Preclinical Screening Platform for Pain (PSPP)

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National Institute of Neurological Disorders and Stroke (NINDS)
Mission and Strategy

**Accelerate the Discovery and Pre-Clinical Development of Non-Addictive Treatments for Pain**

- The NIH HEAL Initiative aims to improve treatments for opioid misuse and addiction and to enhance pain management
- Build an understanding of the development and prevention of chronic pain
- Discover and validate novel targets for safe and effective pain treatment
- **Engineer a preclinical testing platform to identify and profile non-addictive therapeutics for pain**
- Support translational programs in therapy development, discovery and development of biomarkers
- Provide a robust clinical trials network to test new therapies for pain conditions in adults and children
HEAL Programs for Pain

Discovery

Preclinical Development

Clinical Trials

Implementation/Dissemination

Acute to Chronic Pain Signatures

Discover and Validate Novel Targets

Preclinical Screening Platform

Small Molecules and Biologics Development

Device Development

Discovery and Validation of Biomarkers, Biomarker Signatures, and Endpoints

Data & Asset Sharing Partnership

Early Phase Pain Investigation Clinical Network

Back Pain Research Consortium

Hemodialysis Pain Management

Pain Effectiveness Research Network

Pragmatic and Implementation Studies for the Management of Pain
Timeline to Establishing PSPP

2017
- NASEM Workshop
- Oct
- HEAL Initiative

2018
- Pain screening proposal approved by OD
- May
- External Consulting Board established
- Sept
- Pilot program established
- Oct

2019
- PSPP launched
- Jan
- Animal Models Workshop
- Mar
One-stop preclinical testing platform to accelerate discovery of non-addictive, effective therapies

Efficient, rigorous screening resource
- Adhere to ARRIVE guidelines
- Testing is randomized, blinded, and both sexes are included
- Group size is determined by power analysis
- Testing site is blinded to asset
- Participant intellectual property protected
- Public database to highlight rigor and best practices
Participation in PSPP

- PSPP is currently accepting assets for evaluation continuously, on an ongoing basis.
- Researchers from academic institutions or industry in the U.S. and internationally are eligible to submit assets for screening.
- To start the process, participants contact us for more information and to discuss research goals, resources, and timelines.
- A signed confidentiality agreement between NINDS and each potential participant is required before submission of agents for evaluation.
- Under NINDS direction, preclinical screening of test candidates is performed by contract facilities on a blinded and confidential basis.
- Since opening program up to participants two months ago, PSPP has had discussions with 20 parties.
PSPP Sample Submission and Logistics

- **Asset Shipped to Handling Site**
- **Registration Documentation Review**
- **Handling/Processing Blinding & Shipping**
- **Asset Shipped to Contract Test Site**
- **Asset Received at the Contract Site**
- **Design Screening Strategies & Place Test Orders**
- **Data Analyzed & Plan for Next Steps**
- **Participants**

NINDS Staff
Handling/Processing Staff
Contractor Staff

NINDS Database
External Consulting Board (ECB)

The ECB provides independent input and guidance on scientific and strategic priorities and implementation

<table>
<thead>
<tr>
<th>ECB Member</th>
<th>Institution/affiliation</th>
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<tbody>
<tr>
<td>Daniela Salvemini, PhD</td>
<td>Saint Louis University</td>
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<tr>
<td>Ursula Wesselmann, MD, PhD, D.T.M.&amp;H.</td>
<td>University of Alabama</td>
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<tr>
<td>Andrew Hershey, MD, PhD, FAAN, FAHS</td>
<td>Cincinnati Children’s Hospital</td>
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<tr>
<td>Gregory Scherrer, Pharm D, PhD</td>
<td>University of North Carolina</td>
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<tr>
<td>Jeff Kennedy, PhD</td>
<td>Consultant</td>
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<tr>
<td>Stevens Negus, PhD</td>
<td>Virginia Commonwealth University</td>
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<tr>
<td>Donna Hammond, PhD</td>
<td>University of Iowa</td>
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<tr>
<td>Bavani Shankar, MBA</td>
<td>AstraZeneca</td>
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Testing Strategy: Screen, Profile, and Validate

- **Optimization based on ECB input:**
  - Screening for opioid receptor binding & pharmacokinetic profiles
  - Pharmacokinetics study based on stage of asset being tested
  - Side effect profile assessed
  - Assets are evaluated for abuse liability
  - Need to identify appropriate non-evoked pain endpoints

![Diagram](attachment:testing_strategy_diagram.png)
Tier 3: aim to optimize disease relevant models

- For example, evaluation of migraine models:
  - Models:
    - Nitroglycerin, primed versus unprimed
    - Cortical spreading depression
    - Inflammatory soup
  - Test subjects:
    - rat vs mouse
    - male vs female
  - Endpoints:
    - plantar vs periorbital mechanical thresholds
    - validation of evoked (allodynia) vs non-evoked endpoints (e.g. photo/phonophobia)
  - Translatability
## Non-Evoked Endpoints Evolving Debate: No Consensus in the Field

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Pros</th>
<th>Cons</th>
<th>Translatability</th>
<th>Recommendations</th>
<th>Rank</th>
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<tbody>
<tr>
<td>Place escape / avoidance</td>
<td>Natural behavior; does not require training</td>
<td>Need to automate and structure differently for bilateral pain conditions</td>
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<tr>
<td>Licking, biting, lifting, guarding behaviors</td>
<td>Natural behavior; can be automated</td>
<td>Not applicable to all models</td>
<td>Seems to translate</td>
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<tr>
<td>Grimace</td>
<td>Automation being developed</td>
<td>Time and effort intensive (currently)</td>
<td>Not established</td>
<td>Needs further development; current scoring system has duplicative criteria</td>
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<tr>
<td>Burrowing</td>
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<td>Cannot be used alone</td>
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<td>Wheel running</td>
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<td>Confound: exercise can alleviate pain</td>
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<td>Nesting</td>
<td></td>
<td></td>
<td></td>
<td>Not applicable to rats</td>
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<td>Gait analysis</td>
<td></td>
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<td>This is not a measure of pain</td>
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<tr>
<td>Open field (rearing, horizontal, &amp; vertical locomotion)</td>
<td>Adjunct test that can help interpret false negatives and false positives in other tests</td>
<td>Requires distance and pattern analysis</td>
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Workshops Informing PSPP

Jan. 30-31, 2019

Feb. 6, 2019

Feb. 7-8, 2019
PSPP: Key Elements

1) Endpoint refinement/development to address gaps
2) Validated models configured into customized, asset-dependent flowcharts
3) Flexible decision-making process with input from participant
4) Rigor, confidentiality and IP protection
5) Commitment to appropriate data sharing
Timelines (2018-2023)

2018
- Program approved
- ECB formed
- Market research conducted
- RFP drafted
- Workshops planned
- Personnel identified
- Pilot program established

2019
- Workshops held
- Personnel hired
- Outreach activities
- Initiate model and protocol development
- RFP posted
- Award contract
- Enroll participants
- Asset evaluation

2020-2021
- Incorporate non-evoked endpoints
- Optimize and validate disease specific models
- Explore non-rodent species
- Test new assets and complete profiling of existing assets
- Establish testing paradigms for devices

2022-2023
- Convene workshop
- Evaluate initial goals and objectives and advances made
- Determine next steps