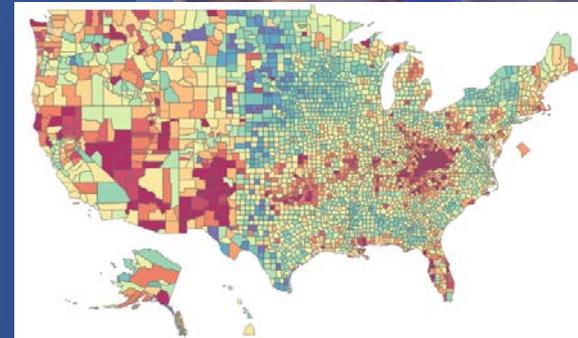
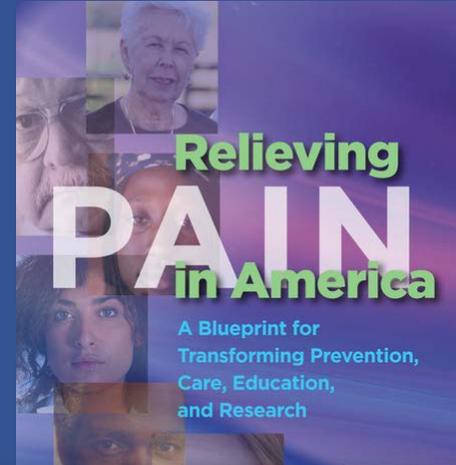
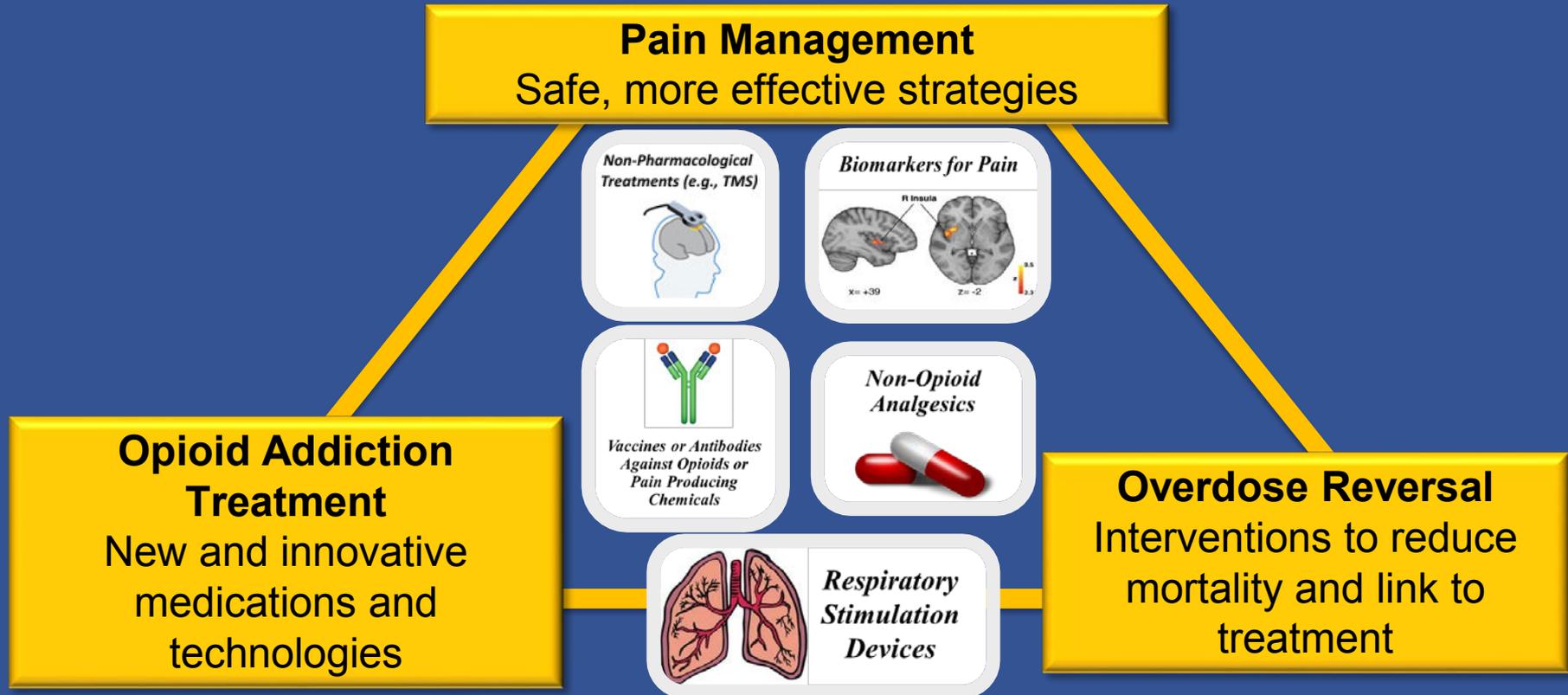


Crisis of Addiction and Pain in America

- >2M Americans are addicted to opioids
 - Most started with prescription medicines
- 100M American adults are burdened by chronic pain
 - >25M report *daily* pain
- Research has revolutionized our understanding of addiction and pain
 - Rapid translation of new knowledge into non-addictive approaches to pain management is urgently needed



NIH Seeks to Respond to the Crisis... With Research

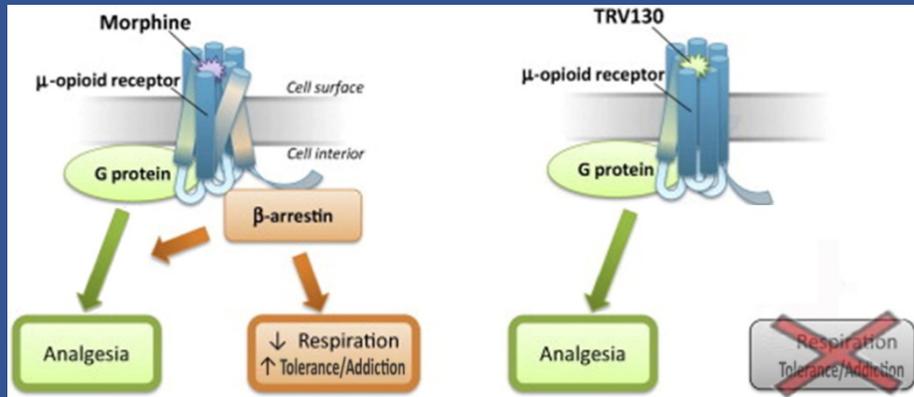
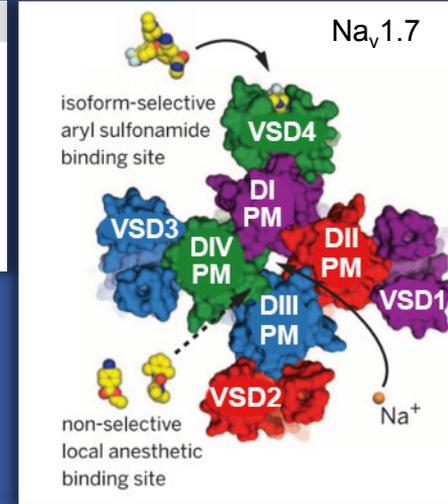


Some Successful NIH-Supported Innovations

NATURE|Vol 444|14 December 2006

An *SCN9A* channelopathy causes congenital inability to experience pain

James J. Cox^{1*}, Frank Reimann^{2*}, Adeline K. Nicholas¹, Gemma Thornton¹, Emma Roberts³, Kelly Springell³, Gulshan Karbani⁴, Hussain Jafri⁵, Jovaria Mannan⁶, Yasmin Raashid⁷, Lihadh Al-Gazali⁸, Henan Hamamy⁹, Enza Maria Valente¹⁰, Shaun Gorman¹¹, Richard Williams¹², Duncan P. McHale¹², John N. Wood¹³, Fiona M. Gribble² & C. Geoffrey Woods¹



Nasal spray device



New NIH Initiative to Address the Crisis: **HEAL: Helping to End Addiction Long-term**

- Collaborative, cross-cutting research
 - From basic to behavioral – and everything between
 - Innovative partnerships – across agencies, sectors, organizations – will ensure rapid progress
- \$500M/year provided by Congress in FY18 Omnibus
- Advances national priorities for pain, addiction research...

NIH HEAL Initiative: Selected Priorities for 2018

Opioid Use Disorder

- Improve therapeutic approaches to addiction and overdose
- Carry out real world implementation research to optimize interventions
- Evaluate treatments, consequences of Neonatal Opioid Withdrawal Syndrome (NOWS)

Pain Management

- Understand neurobiology of chronic pain
- Develop new non-addictive treatments for pain
- Build Clinical Trial Network for chronic pain

VIEWPOINT

Helping to End Addiction Over the Long-term

The Research Plan for the NIH HEAL Initiative

Francis S. Collins, MD, PhD
National Institutes of Health, Bethesda, Maryland.

Walter J. Koroshetz, MD
National Institutes of Health, Bethesda, Maryland; and National Institute of Neurological Diseases and Stroke, Bethesda, Maryland.

Nora D. Volkow, MD
National Institutes of Health, Bethesda, Maryland; and National Institute on Drug Abuse, Bethesda, Maryland.

Extraordinary focus by all segments of society is required to respond to the nation's opioid crisis. Now is the time to channel the efforts of the scientific community to deliver effective—and sustainable—solutions to this formidable public health challenge. Recognizing this opportunity, Congress added \$500 million to the base appropriation of the National Institutes of Health (NIH), starting in fiscal year 2018.¹ The NIH will invest these much-needed resources to support science that advances national priorities for addiction and pain research² with a bold new trans-NIH initiative called Helping to End Addiction Long-term (HEAL).³ In this Viewpoint, we outline the initial components of this cross-cutting, interdisciplinary program.

More than 25 million US adults are affected by daily pain.⁴ More than 2 million individuals in the United States have an opioid use disorder (OUD), most starting with opioid analgesics prescribed to them or procured from diverted medications, but once addicted, often shift-

Table. Research Plan for the NIH HEAL Initiative

Opportunities	Components
Improving Treatments for Opioid Misuse and Addiction	
New treatments for addiction	Identify new targets, develop new medications/immunotherapies; reformulate existing medicines
	Improve overdose reversal medicines
	Develop new therapies for opioid-induced respiratory depression
Optimization of effective treatments for addiction	Enhance NIDA Clinical Trials Network for opioid research
	Establish Justice Community Opioid Intervention Network
	Initiate HEALing Communities Study
NOWS	Expand ACT NOW pilot study; use results to conduct clinical trials to determine best practices for clinical care of NOWS
Enhancing Pain Management	
Better understanding of chronic pain	Establish Acute to Chronic Pain Signatures program

Additional Research Priorities

- Prevention (beyond improving prescriptions practices for pain)
- Precision treatments for addiction
- Non-pharmacological treatments
- Integrated models of pain management
- Linkages between pain, addiction, mental health
- Education



Follow HEAL on our Website...



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NIH HEAL INITIATIVE

HEAL Initiative

[Prevent Addiction](#)

[Improve Treatments](#)

[Public-Private Partnership](#)

[Events](#)

[News and Announcements](#)

[Resources](#)

In April 2018, NIH launched the HEAL (Helping to End Addiction Long-term) Initiative, an aggressive, trans-agency effort to speed scientific solutions to stem the national opioid public health crisis. This Initiative will build on extensive, well-established NIH research, including basic science of the complex neurological pathways involved in pain and addiction, implementation science to develop and test treatment models, and research to integrate behavioral interventions with Medication-Assisted Treatment (MAT) for opioid use disorder (OUD). Successes from this research include the development of the nasal form of naloxone, the most commonly used



www.nih.gov/heal-initiative

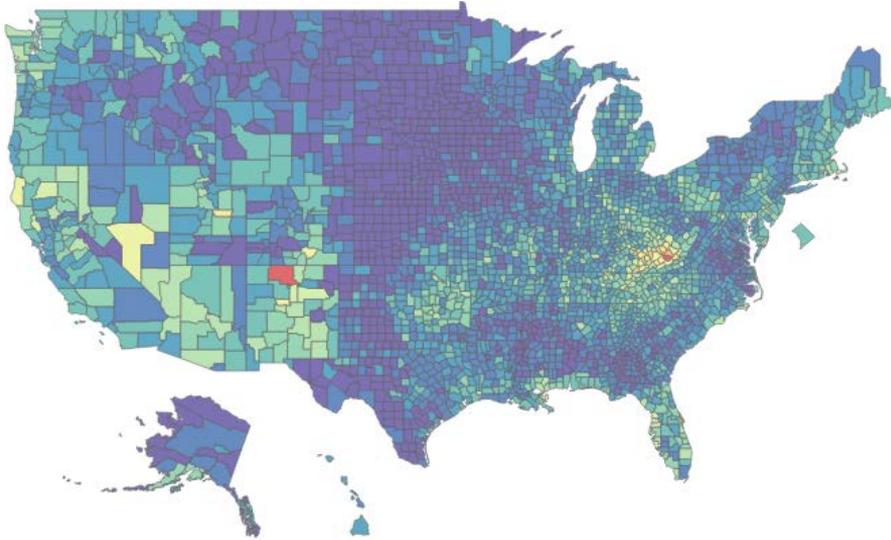
Nora Volkow, M.D.

Director, National Institute on Drug Abuse

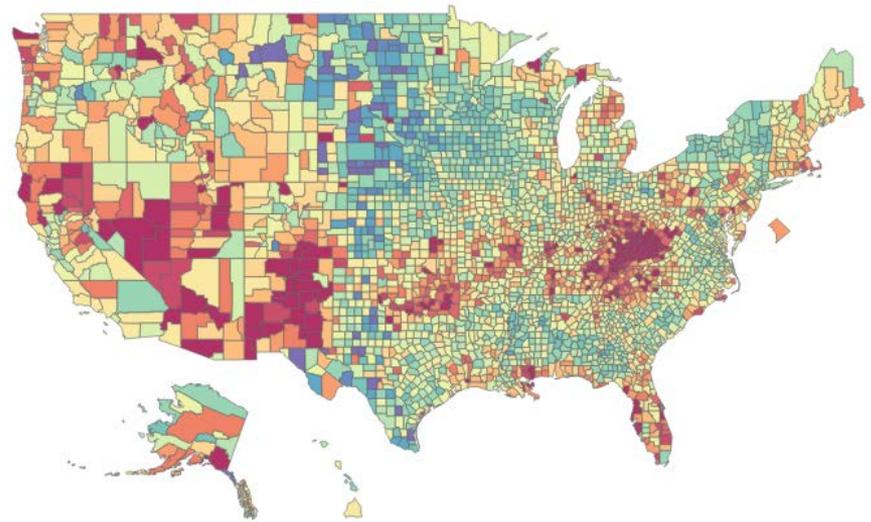
IMPROVING TREATMENTS FOR OPIOID MISUSE AND ADDICTION

The Crisis: National Overdose Death Rates

1999



2016



Legend for estimated age-adjusted death rate (per 100,000 population)



Exciting Recent Developments on NIH-Supported Treatments

- XR-Naltrexone and Buprenorphine-Nx
 - Shown to be equally safe, effective in preventing relapse
- Sublocade™ (Buprenorphine ER), once-a-month injectable
 - FDA Approval, November 2017
- Lofexidine: treats opioid withdrawal symptoms
 - FDA approved May 16, 2018



THE LANCET

Vol 391 January 27, 2018

Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial

Joshua D Lee, Edward V Nunes Jr, Patricia Novo, Ken Bachrach, Genie L Bailey, Snehal Bhatt, Sarah Farkas, Marc Fishman, Phoebe Gauthier, Candace C Hodgkins, Jacque King, Robert Lindblad, David Liu, Abigail G Matthews, Jeanine May, K Michelle Peavy, Stephen Ross, Dagmar Salazar, Paul Schkolnik, Dikla Shmueli-Blumberg, Don Stablein, Geetha Subramaniam, John Rotrosen

Medscape

FDA Panel Backs Approval of Lofexidine for Opioid Withdrawal

March 28, 2018

HEAL – Opioid Misuse and Addiction

New Treatments for Addiction, Overdose Prevention and Reversal

- New ER formulations of existing medications to treat OUD
- Stronger, longer-acting formulations to counteract overdose
- Interventions against respiratory depression induced by opioids, other than MOR antagonists
- Novel medications (new targets) to treat withdrawal, craving, progression, and prevent relapse and overdose
- Immunotherapies
- Projected Impact:
 - 15 Investigational New Drug (IND) applications
 - 5 New Drug Applications (NDAs)

HEAL – Opioid Misuse and Addiction

Novel Immunotherapies for OUD

- Decrease challenges associated with relapse in OUD treatment:
 - Provide a needed safety net for patients at “high risk” of OD
 - Complement existing therapies for OUD
 - Reduce long-term opioid use and overdose, with minimal risk of side effects
- Opioid vaccines will not interfere with use of:
 - Non-opioid pain relievers
 - Structurally distinct opioids for emergency situations

HEAL – Opioid Misuse and Addiction

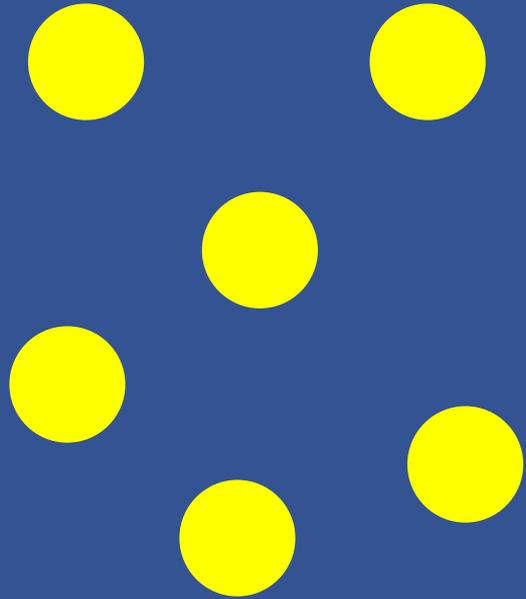
Novel Immunotherapies for OUD

- Opioid Vaccine Consortium
 - Vaccine development
 - Immunogen design and optimization
 - Adjuvants to improve antibody affinity, titers, and duration
 - Formulation, dosing, and delivery
 - cGMP manufacturing
- Vaccine pre-clinical testing in animal models
 - Vaccine efficacy, Pharmacology and toxicology
- Phase I-II clinical trials

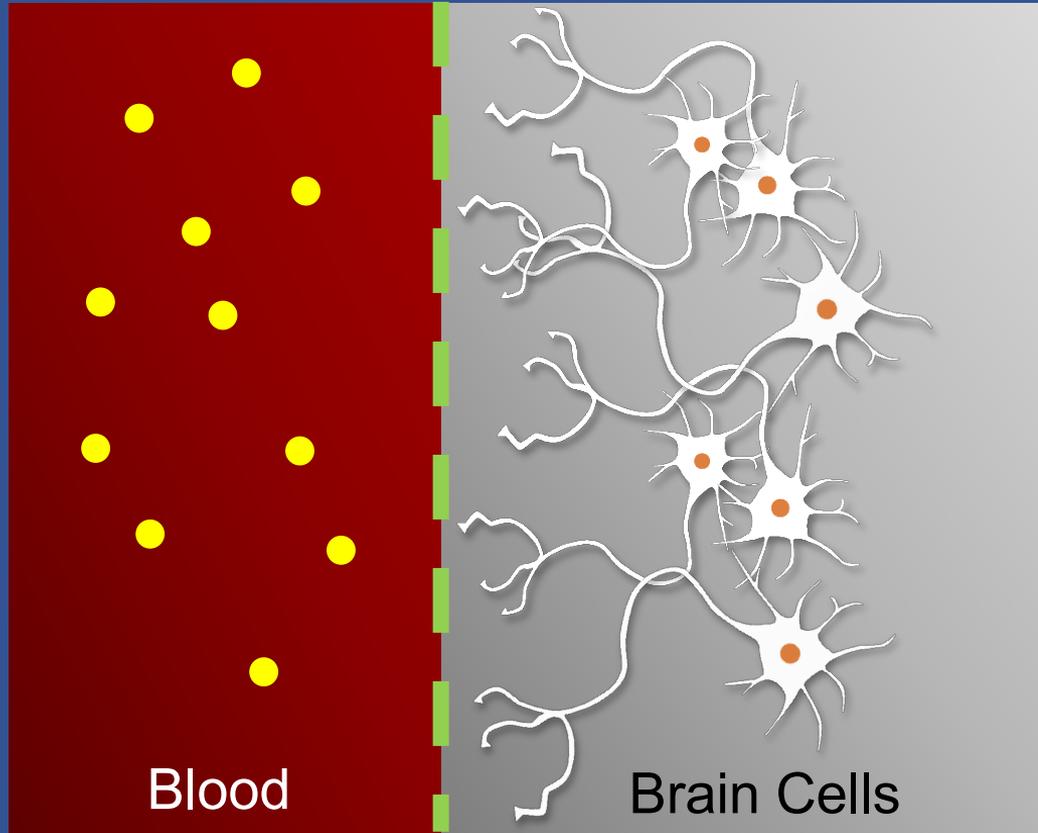
HEAL – Opioid Misuse and Addiction

Improve Therapeutic Approaches to Addiction

Using antibodies to help block drug from entering the brain



Opioid



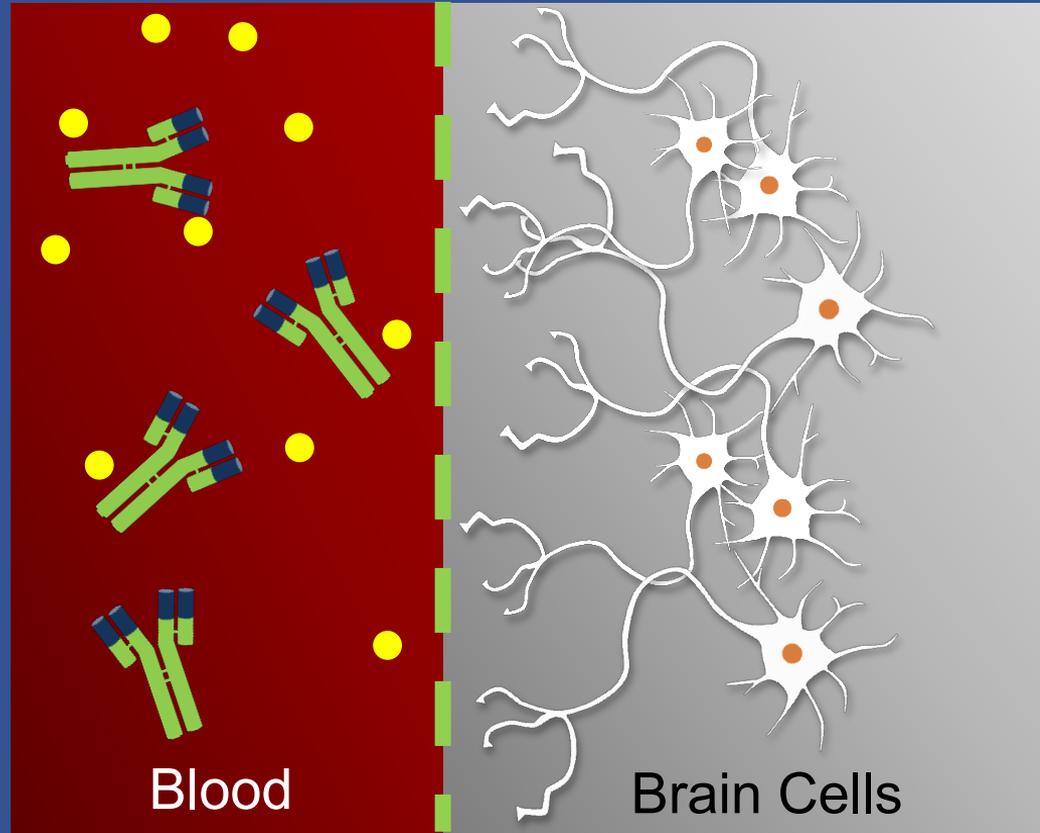
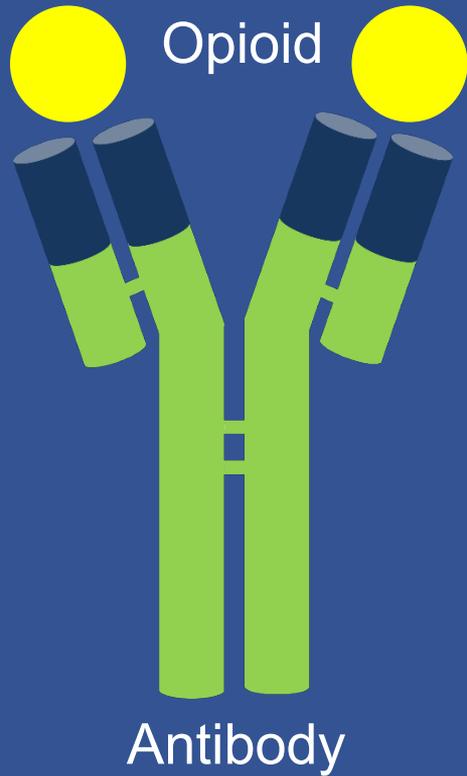
Blood

Brain Cells

HEAL – Opioid Misuse and Addiction

Improve Therapeutic Approaches to Addiction

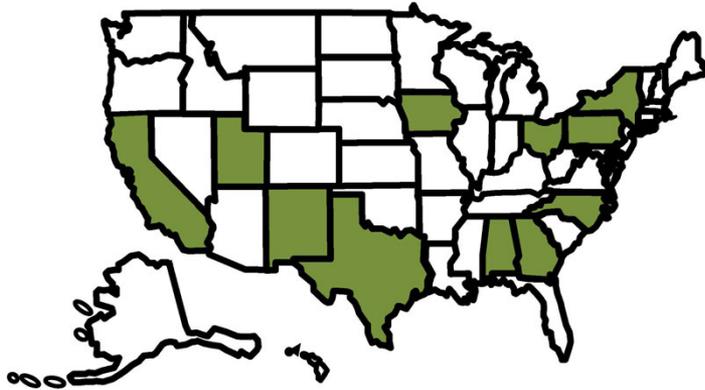
Using antibodies to help block drug from entering the brain



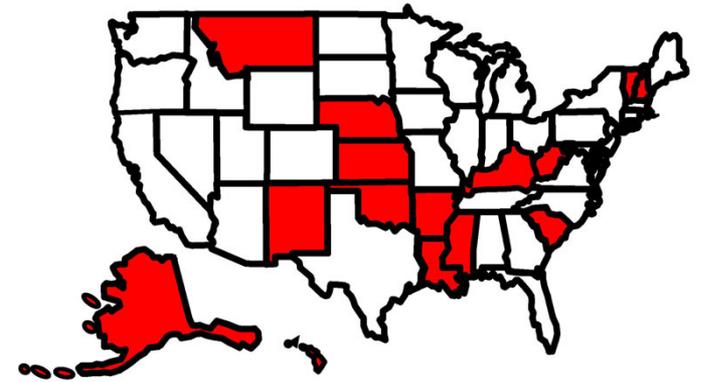
HEAL – Opioid Misuse and Addiction

Advancing Clinical Trials in NOWs: Pilot Study

Neonatal Research Network Centers
(2016-2021)



IDeA States Pediatric Clinical
Trials Network



- 1 year pilot funding from Director's Discretionary Fund 2017
- 20 clinical sites participating
- Assess prevalence of NOWs at different sites, current approaches to treatment, and develop common protocols for future studies

HEAL – Opioid Misuse and Addiction

Expanded ACT NOW

- Clinical trials for care of infants with NOWs
 - Determine effectiveness of currently used medications to treat withdrawal
 - Compare pharmacologic approaches to drug-free strategies
 - Eat, sleep, console
 - Assess impact of prenatal exposure to opioids
 - Effects on developing brain structure and function
 - Higher risk for school performance problems
 - Long-term risk for addiction
- Determine best practices to improve short- and long-term outcomes

HEAL – Opioid Misuse and Addiction

Enhanced Clinical Trials Network

- NIDA collaboration with academics and community providers
 - Develop, validate, refine, and translate into practice new treatment options
- Expand the size and scope of the CTN
 - Expand clinical research capabilities of CTN with ED and primary health care providers
 - Facilitate implementation science
 - Develop and validate new models of OUD care and new metrics for evaluation
- Contribute to improved quality of and access to treatment for OUD
 - Introduce sustainable interventions in highly impacted areas
 - Implement OUD treatment practices in general medical and specialty settings
 - Expand clinical research workforce in OUD screening and treatment

HEAL – Opioid Misuse and Addiction

Justice Community Opioid Innovation Network

- Increase collaborations between justice systems and community-based treatment providers to improve continuity of care
 - Enhance access and retention in OUD treatment
- Justice community-related research through network of investigators
 - National survey of addiction treatments in jails, prisons and communities
 - Effectiveness and implementation studies of new and existing medications, interventions, and technologies in justice settings
 - Leveraging existing data sources
 - Developing innovative research methods

HEAL – Opioid Misuse and Addiction

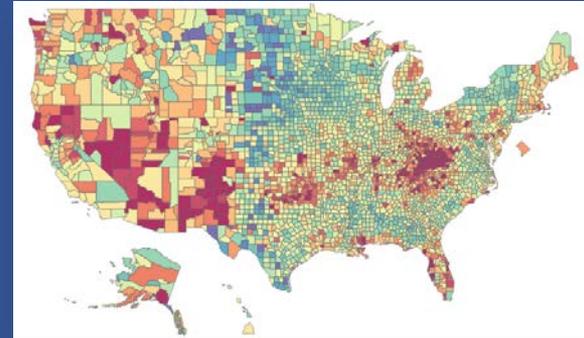
Optimize Effective Treatments

An Immediate Challenge

- OUD crisis is escalating
- Most Americans with an OUD (~80%) don't get effective treatment

Can we draw on all we know *now...* and develop integrated intervention strategies to stem the crisis *quickly*?

- Study ways to integrate evidence-based interventions comprehensively
 - In select areas highly affected by the crisis...



HEAL – Opioid Misuse and Addiction

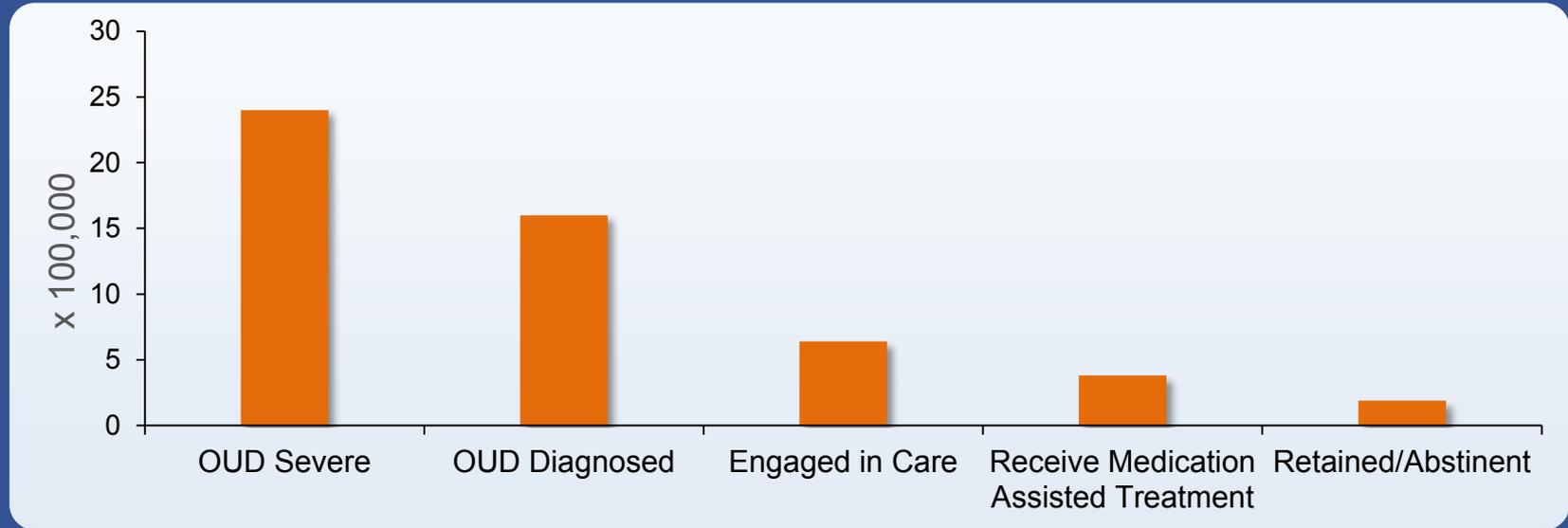
Optimize Effective Treatments

- *Pilot Demonstration Project* – a competitive process involving wide-ranging federal, state, local partnerships, integrating ALL of the stakeholders
 - Health care (ED and primary care), criminal justice, treatment programs, government agencies, emergency rooms, first responders
- Test and evaluate evidence-based prevention and treatment interventions in select communities to
 - Prevent OUD and OD
 - Screen and diagnose
 - Engage and retain in medication-assisted treatment
 - Help sustain long-term recovery
- *Goal: Decrease OD deaths and OUD*



HEAL – Opioid Misuse and Addiction

Optimize Effective Treatments



Pilot Demonstration Project – a competitive process involving wide-ranging federal, state, local partnerships, integrating **all** of the stakeholders

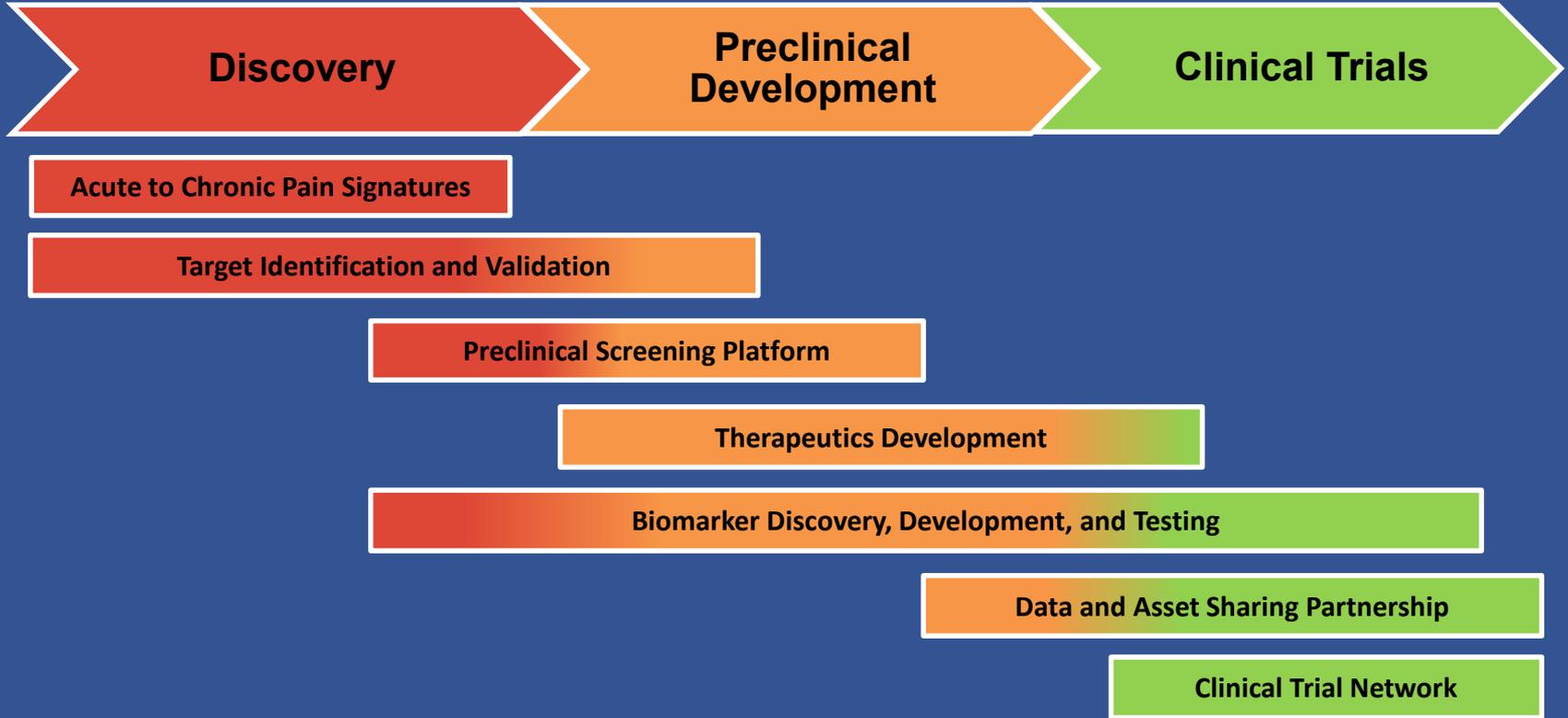
- Health care, criminal justice, treatment programs, government agencies
- Care providers including ER, primary care, mental health, first responders

Walter Koroshetz, M.D.

Director, National Institute of Neurological Disorders and Stroke

ENHANCING PAIN MANAGEMENT

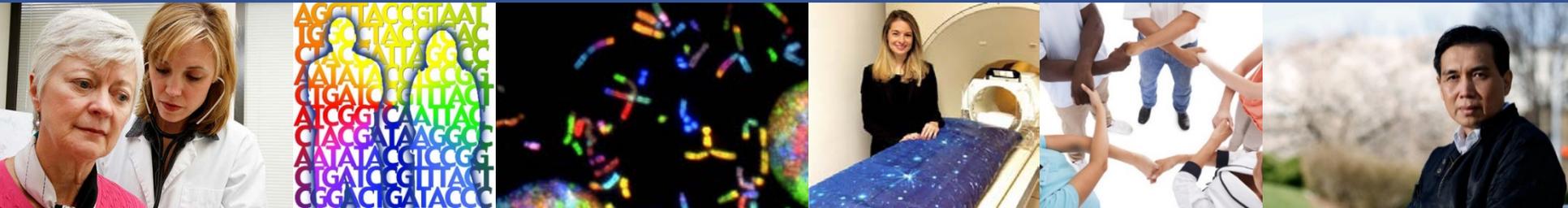
Overview of FY18 HEAL Programs for Pain



HEAL – Pain Management

Acute to Chronic Pain Signatures

- Identify a *mechanistic objective signature* to identify those at risk for transition to chronic pain
 - Phenotyping, genotyping, imaging, -omics
- Desired outcomes
 - Mechanisms
 - Novel druggable targets
 - Cohort stratification
 - Prevention strategies



HEAL – Pain Management

Develop New Non-Addictive Treatments for Pain

- Opioids are often not effective for chronic pain and carry risks
- NIH and **private sector partners** to develop non-addictive pain management approaches
 - Predict and track treatment responses
 - Test new drugs
 - Define clinically meaningful outcomes
 - Establish a clinical pain research network to test new therapies

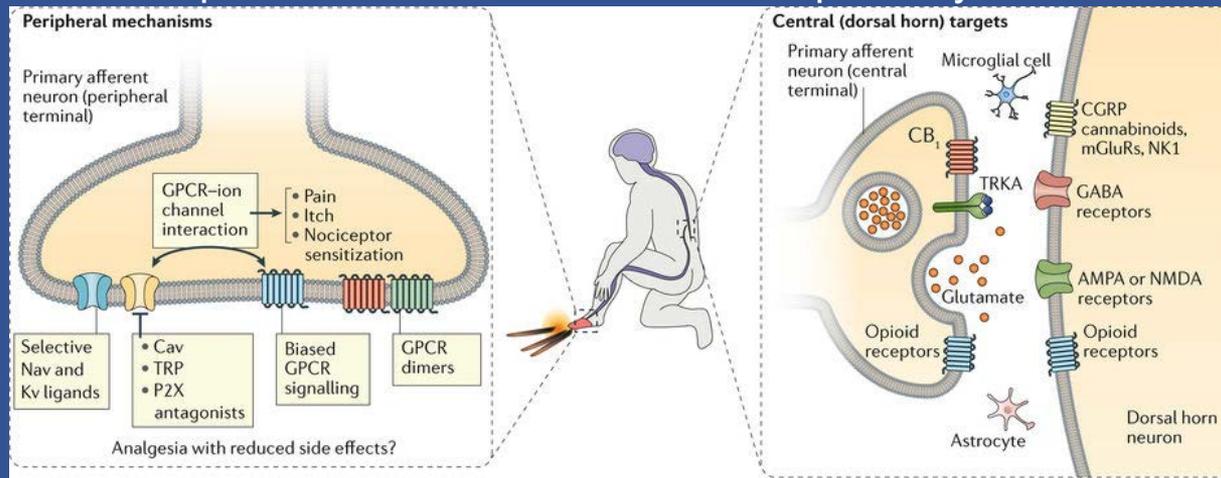


HEAL – Pain Management

Discover and Validate Novel Treatments for Pain

- Identify potential new therapeutics: small molecules, biologics, natural products; focused neuromodulation by device
- Coordinate best science across research network

Modulate pain circuits and their molecular pathways



HEAL – Pain Management

Preclinical Screening Platforms

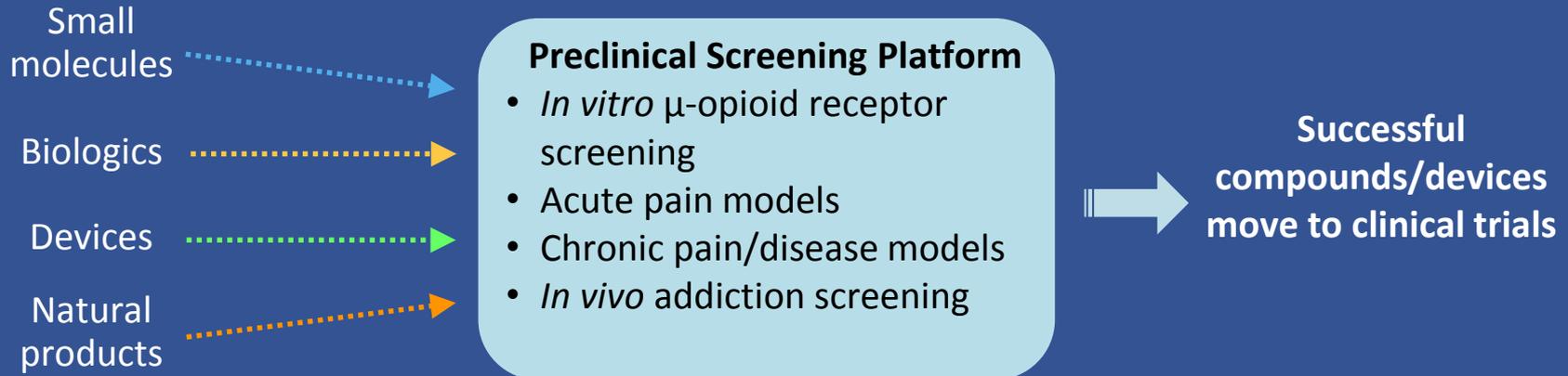
- Develop human cell/tissue models
 - Peripheral, spinal, and brain
 - Normal and diseased physiologies
 - iPSC-derived neurons, 3D printed organoids, tissue chips
- Advance investigational drugs directed toward new targets
 - Human tissue constructs to identify new probes/drug leads
 - Automated chemical synthesis
 - Artificial Intelligence to identify new chemical structures
 - IND-enabling studies



HEAL – Pain Management

Preclinical Screening Platforms

- Incentivize academic, industry communities to accelerate discovery of non-addicting but potent therapies for pain
 - Develop or refine animal models of specific pain conditions
 - Provide access to research community
 - Generate high quality data to support business partnerships, translational programs



HEAL – Pain Management

Discovery and Preclinical Development



HEAL – Pain Management

Data Sharing and Asset Repurposing

- *Ultimate goal:* enable companies to access data that will speed their development efforts
- *Data sharing:* relevant clinical, preclinical, pharmacokinetic data
- *Asset Repurposing:* accruing, analyzing pharmacological assets from academia, pharma, device companies

Structured data repository Data storage
Report generation and analysis Develop dossiers on submitted assets
Data sharing of prior pain efforts Industry partners review data from successful and failed pain therapy programs to inform in house strategies
Asset prioritization / scientific review Prioritization and triaging to clinical trials network

HEAL – Pain Management

Discovery and Development of Biomarkers for Pain

- Better define patient populations and response to therapies being tested; accelerate non-addictive pain therapy development
- Discovery
 - Markers would include:
 - Quantitative sensory tests
 - Neuroimaging
 - Circulating markers (-omics)
 - Phenotypic characteristics
 - Genetic markers
 - Biomarker, Endpoint, Biomarker Signature Projects
 - In diverse pain conditions
- Validation
 - *Response biomarkers*
 - *Predictive biomarkers*
 - Study types
 - Retrospective
 - Pilot prospective
 - Prospective – in conjunction with the **Clinical Trials Network....**

HEAL – Pain Management

Clinical Trials Network for Pain

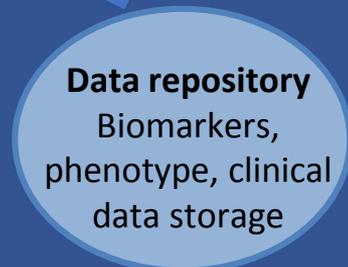
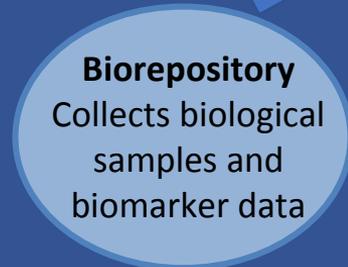
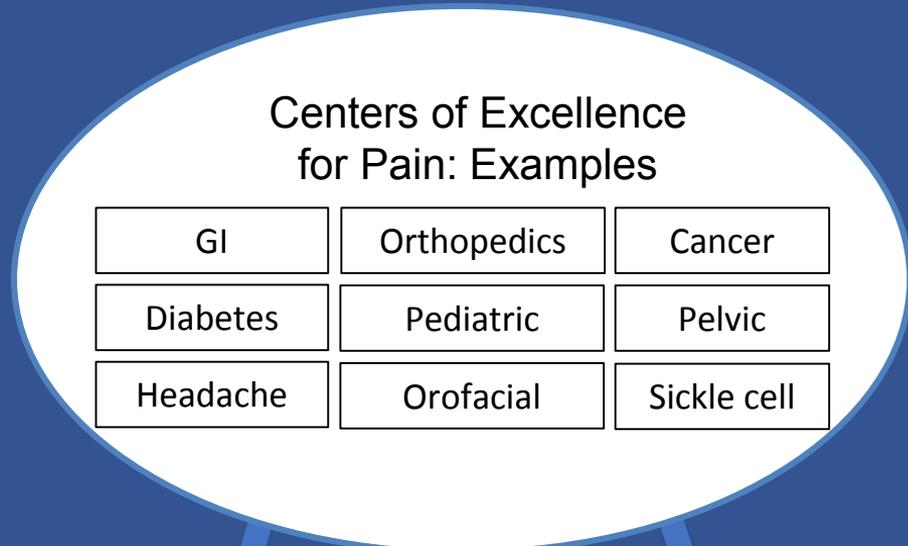
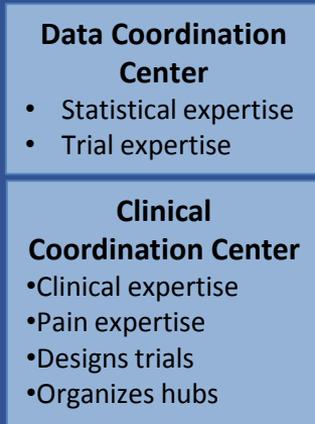
- Goal: improve quality, consistency, efficiency of clinical trials for pain
 - Focus on well-defined pain conditions with high unmet need
 - Incentivize, accelerate Phase II trials
 - Test compounds and devices from industry, academia
 - Incorporate biomarker studies
 - Accommodate other platform trial designs
- Build on existing NIH investments; hub and spoke design
- Reduce the time to start, enroll, run, and complete trials



HEAL – Pain Management

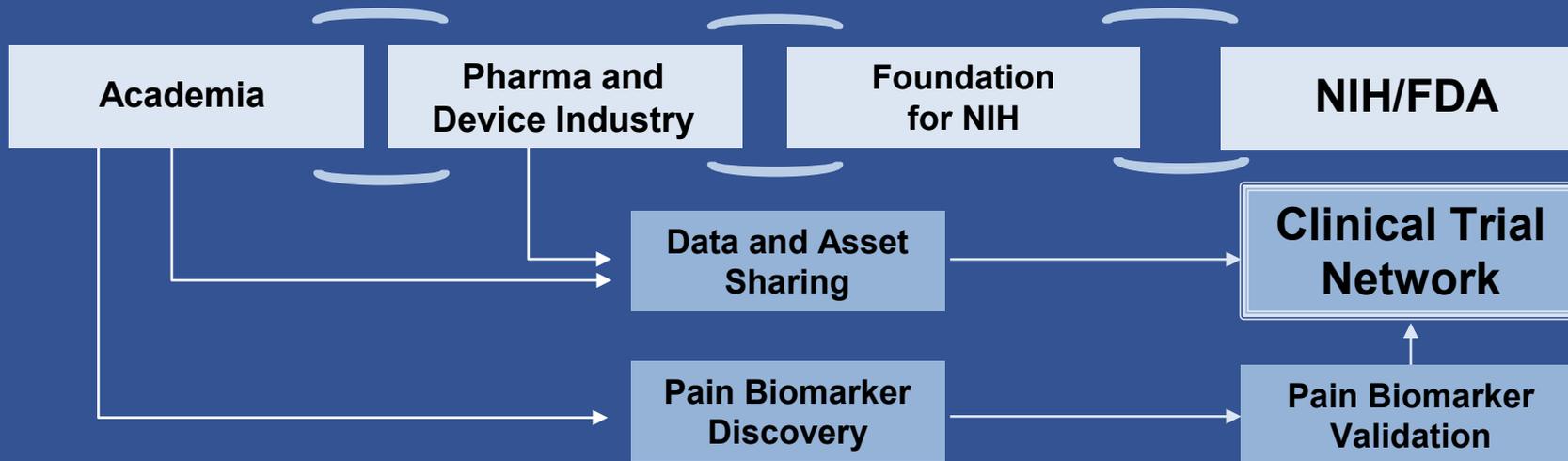
Clinical Trials Network for Pain

Biomarkers
and assets
from PPP,
other sources



HEAL – Pain Management

Public Private Partnerships

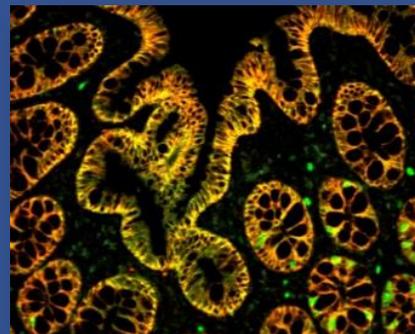
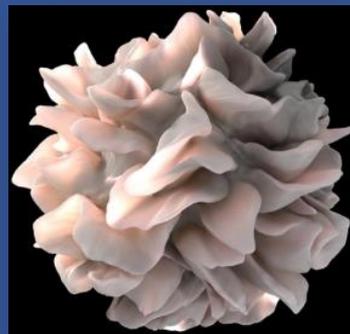
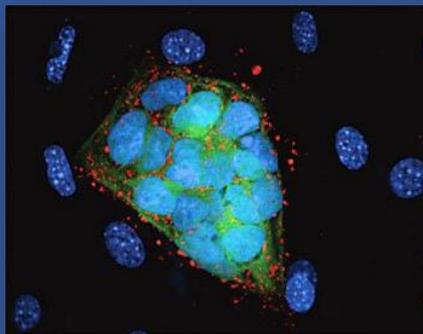


QUESTIONS?



NIH... *Turning Discovery Into Health*

www.nih.gov/hope



Research Plan for the NIH HEAL Initiative

Opportunities	Components
Improving Treatments for Opioid Misuse and Addiction	
New treatments for addiction	Identify new targets, develop new medications/immunotherapies; reformulate existing medicines
	Improve overdose reversal medicines
	Develop new therapies for opioid-induced respiratory depression
Optimization of effective treatments for addiction	Enhance NIDA Clinical Trials Network for opioid research
	Establish Justice Community Opioid Intervention Network
	Initiate HEALing Communities Study
NOWS	Expand ACT NOW pilot study; use results to conduct clinical trials to determine best practices for clinical care of NOWS
Enhancing Pain Management	
Better understanding of chronic pain	Establish Acute to Chronic Pain Signatures program
New nonaddictive pain treatments	Identify new targets for pain treatment
	Engineer preclinical testing platforms to profile potential nonaddictive treatments
Public-private HEAL Partnership to speed movement of nonaddictive treatments through clinical pipeline	Enhance data and asset sharing
	Validate biomarkers to inform neurotherapeutic and pain clinical research
	Establish clinical trials network to support and accelerate trials of nonaddictive pain therapies