



Challenges and Hurdles to Translational Pain Research

NIH Pain Consortium
11th Annual Symposium

Bethesda, MD

Pain – So what's the problem?



- It's common
 - Chronic pain - ~25% of the population, >50% of veterans, overall prevalence is increasing as is disability
 - Acute pain - Moderate-severe in ~30% postoperatively
 - Cancer pain - >50% all stages, >30% after cure
- It's costly
 - Chronic pain - \$600B annually in the US, and costs are increasing faster than overall healthcare
 - Acute pain - Discharge, readmission, recovery, complications
 - Cancer pain - Direct + Indirect ~\$900/mo
- It's difficult to treat
 - Drug Trials - <50% of participants receive >50% pain relief
 - Multiple treatments and multimodal treatment is common
 - Functional improvements difficult to demonstrate

What then are the options for treatment?



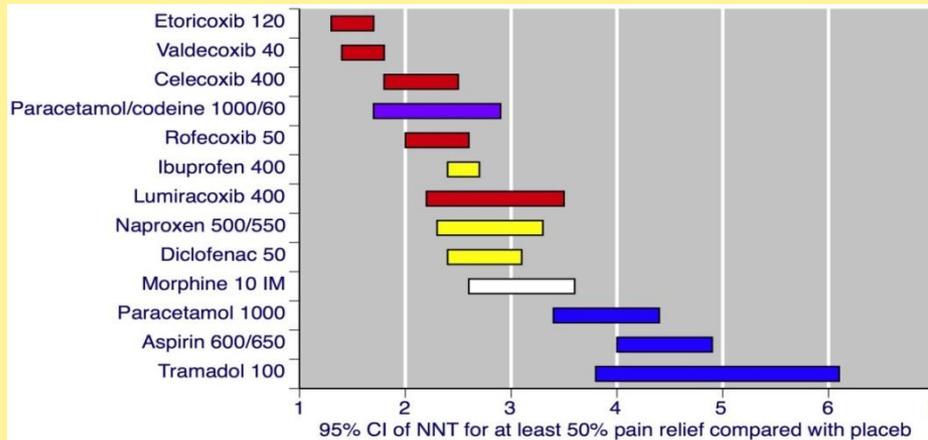
Many medicines, few cures
Benjamin Franklin



Numbers Needed to Treat/Harm (NNT/NNH)



Acute Pain, 50% Relief



Oxford League Table, 2007

Chronic Pain, 50% Relief

Drug	Condition	NNT 50% relief	NNH
Opioids ^{1,2}	Neuropathic pain	2.5 ^{1,2} - 4.3 ¹²	4.2 - 8.3
Tramadol ^{3,4}	Neuropathic pain Post-surgical	3.4 ³ - 4.7 ¹² 2.4 - 4.8 ⁴	8.3
TCAs: Amitriptyline ⁵ Nortriptyline	Neuropathic pain	3.6 ^{5,12}	6 (minor) - 28 (major)
Gabapentin ^{6,7} Pregabalin ^{8,9}	Neuropathic pain Central Neuropathic Diabetic neuropathy PostHerpeticNeuralgia Fibromyalgia	7.2 - 7.7 ¹² 5 ⁸ 2.9 - 5 ^{6,8} 3.9 ⁸ 13-22 ⁹	3.7 (minor)
SNRIs: Venlafaxine ⁵ Duloxetine ¹⁰	Neuropathic pain	3.1 ⁵ 6 - 8 ¹⁰	16.2 (major) 9.6 (minor)
Paracetamol ¹¹	Chronic arthritis	4-5 ¹¹	12 (GI SEs)
Lignocaine patch ¹² Capsaicin patch ¹³	Peripheral Neuropathic Pain	4.4 ¹² 10.6 ¹³	Minimal

Gov't. of Western Australia
Dept. of Health

What has changed in 20 years?



1996

- NSAIDS
- Acetaminophen
- Opioids
- Antidepressants
- Gabapentin
- Tramadol
- Capsaicin
- Lidocaine

2016

- Same (COX2)
- Same (IV)
- Same (Formulations)
- Same (More SNRI's)
- Same (Pregabalin)
- Same (Tapentadol)
- Same (Patch)
- Same (Patch)
- Omega conotoxin
- Botulinum toxin

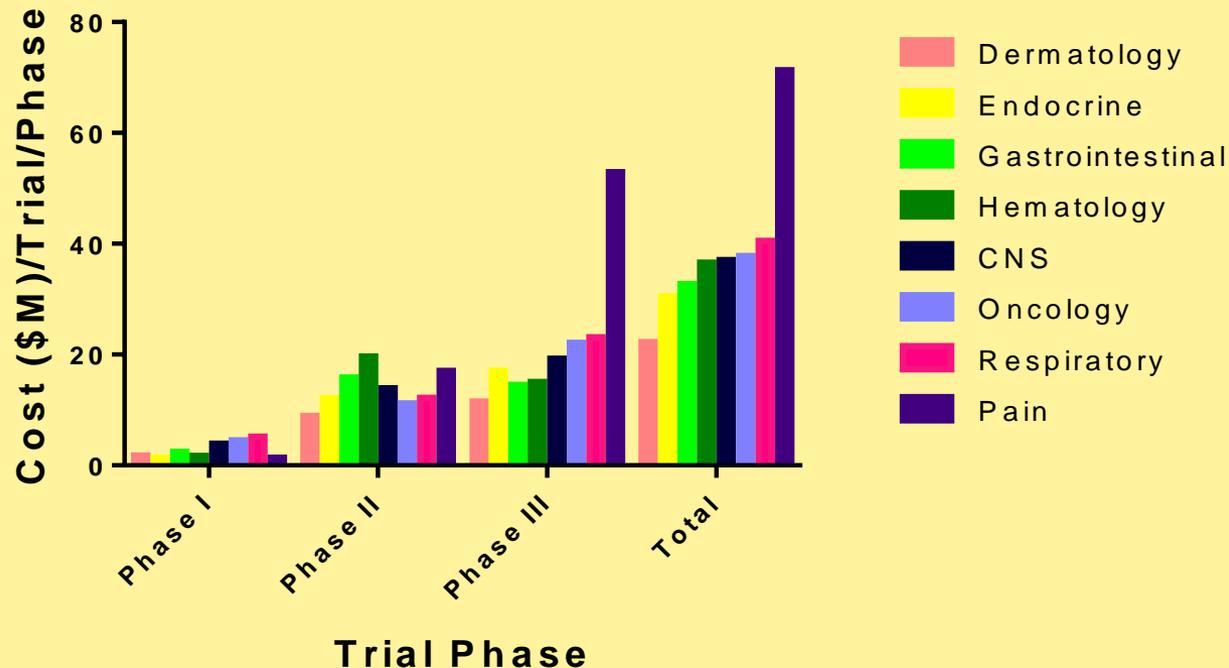
What approaches were used in trials?

(A very Short List)



- CCR2 antagonists
 - Posttraumatic neuralgia
- TRPV1 antagonists
 - AMG 517 (others), Hyperthermia
 - OA, Dental pain, GERD
- FAAH1 antagonists
 - OA
- NK1 antagonists
 - Postoperative pain
 - PDN
- “Glial inhibitors” (Minocycline, Propentofylline)
 - Persistent pain after discectomy, Hand surgery, Radiculopathy
 - PHN

Trial Costs for Specific Therapeutic Areas



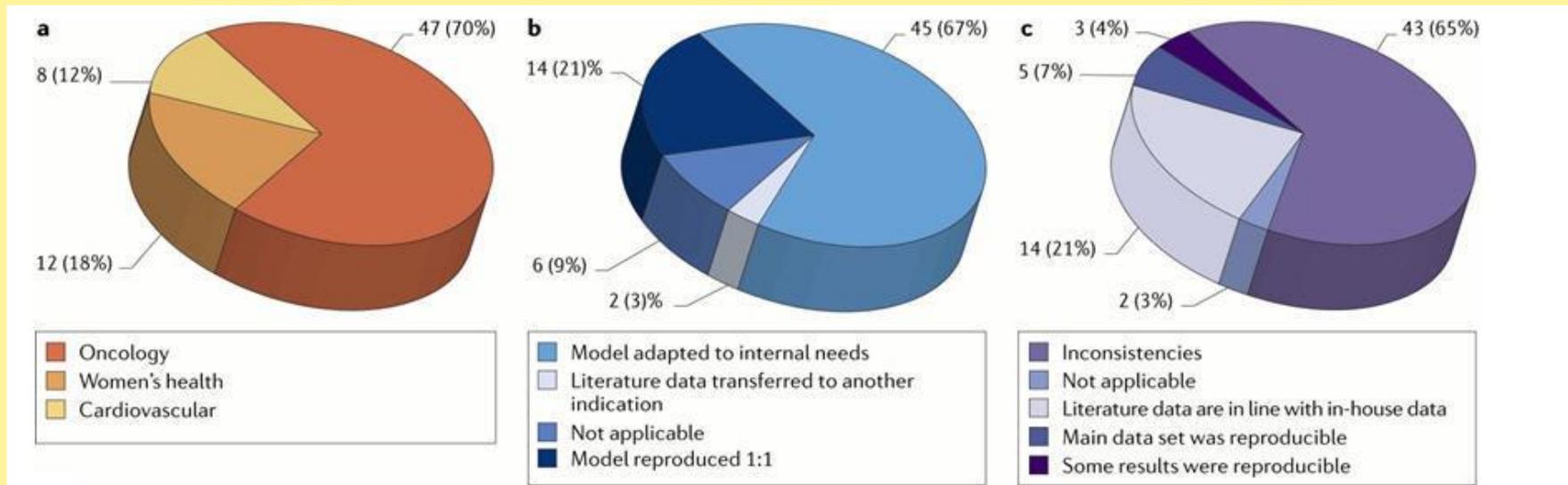
Goal: Optimize preclinical testing to make translation to specific human pain states most likely.

The Reproducibility of Preclinical Testing



“At least 50% of published studies, even those in top-tier academic journals, can't be repeated with the same conclusions by an industrial lab.”

Bruce Booth, venture capitalist, 2011

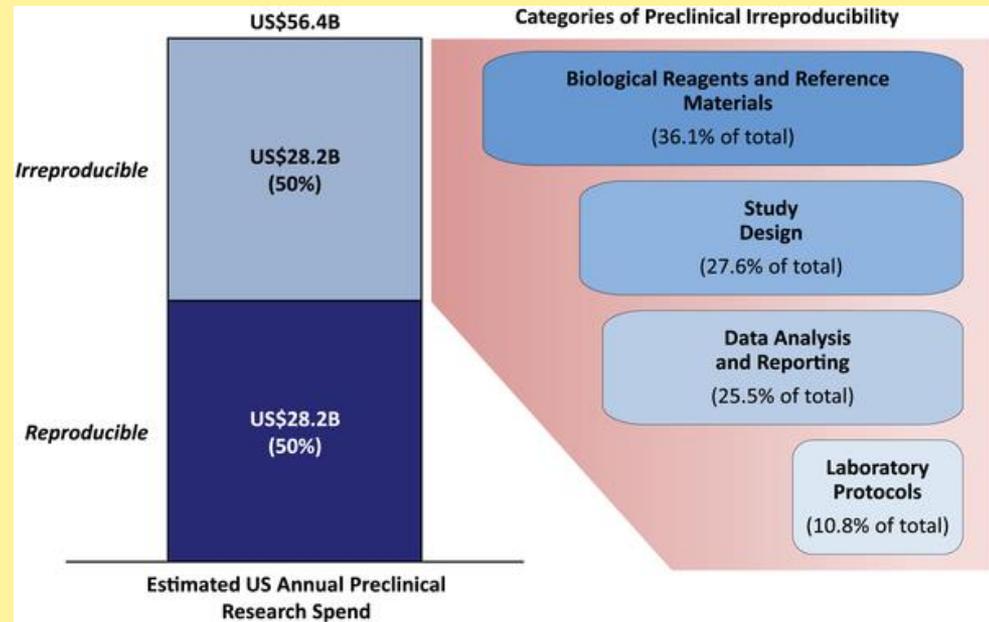
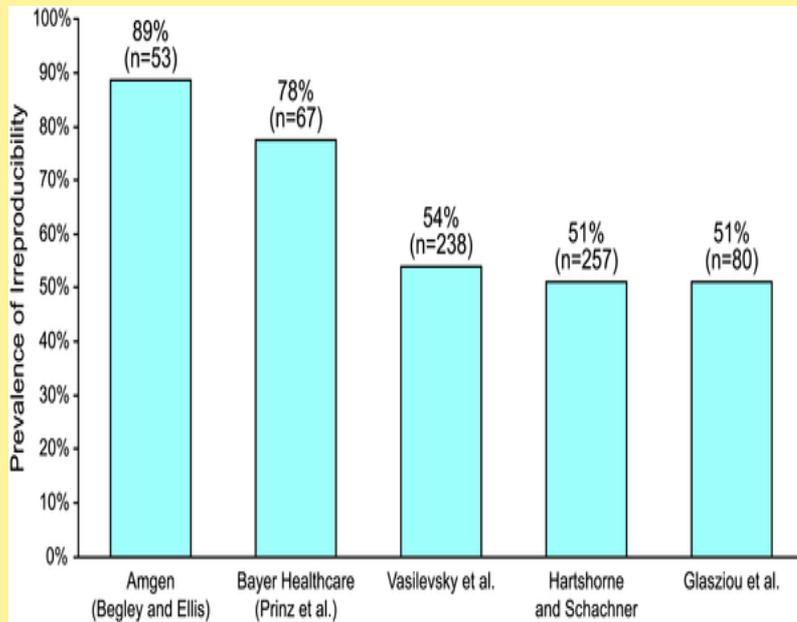


Bayer Healthcare, 67 laboratory projects

The Cost of Irreproducibility



- If 50% of preclinical research is irreproducible, over \$28B is wasted per year in the US alone.



Reporting Guidelines



- Contributing problem: Failure to describe research methods and to report results appropriately
- Guidelines:



CONSORT - Consolidated Standards of Reporting (clinical) Trials



ARRIVE - Animals in Research: Reporting In Vivo Experiments

PPRECISE - Animals in Preclinical Pain Research: Reporting and Methodological Guidelines

NIH - “Rigor and Reproducibility:” Scientific premise, rigor of approach, biological variables, resources and reagents

ARRIVE Checklist

(20 Items)



- **Title**

- Accurate

- **Abstract**

- Concise key details

- **Methods**

- Ethical statement
- Study design
- Specific methods
- Animal details
- Blinding and randomization
- Statistics

- **Results**

- Health and weight
- Numbers analyzed and excluded
- Precision and variance
- Adverse events

- **Discussion**

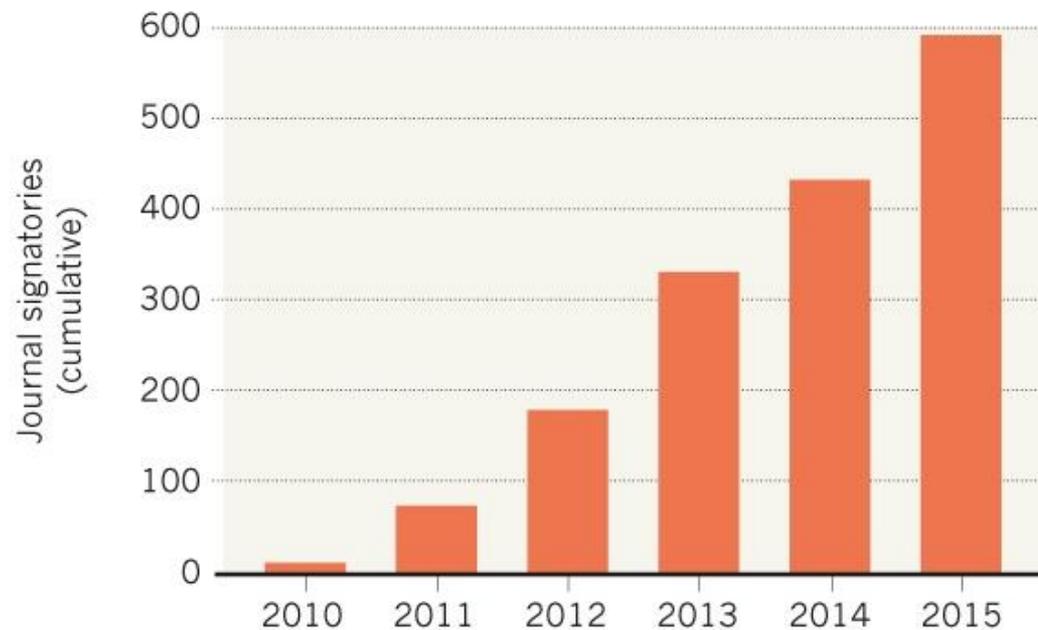
- Interpretation
- Generalization
- Funding sources

Acceptance of ARRIVE Guidelines



SURGE IN SUPPORT FOR STUDY GUIDELINES

In 2015, more than 150 journals signed up to the ARRIVE checklist for animal studies — the highest number of signatories in a single year since it was released.



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Addressing the Preclinical Challenge



- **Models**

- Are the models valid and reliable?
- How is the pain-related physiology of the mouse/rat similar or distinct from humans?
- Are commonly occurring comorbidities included?
- Are the PK/PD properties of the model similar to humans?

- **Measures**

- Are the measures valid?
- Does the response provide an accurate index of a relevant dimension of pain?
- Is the targeted dimension of pain important to the clinical condition being modeled?

Preclinical Models

(Face Validity)



Does the model resemble what we see in the clinic?

Shingles/PHN



Arthritis



Surgery



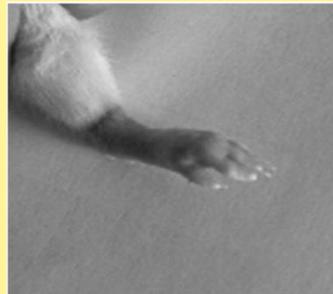
CRPS



Nerve Injury



CFA



Incision



Fracture/Cast



CRPS: The Rodent Fracture-Cast Model



- The most common etiological factors linked to CRPS are distal limb fracture and immobilization.
- Under anesthesia, the distal tibia is fractured and placed in a reinforced cast for 3(mice) to 4(rats) weeks.

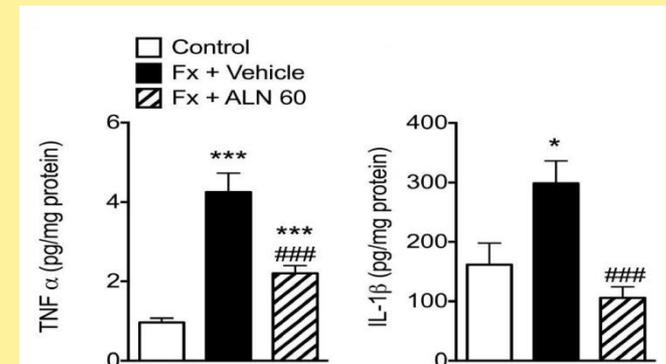
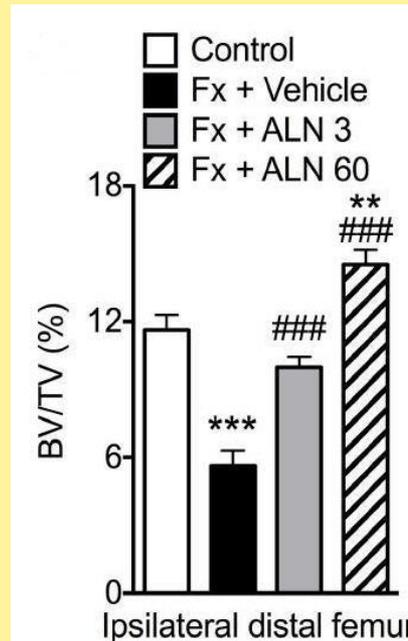
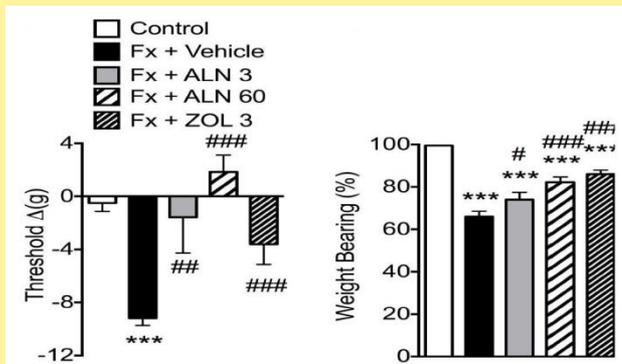


- **Spontaneous extravasation/edema**
- **Warmth**
- **Epidermal thickening**
- **Osteopenia**
- **Allodynia/unweighting**
- **Spontaneous pain**
- **Innate/adaptive immune activation**
- **Anxiety and memory changes**

Example: Bisphosphonate Translation



- **Clinical data:** Several small controlled trials – alendronate, clodronate, pamidronate and neridronate
- **Zoledronate?** – Animal data useful for FDA approval

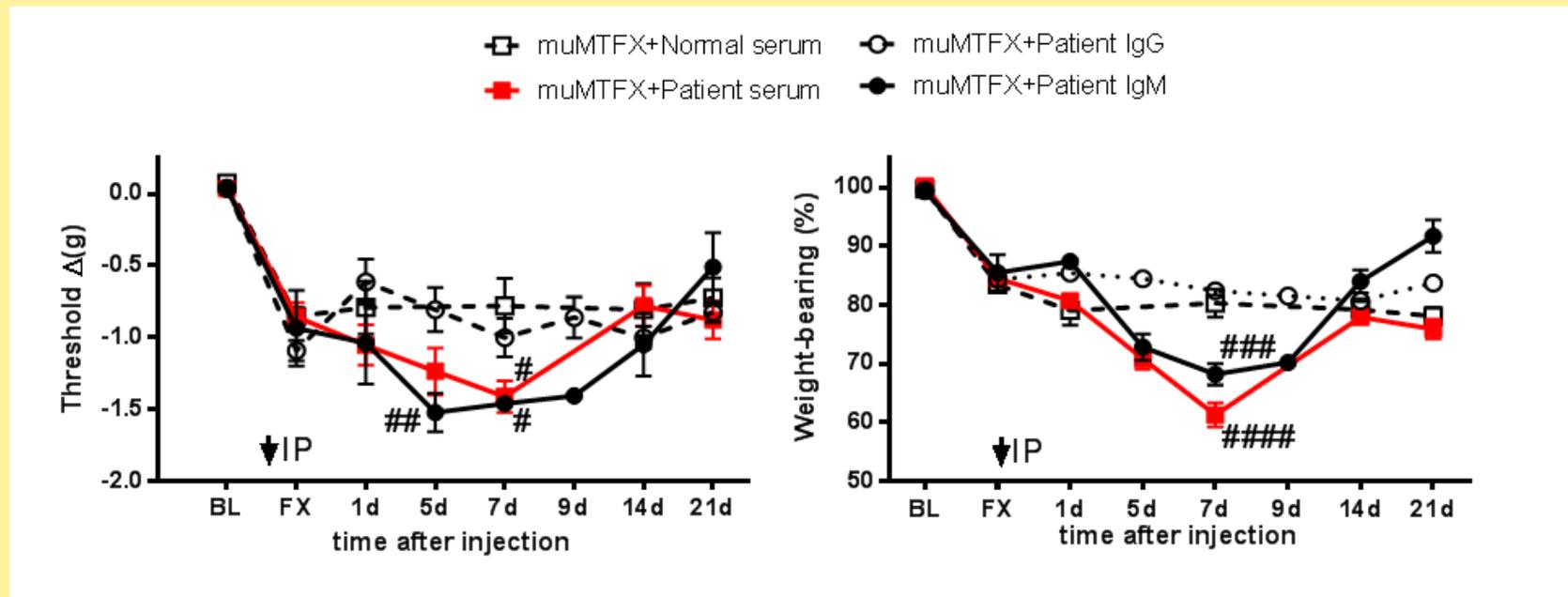


- **Ahmad and Kumar, 2015:** Monthly zoledronate reduces pain in CRPS I after electrical burn

Example: Autoimmunity Translation



- Autoimmunity in CRPS
 - Anti-mACh, beta-2, alpha-1, anti-nuclear antibodies
 - Some patients treated with IVIG



Preclinical Models

(Influence of Sex)



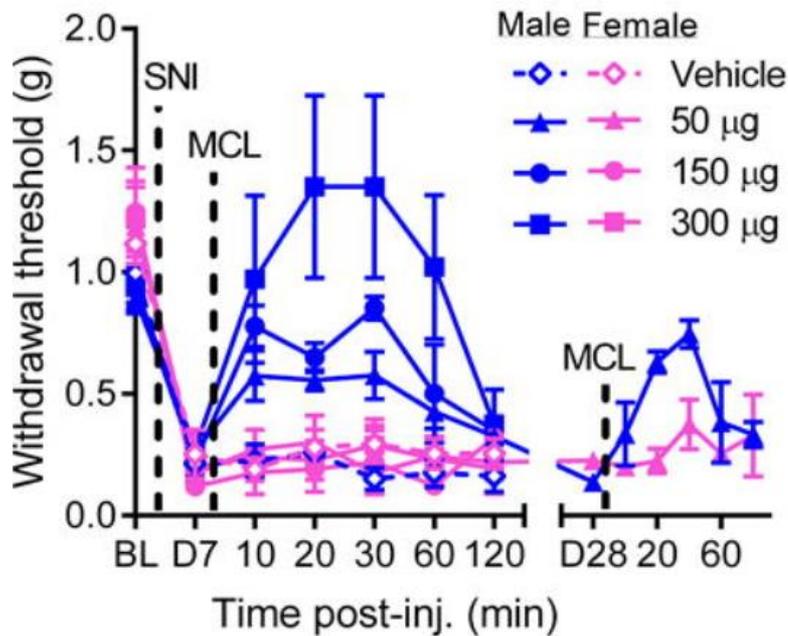
- **Human sex dependence:**
 - Disease prevalence
 - Pain severity
 - Comorbidity susceptibility
 - Analgesic responsiveness/side effect profile
- **Animal model sex dependence:**
 - Degree/duration of nociceptive sensitization
 - Environmental effects
 - Analgesic sensitivity
 - Pathogenic mechanisms
- **NIH: Sex (and other biological variables) should be represented in preclinical studies**

Preclinical Models

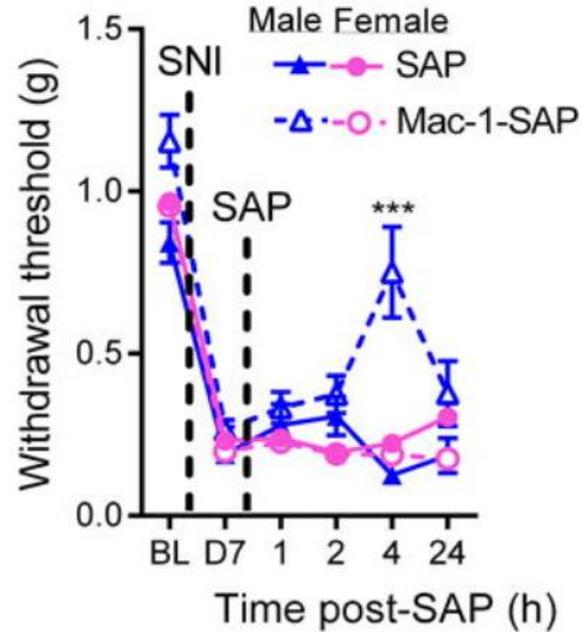
(Influence of Sex)



a. Minocycline



b. Microglial Depletion

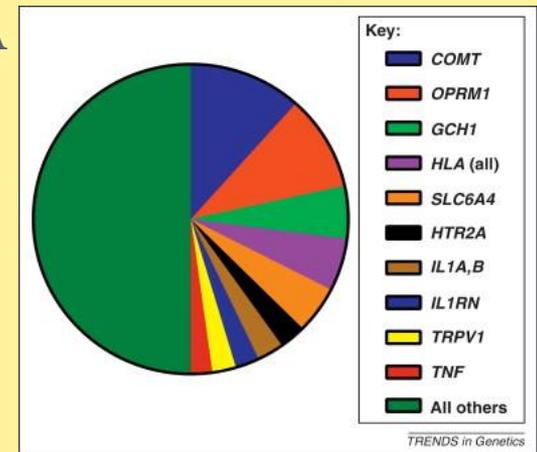


Preclinical Models

(Influence of Genetics, Human Observations)

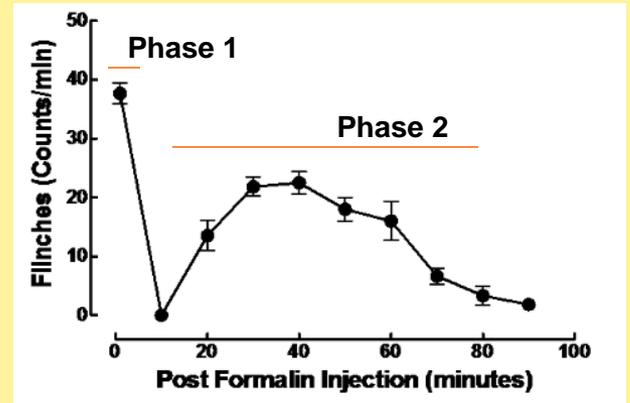


- **Twin studies, heritability**
 - Pain sensitivity: <10% (mechanical) to >60% (cold pressor)
 - Pain syndromes: 25% IBS, 35% axial spine pain, 50% migraine
 - Analgesic sensitivity: 12% morphine (heat), 60% morphine (cold)
 - Side effects: 30% morphine (RR), 59% morphine (nausea)
- **Monogenic (Medelian) pain disorders**
 - SCN9A: Activating (more pain), Inactivating (no pain)
 - Hereditary sensory neuropathies (HSNs), Several genes
 - Fam. hemiplegic migraine, CACNA1A, ATP1A2, SCN1A
- **Gene association studies**
 - COMT, GCH1, MC1R, OPRM1 (pain phenotypes)
 - MDR, CYP2D6 (analgesic responses)

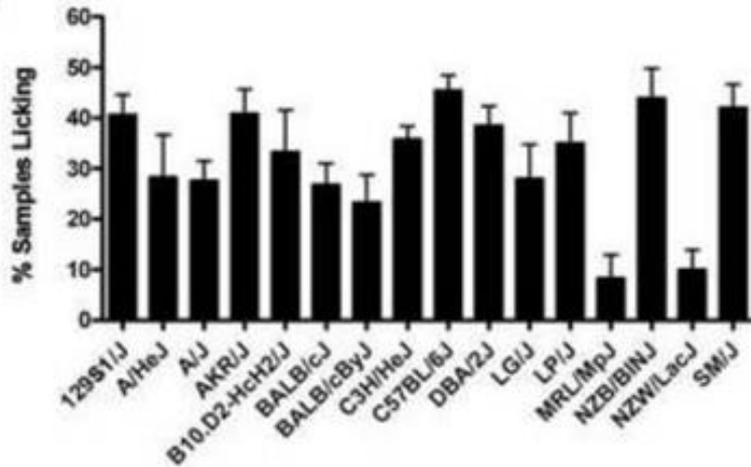


Preclinical Models

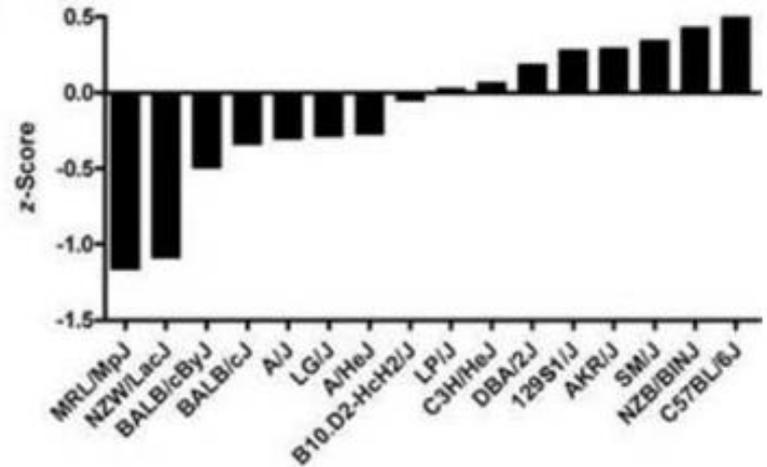
(Influence of Genetics)



A



B



Preclinical Models

(Non-rodent species)



- **Rodents offer:**
 - Cost/time advantages
 - Genetic opportunities
 - Social acceptability
- **Large animals (dogs, horses, primates) offer:**
 - Physiology, pharmacology, PK/PD more similar to humans (sometimes)
 - The natural occurrence of similar diseases, e.g. OA
 - Some functions more easily studied, e.g. gait
 - Ability to work with complex behaviors/cognitive tasks
 - Better size for some testing, e.g. structural/functional imaging
- **Available models**
 - Acute nociception (dogs, primates)
 - Algogen injection (primates)
 - UV sensitization (pigs)
 - OA, ACL injury (dogs)
 - L6, L9 primate nerve ligation model (primates)

Preclinical Measures

(Reflexive Testing)



- “Reflexive” or “evoked” testing
 - Mechanical, e.g. von Frey filaments
 - Thermal, e.g. thermal plantar
 - Very quick, straightforward, objective
 - Inexpensive



- Problems?

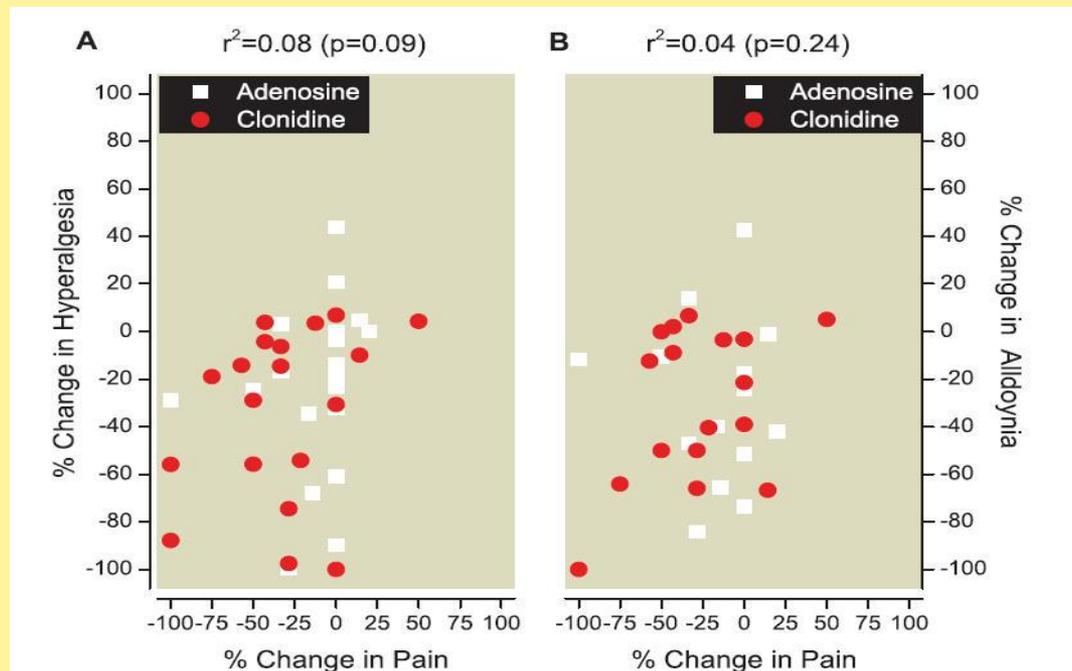
- Nociceptive fiber types activated
- Generally skin tissue targeted
- Clinical complaint: “My pain is almost always there and it limits what I do, my ability to think, being with my family, my sleep and makes me feel depressed.”



Analgesia vs. Anti-hyperalgesia



- Twenty-two subjects with CRPS
- Allodynia and hyperalgesia assessed
- Clonidine 100ug or adenosine 2mg intrathecal

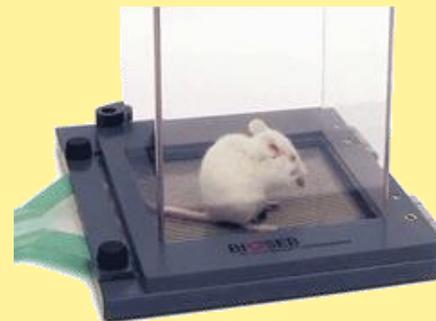


Preclinical Measures (Spontaneous/Ongoing Pain)



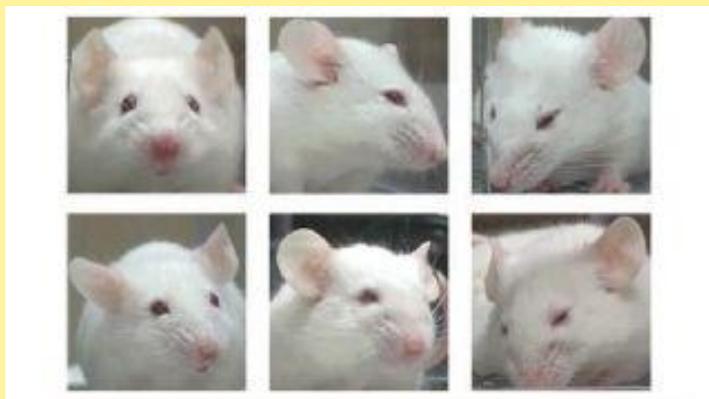
“Body Language”

Flinching, guarding



Postural changes/weight bearing

Face analysis



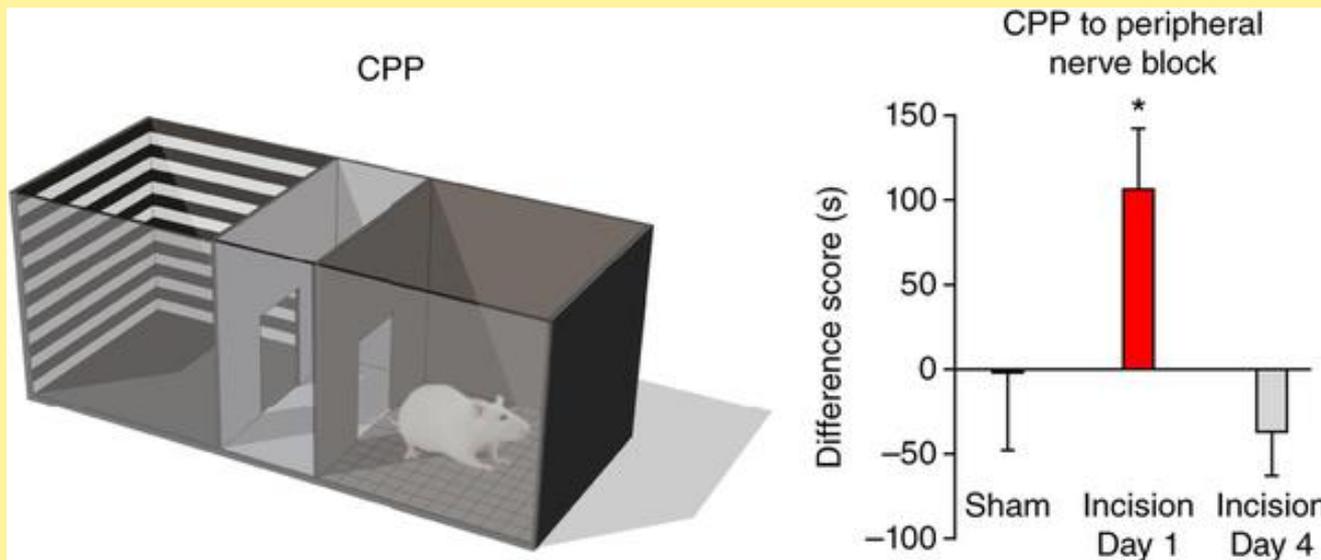
Ultrasonic vocalizations



Preclinical Measures (Spontaneous/Ongoing Testing)



- Conditioned Place Preference



Navratilova and Porreca, 2014

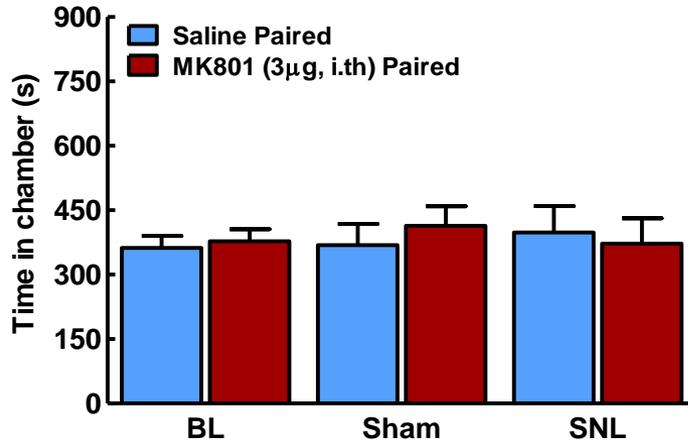
- Other “operant” assays:

- Reward-conflict – receiving a reward with corresponding aversive stimulus
- Avoidance-escape – forced selection between alternative aversive stimuli (one nociceptive)

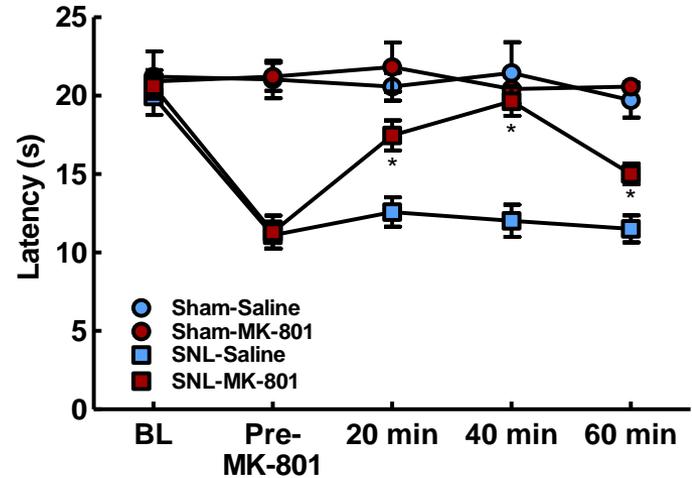
Blockade of hypersensitivity is not the same as blocking ongoing pain



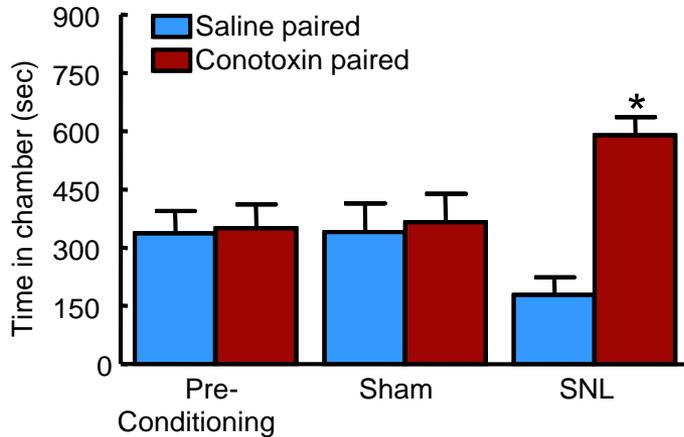
Spinal MK-801 does not induce CPP



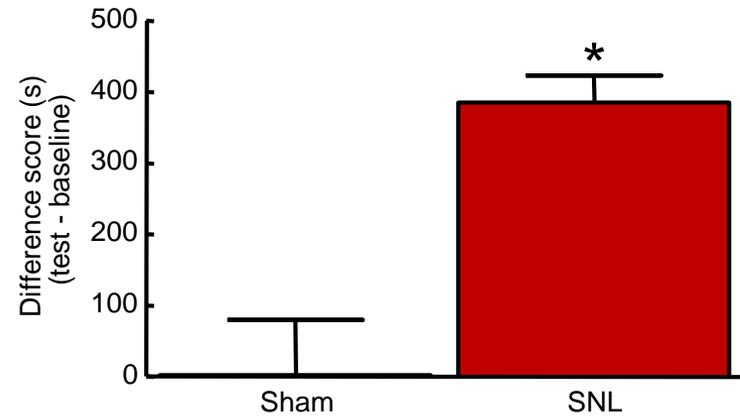
At a dose that fully reverses thermal hypersensitivity



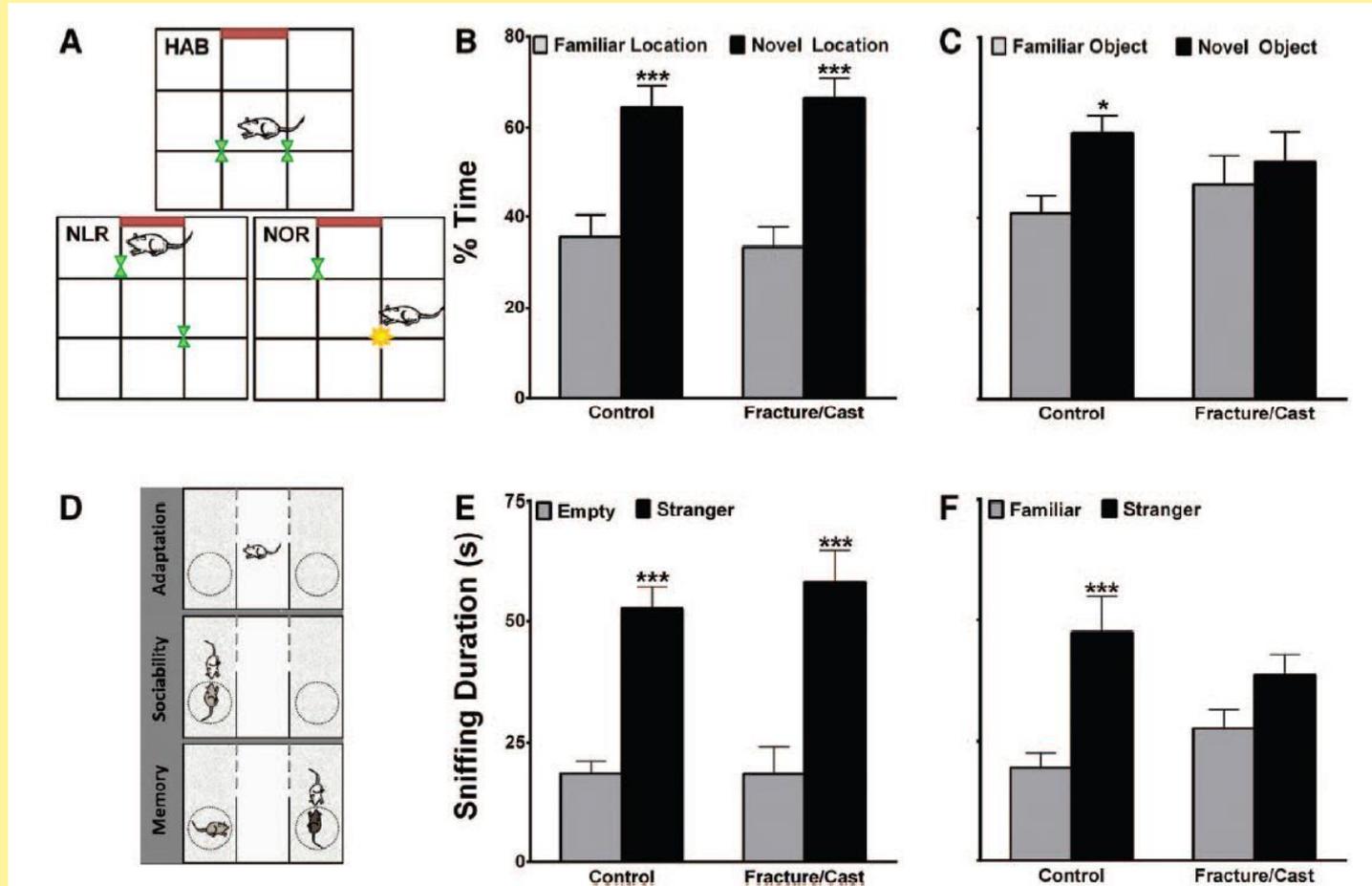
Spinal ω -conotoxin induces CPP



Spinal ω -conotoxin paired chamber



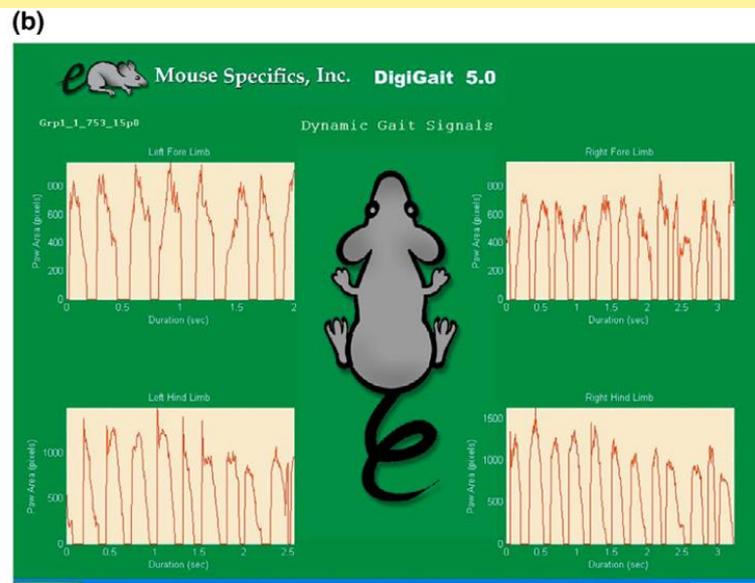
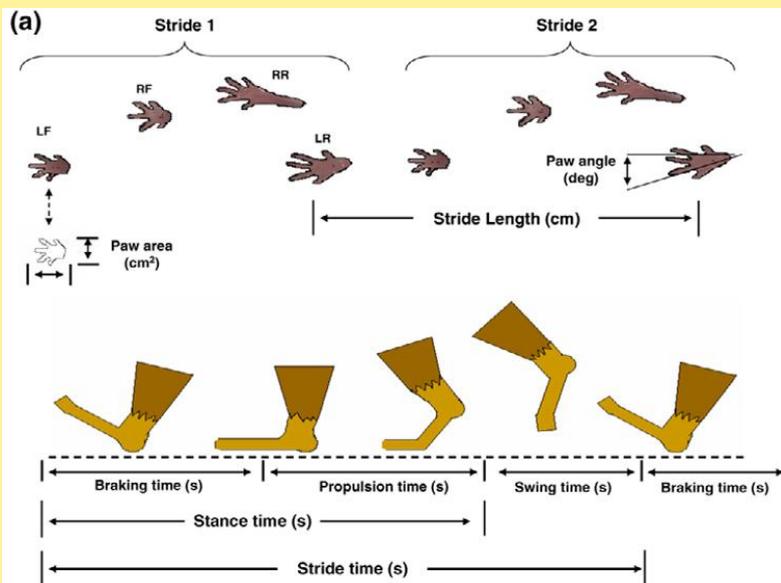
Preclinical Measures (Memory and Social Interactions)



Preclinical Measures (Functional Testing)



- Gait analysis:
 - Incision, Osteo and Rheumatoid arthritis, Multiple sclerosis, CRPS, Chemotherapy-induced pain, Neuropathic pain
 - Analgesics reversed gait abnormalities in some but not all models, e.g. SNI, incision.

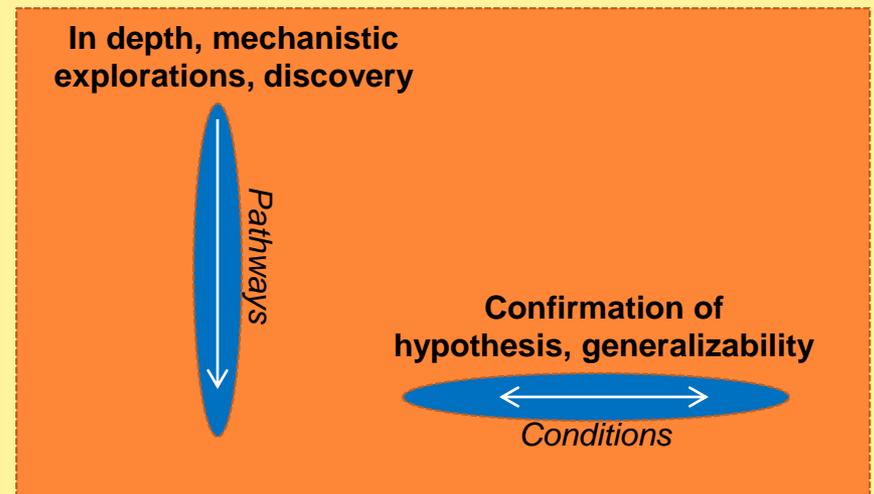


Preclinical Models

(Breadth of Experimental Factors)



- For *discovery*
 - Stringently standardize experimental conditions.
 - Use multiple rigorous, complementary approaches focused on a clear hypothesis, e.g. pharmacological, genetic, biochemical, electrophysiological, optogenetic, etc.
- For *translation* we may specifically examine the impact of:
 - Sex
 - Genetics, species
 - Age
 - Disease comorbidities
 - “Psychological” comorbidities
 - PK/PD



Translational Studies

(Outcome Domains)

IMMPACT: Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials

- Pain
 - Patient report, analgesic use
- Physical function
 - Interference scales
- Emotional function
 - Depression, anxiety
- Pt. impression of change
 - PGIC scale
- Symptoms/adv. events
 - Active/passive capture
- Participants , reporting
 - CONSORT

IMMPAAS: Initiative on Methods, Measurement, and Pain Assessment in Animal Studies

- Pain
 - Evoked, spontaneous, operant
- Physical function
 - Activity, gait, running
- Emotional/cognitive function
 - Depression, anxiety, memory
- Side effects, PK/PD, toxicity
 - Sedation, balance, organ tox.
- Subjects, reporting
 - ARRIVE

Thank you



Stanford University