National Institute of Neurological Disorders and Stroke

Summary of 2019 Animal Pain Models

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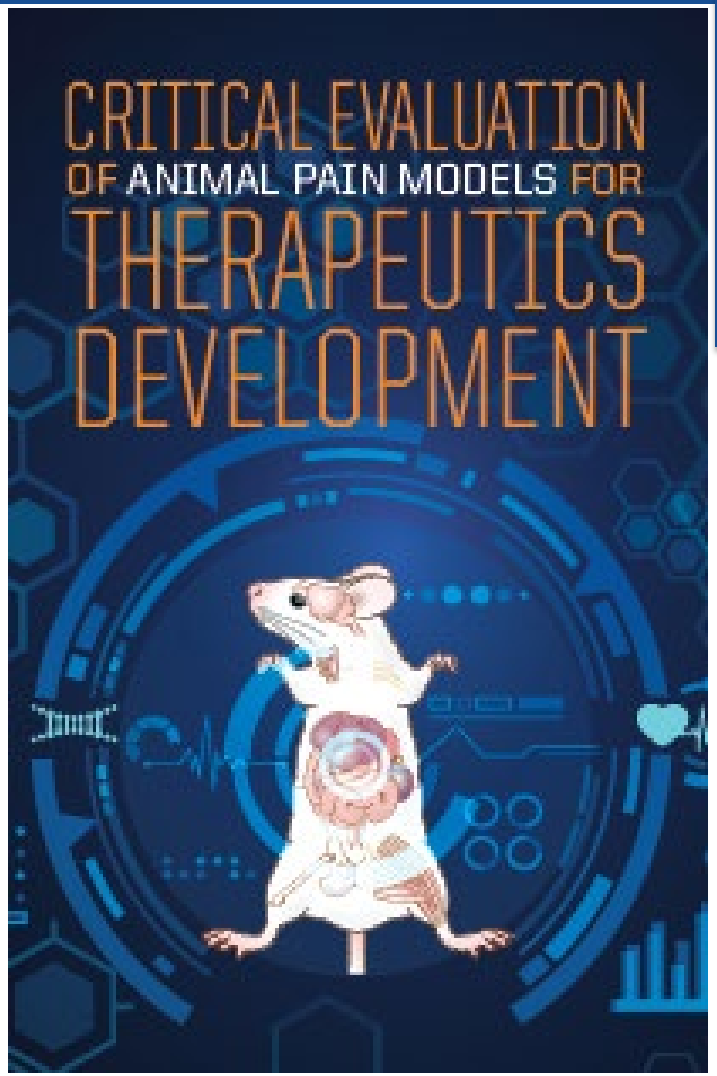
HEAL Partnership Committee (HPC) Face to Face

August 1, 2019

Workshop: NIH Natcher Auditorium Jan. 30-31, 2019

- **Dr. Tony Yaksh** (University of California San Diego)
- **Dr. Jeffrey Kennedy** (JK Associates BioPharma Consulting LLC).
- **Marie Gill** (NINDS)



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Structure of the Workshop

GOAL: **To develop a consensus for the engagement of preclinical models for the development of pain therapeutics.**

- **Preworkshop Survey**
  - **Overview of animal models in >40 sites**

- **Sessions 2.5hr**
  - **Acute Pain**
    - **Cheryl Stucky and James Eisenach**
  - **Chronic Pain**
    - **Jeff Mogil and S. Negus**
  - **Central Pain**
    - **Brad Taylor and Andrew Rice**
  - **Mononeuropathic Pain**
    - **Robert Gereau and Allan Basbaum**
  - **Musculoskeletal Pain**
    - **Kathleen Sluka and Anne-Marie Malfait**
  - **Joint Pain**
    - **Dottie Brown and Jason McDougall**
  - **Visceral Pain**
    - **Beverley Greenwood and Timothy Ness**
  - **Polyneuropathic Pain**
    - **Daniela Salvemini and Calcutt**
  - **Trigeminal Pain**
    - **KC Brennan and Frank Porreca**
  - **Orthopedic Pain**
    - **Laura Stone and Qiufu Ma**
  - **Cancer Pain**
    - **Patrick Mantyh and Ted Price**

Attendees Overview

- 125 Participants
- 40 Invited attendees
- 27 Representatives from Industry
  - 13 different companies
  - academic institutes
  - government agencies
    - NIH
    - DEA
    - FDA
  - Videocast - archived
    - 256 Live views
    - 206 On-demand

https://videocast.nih.gov/summary.asp?live=29187&bhcp=1

co-Chairs and Attendees by Session

125 Participants
40 Invited Attendees

Breakout Session 1			
A. Acute Pain	B. Musculoskeletal Pain	C. Cancer Pain	D. Mononeuropathic Pain
Burstein	Brennan	Brown	Basbaum
Eisenach	Dworkin	Calcutt	Christoph
Houle	Lehto	Mantyh	Gereau
McDougall	Ma	Ness	Goadsby
Negus	Malfait	Pomonis	Grace
Stucky	Munro	Price	Greenwood
Yaksh	Sluka	Whiteside	Kennedy
Pradhan	Stone		Mogil
			Porreca
			Rice
			Salvemini
			Taylor

Breakout Session 2			
A. Chronic Pain	B. Joint Pain	C. Visceral Pain	D. Polyneuropathic Pain
Lehto	Whiteside	Basbaum	Calcutt
Eisenach	Pradhan	Brennan	Dworkin
Grace	Brown	Burstein	Gereau
Kennedy	Ma	Christoph	Munro
Porreca	Malfait	Goadsby	Price
Sluka	McDougall	Greenwood	Rice
Mogil	Stone	Ness	Salvemini
Negus	Pomonis	Yaksh	Taylor
Stucky	Houle	Mantyh	

Breakout Session 3		
A. Central Pain	B. Orthopedic Pain	C. Trigeminal Pain
Basbaum	Brown	Brennan
Christoph	Kennedy	Burstein
Dworkin	Ma	Goadsby
Eisenach	Malfait	Lehto
Gereau	Mantyh	Munro
Grace	McDougall	Porreca
Greenwood	Negus	Pradhan
Mogil	Sluka	Price
Ness	Stone	Stucky
Rice	Whiteside	Houle
Taylor	Pomonis	
Yaksh		
Calcutt		
Salvemini		

Deliverables

Define commonly accepted operational parameters of the described behavioral models.

Animal: e.g., Species, strain, sex, age

Stimulus: e.g., Thermal (Hargreaves; hot plate; tail flick, skin twitch; calibrated temperature; rate of rise); paw compression; weight bearing; tactile stimulation (von Frey filaments; up down/ repeated application), formalin evoked flinching (e.g. dorsum vs plantar injection)

Stimulus environment: e.g., Device type/source; Chamber (dimensions, lumination)

End points/ metric: e.g., Hindpaw/tail withdrawal (latency/threshold intensity; paw licking, grooming affected body part, vocalization; flinching count or time, place preference (preferred/non-preferred chamber)

Consider approaches/processes to select preclinical models to evaluate analgesically-targeted molecular candidates

Mechanistic/face validity: e.g., Hyperalgesia, inflammation of joint, sensitization of peripheral terminals

Predictive validity: e.g., How well do drugs with defined clinical efficacy co-vary with preclinical efficacy?

Reliability: e.g., Coefficient of variation across time in a given facility

Efficiency: e.g., Ease of implementation (training, reproducibility of measurement system, “low, medium, high” throughput?)

Deliverables

Define guidelines for defining adverse events to allow estimation of therapeutic ratio in a given model

Define utility of non-rodent animals as analgesic study models (using evoked or natural pathology).

ISSUES TO CONSIDER IN MODELS FOR ANALGESIC DRUG DEVELOPMENT
What are critical model properties?

Adverse events: What is the minimum standard for defining a significant adverse event, toward providing doses to permit establishing a therapeutic ratio?

Characterization of dependence and abuse potential. What are the minimum criteria for assessing intrinsic reinforcing properties of drugs and abuse potential?

SURVEY TABLES: Overview of Pre-clinical Models to Develop Analgesic Drugs

Example Recommendations- ACUTE PAIN

Pain models/assays	Model 1	Model 2	Model 3
Model Construct	Skin + muscle incision (Brennan)	Laparotomy with/without organ manipulation	Carrageenan, CFA, Formalin, Capsaicin
Species	Rat and Mouse	Rat and Mouse	Rat and Mouse
Strain	Depends on the question; Mice: tests are strain-dependent; Rats inbred vs. outbred; Largest signal to noise ratio	Depends on the question; Mice: tests are strain-dependent; Rats inbred vs. outbred; Largest signal to noise ratio	Variable for Rat and Mouse
Sex	Females and Males	Females and Males	Females and Males
Stimulus	**Battery of tests:** 1) von Frey; 2) volitional activity (rearing, gait, nest building, 24 hr activity monitoring); 3 Grimace	**Battery of tests:** 1) von Frey; 2) volitional activity (rearing, gait, nest building, 24 hr activity monitoring); 3 Grimace	Discussed but no consensus; may be surrogate models of uncertain relevance
Preferred Endpoint	Consider composite score of all 3 assays	Consider composite score of all 3 assays	
Minimum endpoint criterion response	~30% return to baseline	~30% return to baseline	
Active comparator (efficacious drug)	NSAIDS and opioids	NSAIDS and opioids	
Inactive control	Yes, but which? Maybe THC, 5HT3 antagonist, NK1 antagonist	Yes, but which? Maybe THC, 5HT3 antagonist, NK1 antagonist	

Example Recommendations- ACUTE PAIN

Rank-order/prioritization of models	Model 1 Skin + Muscle	Model 2 Laparotomy	Model 3 Carrageenan, CFA, Formalin, Capsaicin
Face and/or construct validity	High	High	Questionable
Reversal of pain state by active drug	Yes by NSAIDs and opioids	Yes by NSAIDs and opioids	Yes by NSAIDs
Baseline differential pre/post-injury	Large dynamic range	Large dynamic range	Large dynamic range
Ease of model creation/performance	Easy	Easy	Super Easy
High throughput (screening)	#2 in throughput	#3 in throughput	#1 in throughput
If your list contains more than one model/pain assay, would you recommend running only the highest ranked model or more than one?	Highly validated Recommend, #1	Recommend, #2; May be even more clinically relevant to humans; though not as widely used	Concern about human relevance

Example Recommendations- ACUTE PAIN

General Questions				
Are rodent models adequate, or are models in other species and/or large animals (pig, dog, etc.) important to consider and why?	May be valuable to consider pig model since pig skin and innervation may be more similar to human than rodent; incision model easy to do in other species			
What are the perceived gaps (face or construct but NOT predictive validity) in the currently available models?	Carrageenan, CFA, Formalin may not replicate acute inflammatory pain in humans well			
Needs for outcomes that better reflect human pain qualities	*Need to assess the suffering and **affective components** associated with pain: Grimace? Guarding? Motivated complex (hedonic) behaviors *Need to assess the spontaneous pain in a straight-forward way Pain at rest (breathing) Pain during movement			

Workshop Summary - Whitepaper

Critical Evaluation of Animal Pain Models for Therapeutics Development Workshop

National Institute of Neurological Disorders and Stroke

January 30-31, 2019

Bethesda North Marriott Hotel and Conference Center
Rockville, Maryland

This meeting summary was prepared by Lucas Smalldon, Rose Li and Associates, Inc., under contract to Infinity Conference Group. Review of earlier versions of this meeting summary by the following individuals is gratefully acknowledged: Samuel Thomas, Nancy Tuvesson.

~83 page – to be disseminated through the NIH HEAL website