PTH265

The NIH HEAL Initiative Preclinical Screening Platform for Pain (PSPP) efforts to validate rodent models of pain and migraine

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Background

The Preclinical Screening Platform for Pain (PSPP) program aims to accelerate the discovery and development of new non-opioid, non-addictive pain therapeutics. Towards that goal, PSPP accepts small molecules, biologics, natural products and devices from industry, academia or government asset owners from across the world. PSPP evaluates assets in a range of in vitro functional assays, pharmacokinetics, side effect profile, abuse liability as well as preclinical pain models. PSPP is collaborating with PsychoGenics, Inc. to validate preclinical models and endpoints to advance profiling of novel assets.

Methods

Chemotherapy-induced peripheral neuropathy (CIPN): Paclitaxel was injected at several doses on alternate days to determine the optimal dose and route of administration. Oxaliplatin was injected 2 days per week for 4 weeks. Hind paw tactile sensitivity and cold sensitivity were evaluated.

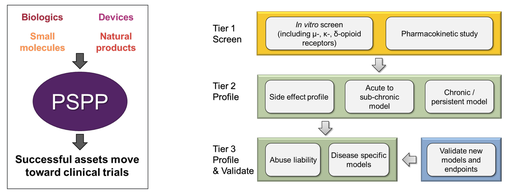
Monosodium iodoacetate (MIA): MIA was injected intraarticularly into the left hindlimb knee joint. Tactile sensitivity, weight bearing, changes in gait, and paw pressure were systematically evaluated in both sexes for 4-6 weeks. Pharmacological validation of the model was established using morphine, duloxetine, and ketoprofen after acute and repeated dosing.

Adult male and female Sprague Dawley rats (N=10, each sex) were used for the MIA and CIPN studies.

Mouse inflammatory soup (IS) dural stimulation model of migraine: Male and female C57BL6/J and CD1 mice (6 weeks of age) were used in these studies. Mice received a dural injection of inflammatory soup (IS; 1 mM histamine, bradykinin, serotonin, 0.1 mM prostaglandin E2; pH 5) under brief isoflurane anesthesia (2-3%) by holding the skin above the skull, inserting an injector (0.65 mm length) through the skull at the lambdoid bone suture, and administering 5 µl of IS. Facial sensitivity was measured by applying a von Frey filament (0.6 g) to the periorbital (forehead) region 10 times such that filament displayed an arch. A 20-30 second interval was used between each application, and the total number of responses (facial swipe, head withdrawal) out of 10 trials were determined and represented as the response frequency.

Rat inflammatory soup (IS) dural stimulation model of migraine: Male Sprague Dawley rats (200-250 gm) received a surgically implanted stainless steel screw guide cannula (P1 Technologies, Roanoke, VA) over the dura at the junction of the superior sagittal and transverse sinus. Rats received an infusion of inflammatory soup (IS; 2 mM histamine, bradykinin, serotonin, 0.2 mM prostaglandin E2; pH 5) under brief isoflurane anesthesia (2-3%) by administering 10µl of IS through the screw guide cannula over a 2-minute period using an infusion pump. Facial sensitivity was measured by applying a series of calibrated von Frey filaments (1-10 gm) to the periorbital region above the left eye and determining the facial sensitivity threshold (evoked grimace, facial swipe, head withdrawal) using an ascending filament application protocol.

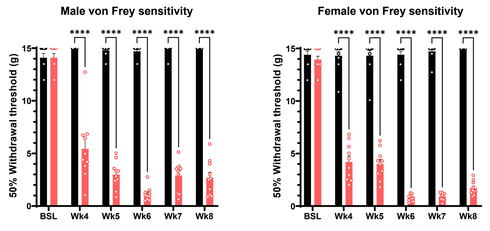
PSPP Testing Strategy

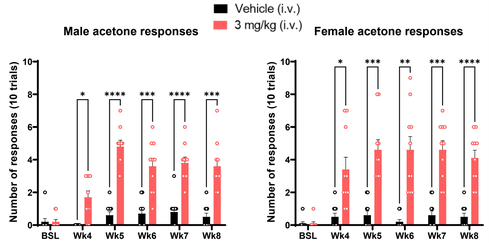


- One-stop resource for preclinical screening of potential pain therapeutic assets
- Small molecules, biologics, devices, or natural products are accepted from academic institutions, industry, and government organizations worldwide
- Under NINDS direction, preclinical screening of assets is performed by contract facilities, PsychoGenics Inc. (PGI), in a blinded and confidential manner
- There is no cost to PSPP participants
- Participant IP and confidentiality are protected

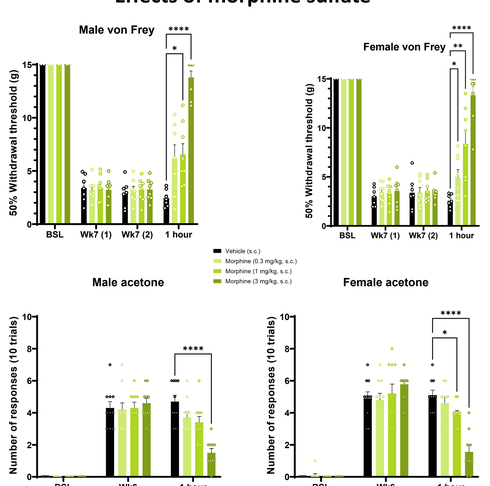
Oxaliplatin CIPN Model

Hind paw tactile and cold hypersensitivity





Effects of morphine sulfate

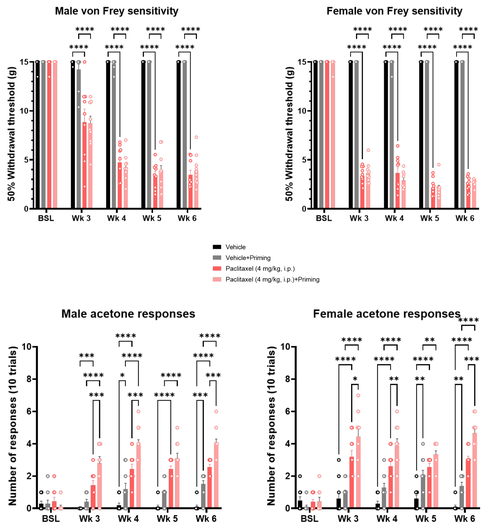


Paclitaxel CIPN Model

Rat plasma exposures

Dose	Route	Male			Female		
		Cmax (ng/ml)	Day 1 AUC (ng.h/ml)	Day 1-7 AUC (ng.h/ml)	Cmax (ng/ml)	Day 1 AUC (ng.h/ml)	Day 1-7 AUC (ng.h/ml)
2 mg/kg	IV	N/A	2,160	8,640	N/A	4,468	17,872
2 mg/kg	IP	139	568	2,272	275	1,165	4,660
4 mg/kg	IP	204	1,780	7,120	376	2,207	8,828
6 mg/kg	IP	276	2,898	11,592	494	4,241	16,964

Hind paw tactile and cold hypersensitivity



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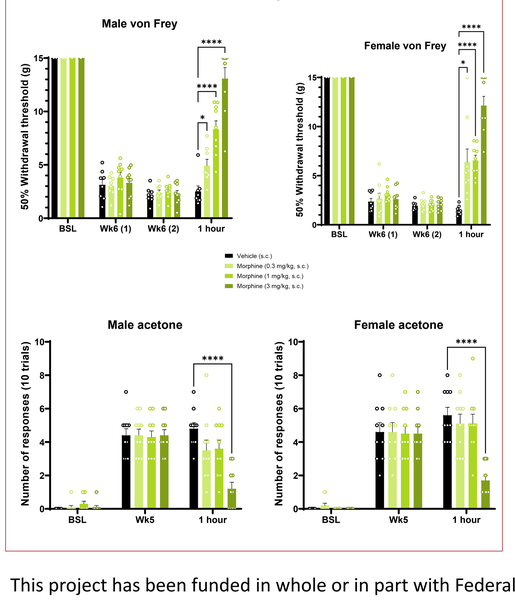
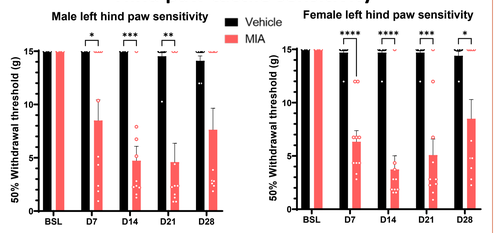
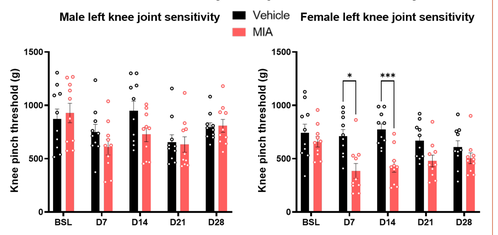


MIA Model

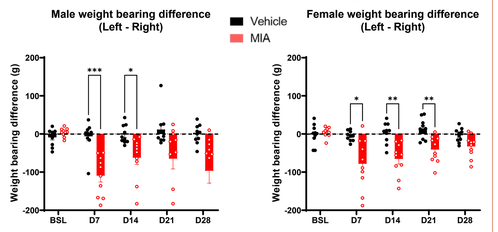
Hind paw tactile sensitivity



Hind limb knee joint pinch sensitivity

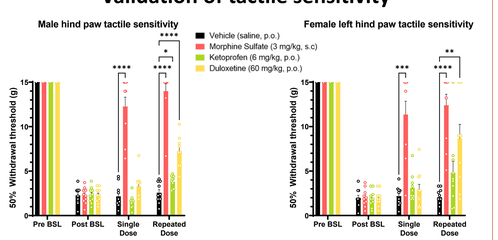


Dynamic weight bearing

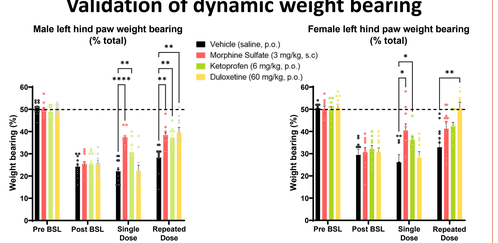


Testing timeline

Validation of tactile sensitivity

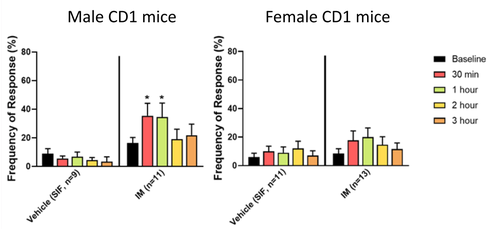


Validation of dynamic weight bearing

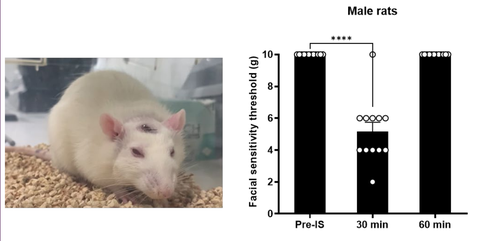


Dural Stimulation Model

Mouse IS dural stimulation model of migraine



Rat IS dural stimulation model of migraine



Summary

- The results from these carefully validated studies using evoked and non-evoked endpoints in the rat MIA model and using both mechanical sensitivity and cold allodynia in the CIPN models suggest that these models may be used to identify and differentiate novel therapeutics for treatment of osteoarthritis and chemotherapy induced neuropathic pain.
- Compared to the MIA and CIPN models, the dural inflammation requires further optimization and validation to incorporate into the profiling program.

Conclusions

These efforts within the NIH HEAL Initiative will accelerate the development of novel non-opioid non-addictive pain and headache therapeutics.

PSPP is currently accepting assets for evaluation

For eligibility and participation inquiries, contact:

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For more information about PSPP, visit (or scan the QR):
https://heal.nih.gov/research/preclinical-translational/screening-platform

NIH - Helping to End Addiction Long-term
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National Institute of Neurological Disorders and Stroke

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