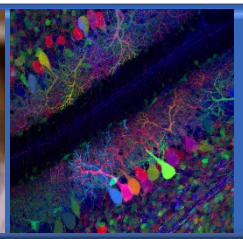
To facilitate discovery of robust biomarkers, biomarker signatures and objective endpoints for pain conditions



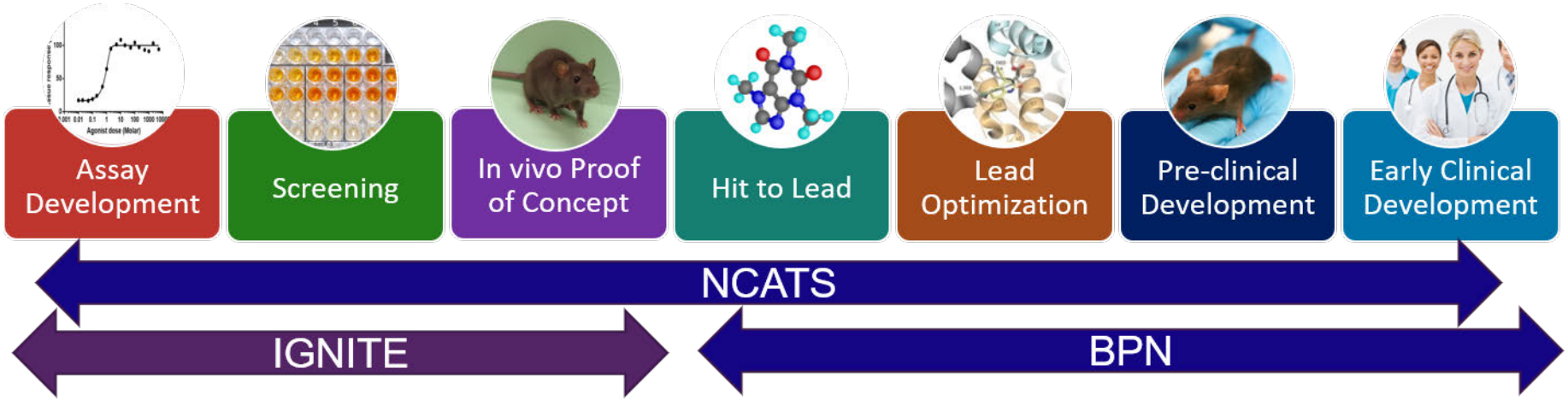
Thomas, D. W. *et al.* Clinical development success rates 2006–2015. *San Diego: Biomedtracker/Washington, DC: BIO/Bend: Amplion* (2016).

Analytical and Clinical Validation of a Candidate Biomarker for Pain

To support analytical and clinical validation of candidate biomarkers for use in the discovery and development of non-opiate alternatives to the treatment of pain conditions using retrospective and/or prospective methods



Therapeutic development programs outside of HEAL:
NCATS intramural, NINDS IGNITE and Blueprint Neurotherapeautics are Models to Bridge the Gaps



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 with goal of IND/IDE

NIH Blueprint for Neuroscience Research

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.

Realigned Program Strengths

Enhanced monitoring & evaluation for program progression

- External Panel of Consultants for implementation, selection of models, assays, tools, nomination of candidate & program progress

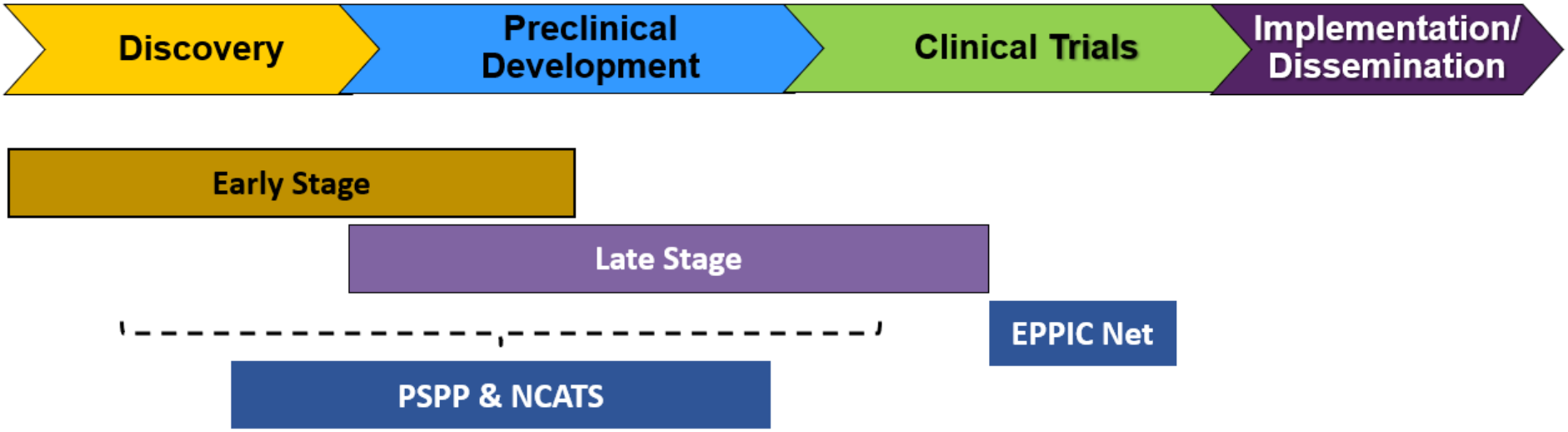
Enhanced coordination

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

Enhanced Participation

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

Realigned HEAL Analgesic Development Program

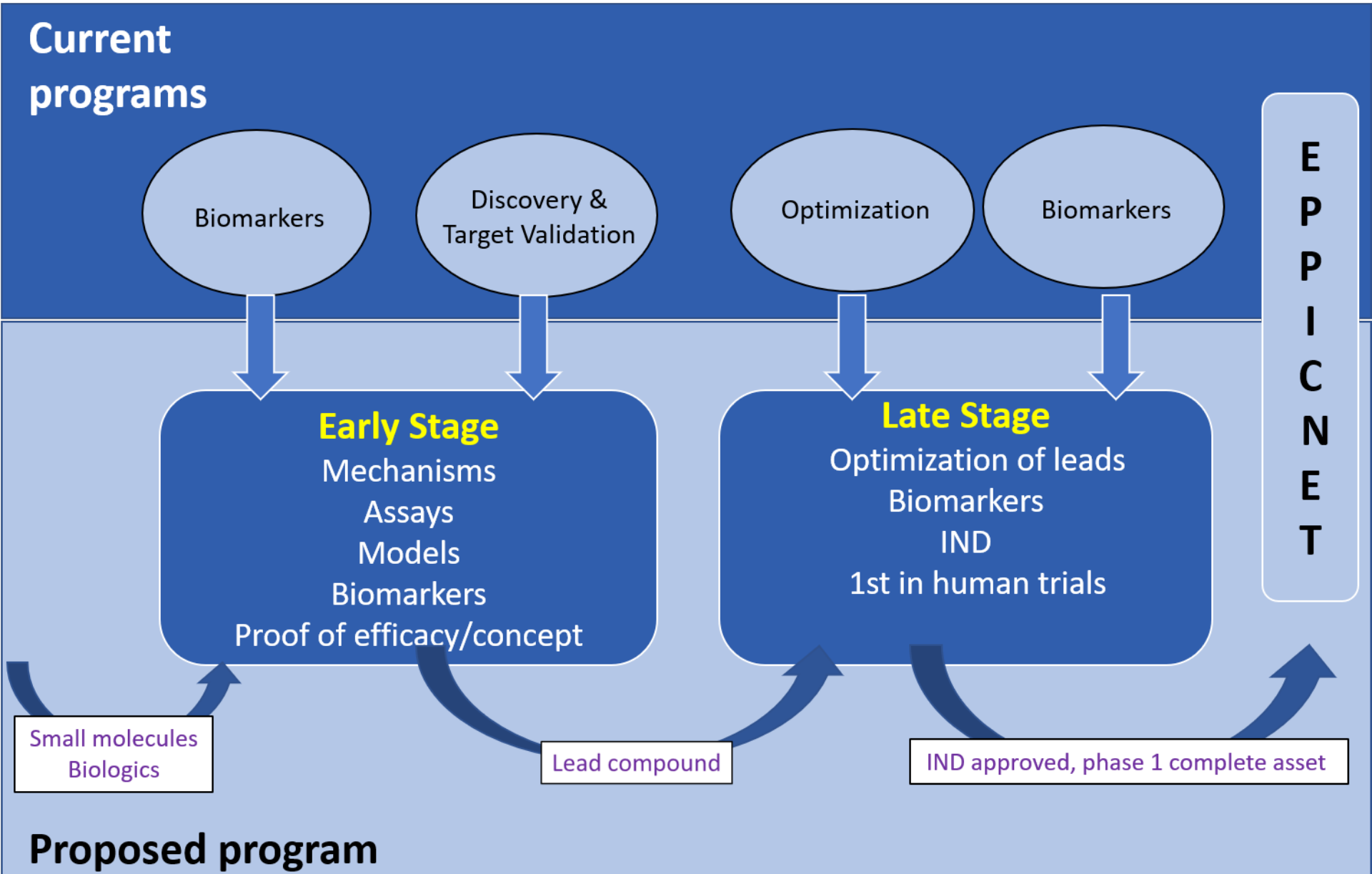


Realign Programs for Analgesics Development:

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

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

Realigned HEAL Analgesic Development Program

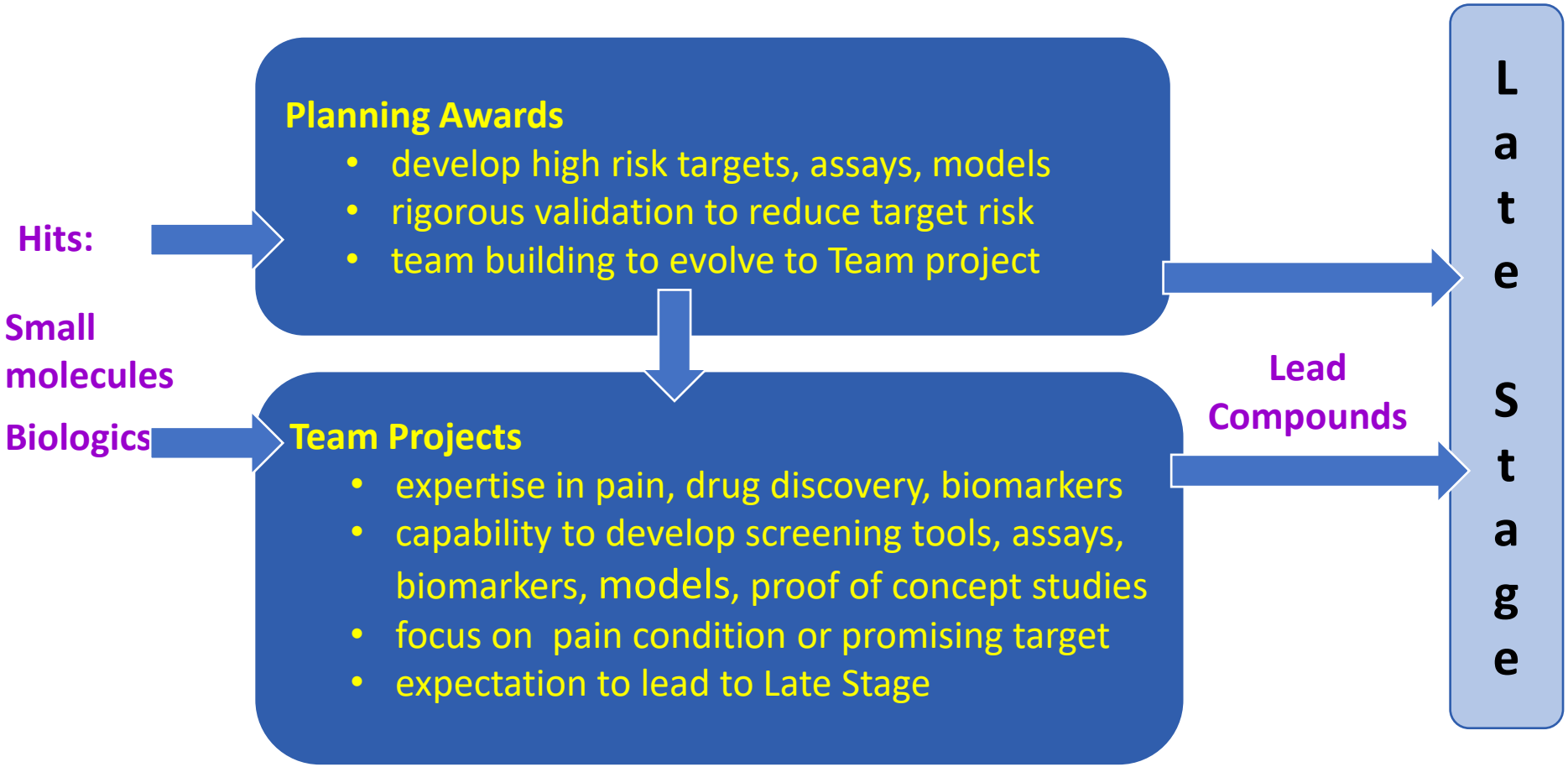


HEAL Analgesic Development Program: *Early Stage*

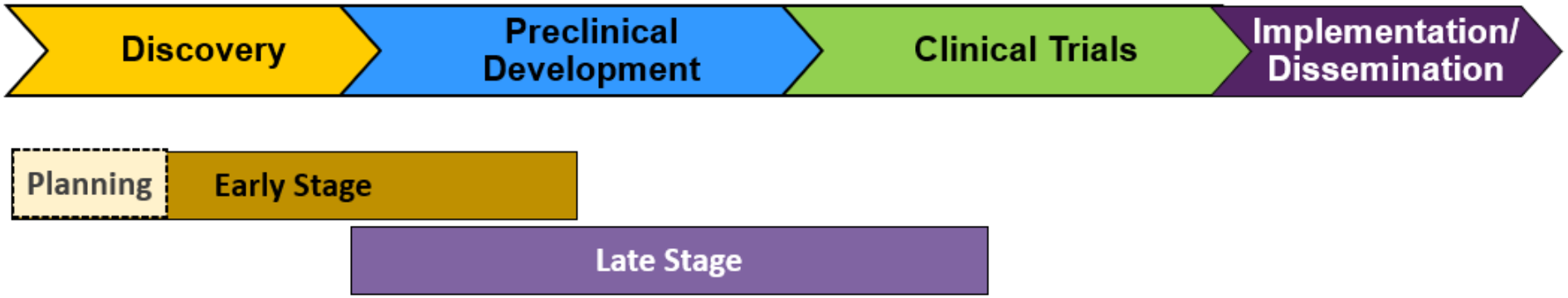
End Goals and Milestones:

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

HEAL Analgesic Development Program: *Early Stage*



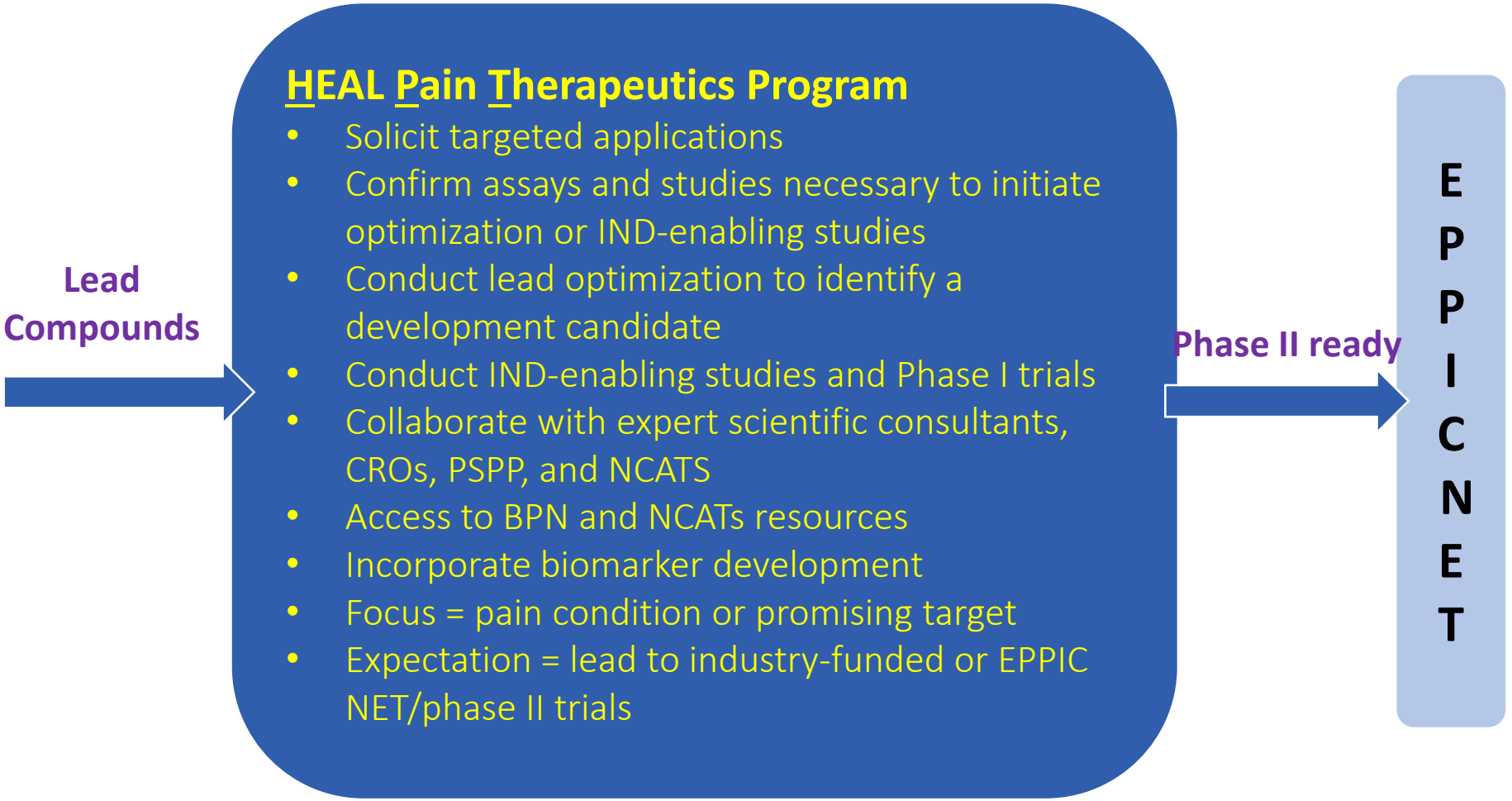
HEAL Analgesic Development Program: *Late Stage*



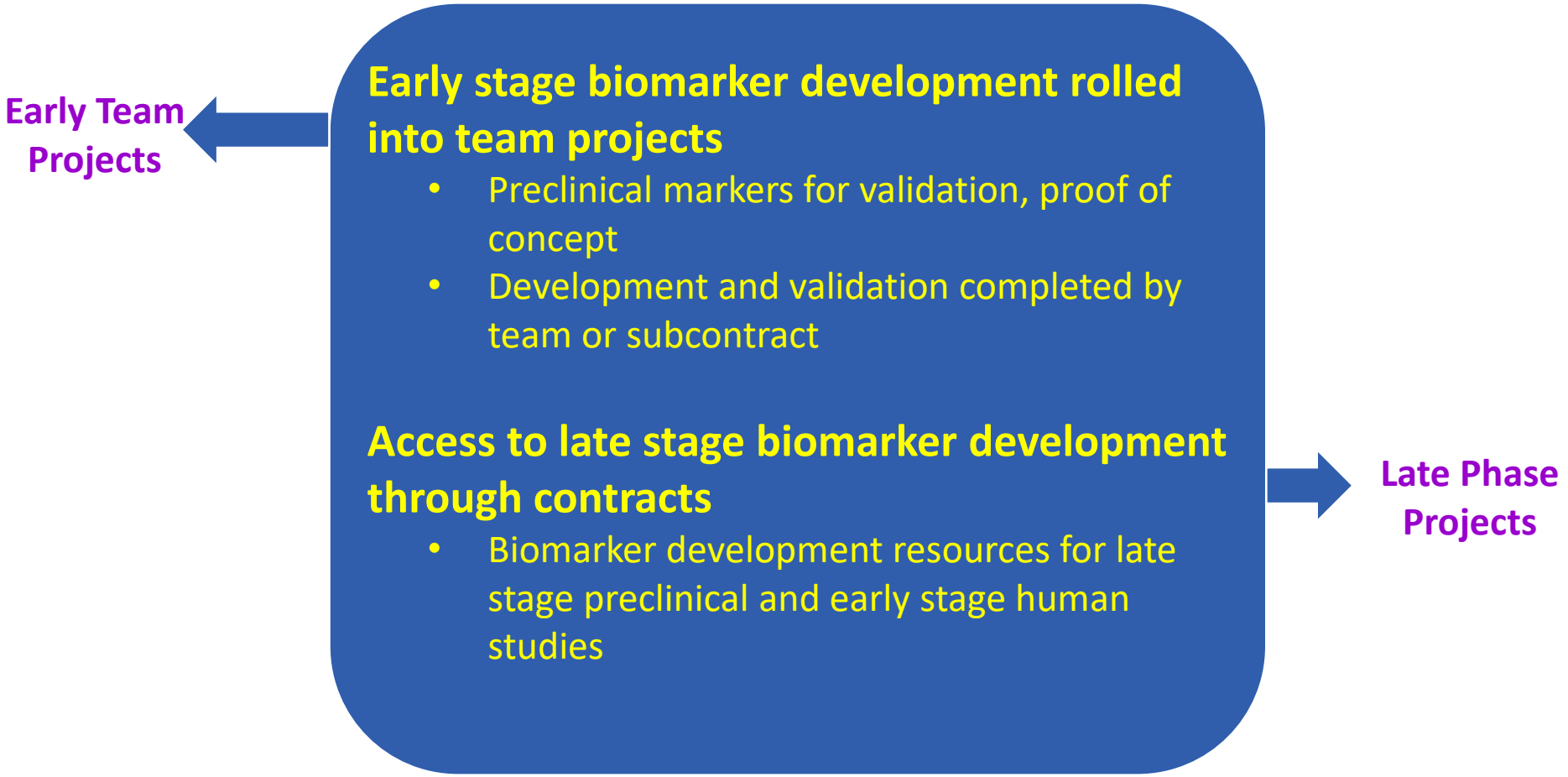
End Goals and Milestones:

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

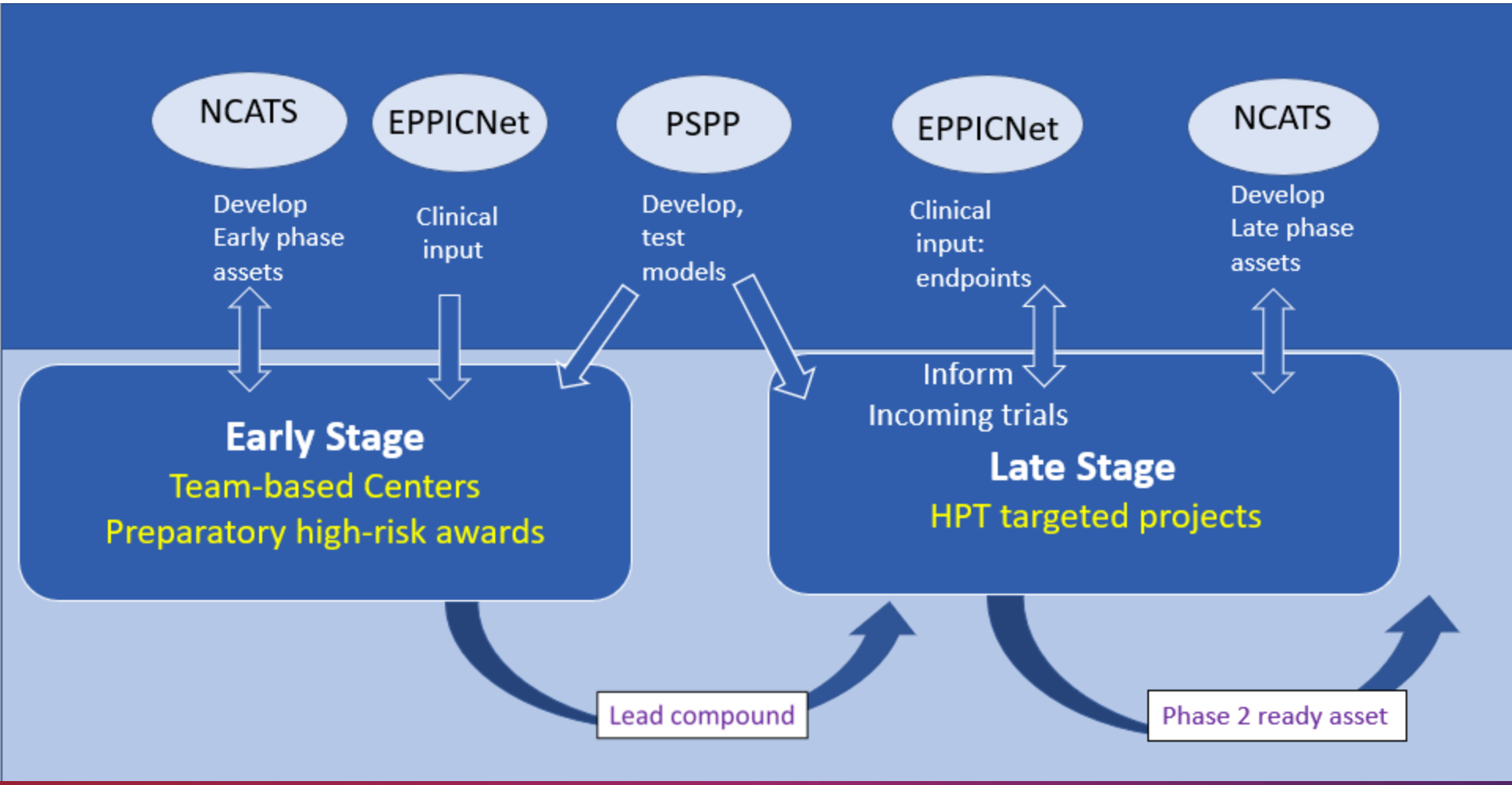
HEAL Analgesic Development Program: *Late Stage*



HEAL Analgesic Development Program: ***Biomarkers***



Leveraging other HEAL programs



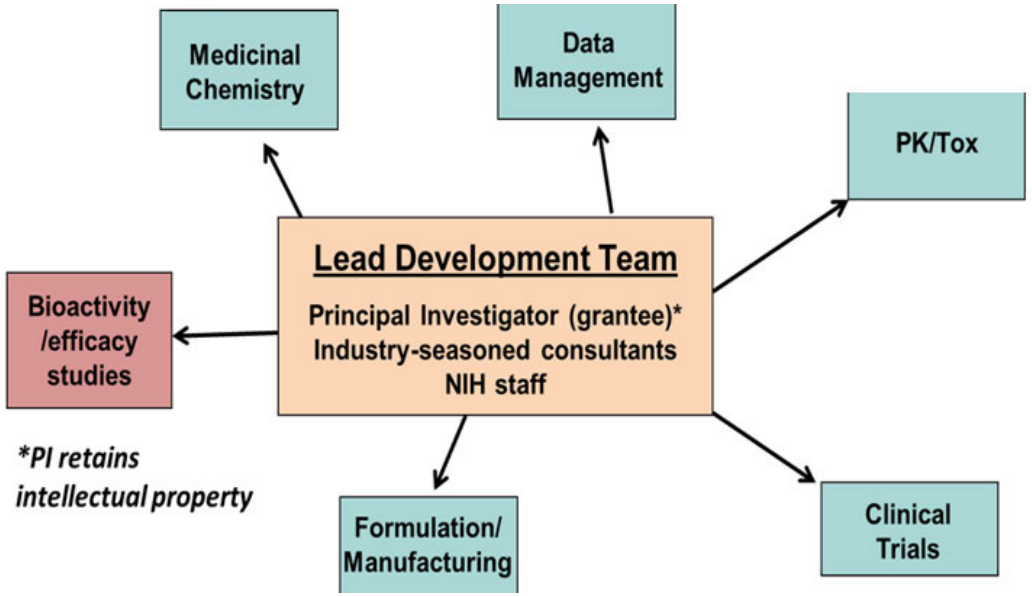
Early Stage:

Build Confidence and Get 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

Late Stage:

Provide Resources Not Readily Available in Academia



Closed Session

Adjourn

Accessible description of Slide 29

Slide 29 presents the number of opioid overdose–related emergency medical service (EMS) runs and emergency department (ED) visits 2018 to 2020 within Kentucky, Massachusetts, Ohio, and New York — the four states participating in the HEALing Communities Study. These data demonstrate the impact the COVID-19 pandemic has had on EMS and ED encounters in each state.

In Kentucky, EMS opioid overdose runs in May 2020 surpassed 900, compared with approximately 600 recorded for the same period in 2018 and 2019, with a slight decrease for June 2020. Similarly, in April and May 2020, ED visits for opioid overdose treatment exceeded the highest historical levels from the last two years, increasing from fewer than 400 to nearly 600 visits, with a dip in June 2020. Both of these trends show increases in opioid overdose encounters during the initial four months (March to June 2020) of the COVID-19 pandemic. Data Sources: Kentucky Board of Emergency Medical Services data and Syndromic surveillance of emergency department visits.

Opioid-related EMS and ED encounters in Ohio follow a similar pattern as Kentucky. EMS runs dramatically increased, to approximately 2,500 in April and May of 2020 compared with the same period in 2018 and 2019, where EMS runs hovered around 2,000. Similarly, Ohio ED visits trended upward in April and May 2020 compared with the two previous years. Data Sources: Ohio syndromic surveillance of emergency department visits.

Massachusetts lacked 2018 data for EMS runs; however, the number of encounters exceeded well over 100 in May 2020, compared with fewer than 100 in May 2019, returning to average values by June 2020. Massachusetts does not have ED visit data for 2018 or 2019; however, the number of ED visits decreased in April around the time of the COVID-19 stay-at-home order, which mirrors a decrease in data related to all ED visits during this time, with an increase between May and June 2020. Data Sources: Massachusetts Department of Public Health; MA Ambulance Trip Information System and Syndromic Surveillance data.

EMS runs associated with opioid encounters are quantified differently in New York than in Kentucky, Ohio, and Massachusetts. In New York, EMS runs where naloxone is administered are counted as opioid encounters. EMS naloxone administration data end in March 2020, limiting the ability to capture emerging trends at the onset of COVID-19. There are no significant changes between the first 3 months of 2020 and 2019. Beginning in 2020, additional diagnostic codes were added to the ED definitions of opioid-related visits, which accounts for much of the increase in the 2020 data compared with the data in 2018 and 2019. ED visits are trending downward beginning in March 2020 through July 2020, where data collection ends. Data Sources: New York State Bureau of Emergency Medical Services and Trauma Systems and Syndromic Surveillance of emergency department visits.

Return to Slide 29