

PRECLINICAL and CLINICAL RESEARCH in PAIN MANAGEMENT



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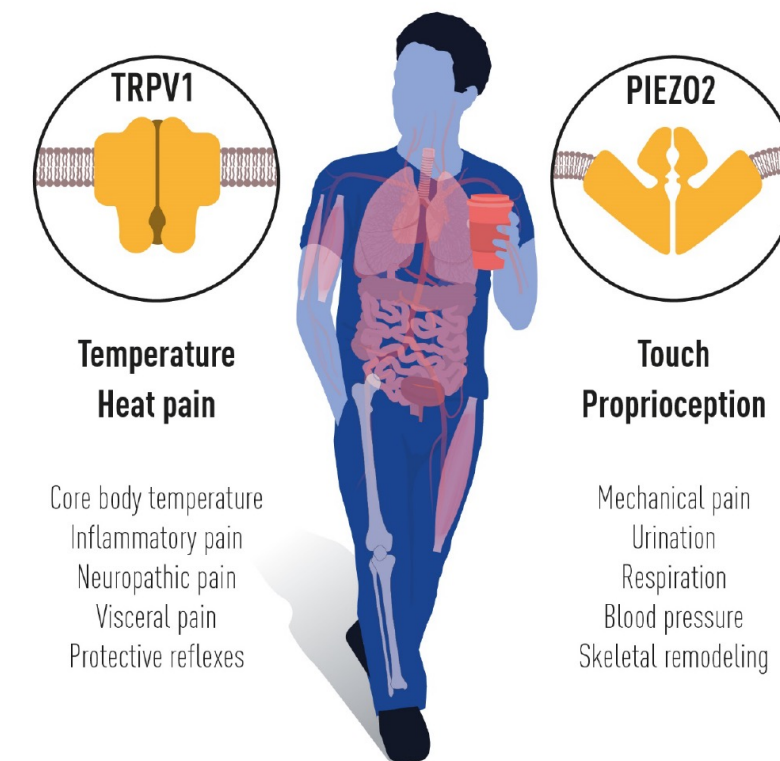
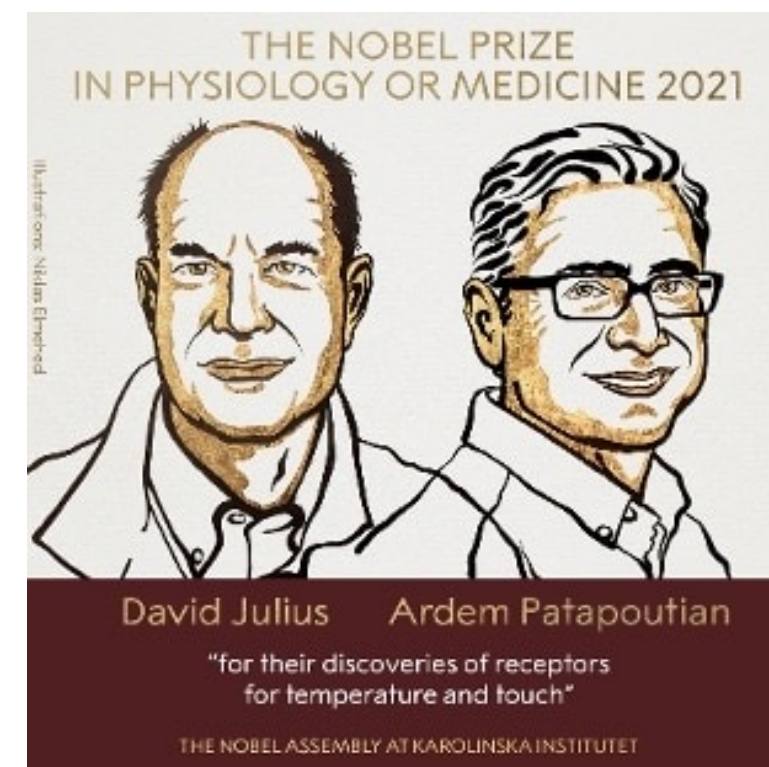
S. Andrea University Hospital
Unit of Anaesthesia
Cancer Pain Management

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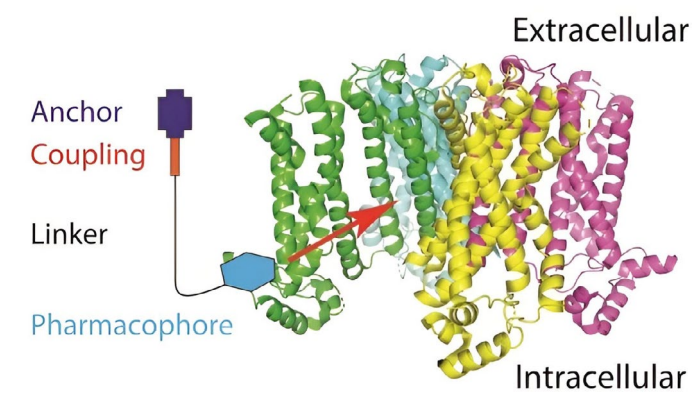
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Nobel Prize in Physiology or Medicine 2021
Molecular Pain researchers



🕒 AUGUST 2, 2023

Potential neuropathic pain treatment shows promise in preclinical tests



BJA



British Journal of Anaesthesia, 131 (4): 745–763 (2023)

doi: 10.1016/j.bja.2023.06.067
 Advance Access Publication Date: 9 August 2023
 Pain

PAIN

An anchor-tether ‘hindered’ HCN1 inhibitor is antihyperalgesic in a rat spared nerve injury neuropathic pain model

Gareth R. Tibbs¹, Rajendra Uprety², J. David Warren³, Nicole P. Beyer¹, Rebecca L. Joyce¹, Matthew A. Ferrer¹, Wilfredo Mellado⁴, Victor S. C. Wong⁴, David C. Goldberg⁴, Melanie W. Cohen⁴, Christopher J. Costa⁴, Zhucui Li³, Guoan Zhang³, Noah E. Dephoure^{3,5}, Dipti N. Barman³, Delin Sun⁶, Helgi I. Ingólfsson⁶, Anthony A. Sauve^{2,1}, Dianna E. Willis^{4,7,*} and Peter A. Goldstein^{1,7,8,*}

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Pain and Analgesic Mechanisms

SPECIAL ARTICLE

Improving Preclinical Development of Novel Interventions to Treat Pain: Insanity Is Doing the Same Thing Over and Over and Expecting Different Results

James C. Eisenach, MD* and Andrew S. C. Rice, MD†

Local Anaesthetics	OFFICIALLY	Opioids
Corticosteroids	★ 40 ★	Anticonvulsants
NSAIDs/APAP	YEARS OLD	Antidepressants

1128 www.anesthesia-analgesia.org

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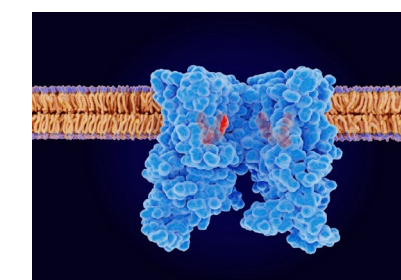
From Lab to Real World: The Steps to Creating New Pain Treatments

Basic research involves experiments in laboratories that seek to understand pain at the molecular and genetic levels

Preclinical research and early-stage drug development involves further investigating the effects of promising basic research and beginning to connect it to humans. Researchers build models and conduct further tests using cells and animals.

Translational research serves as a bridge between basic research and real-world clinical research. This research has four phases: evaluating how well interventions work in controlled clinical settings and in real-world settings, and measuring their impact on health outcomes and on public health.

Clinical research transforms promising theories into actionable solutions. Clinical research trials progress through four stages: from initial safety assessments to large-scale studies and post-approval monitoring.



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Anesthesiology. 2016 November ; 125(5): 846–849. doi:10.1097/ALN.0000000000001340.

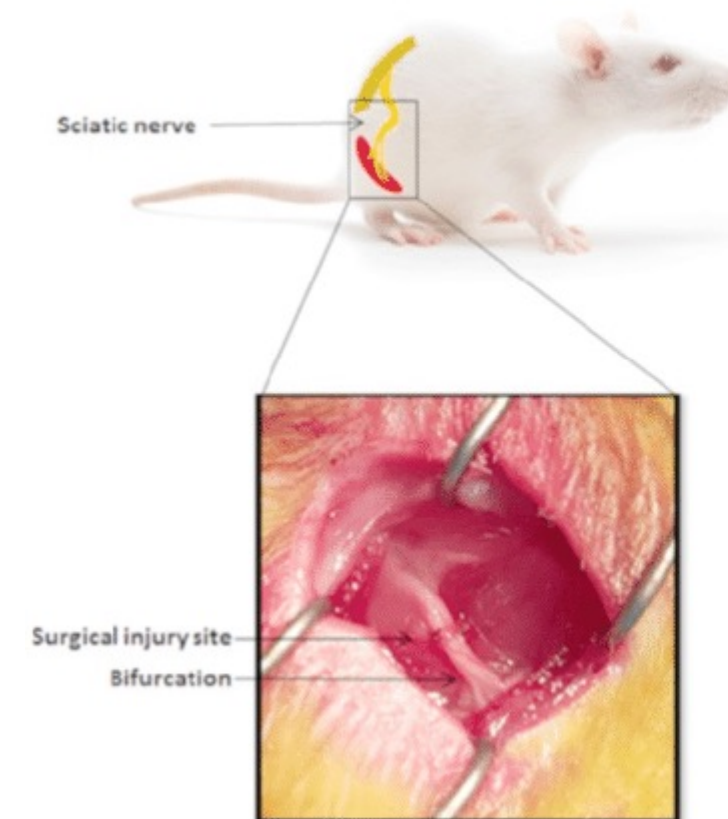
Preclinical Pain Research: Can we do Better?

J. David Clark, M.D./Ph.D.^{1,2}

Poor preclinical pain models

Poor preclinical pain measures

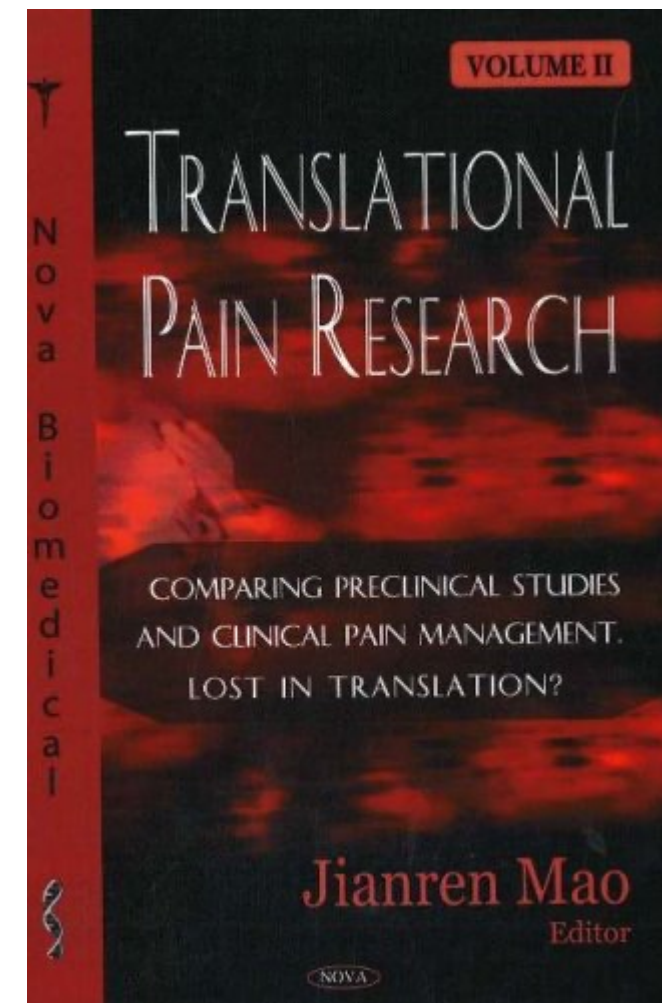
Poor reporting practice



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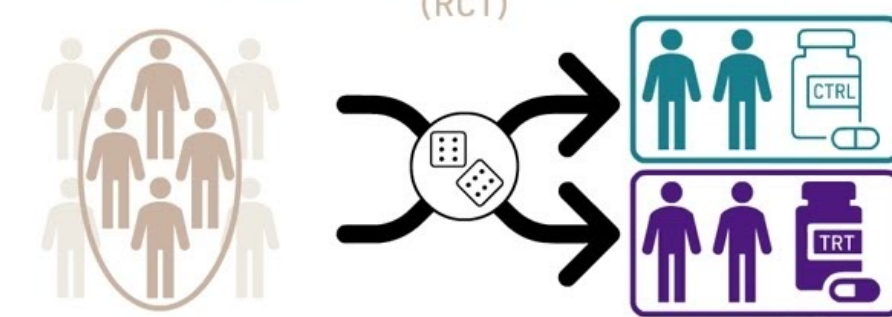
LOST IN TRANSLATION


**LIKELIHOOD of APPROVAL (LOA) for DRUG to progress
 from Phase 1 to Phase 2 and from Phase 2 to Phase 3 (2003-2011)**

	PAIN	PSYCHIATRY	INFECTIOUS DISEASE	RHEUMATOID	SOLID TUMORS
Phase 1 to Phase 2	10.8%	7.2%	16.7%	10.3%	5.7%
Phase 2 to Phase 3	5.9%	12.0%	25.4%	13.9%	8.6%

Extracted from Hayes et al 2014

RANDOMIZED CLINICAL TRIALS (RCT)



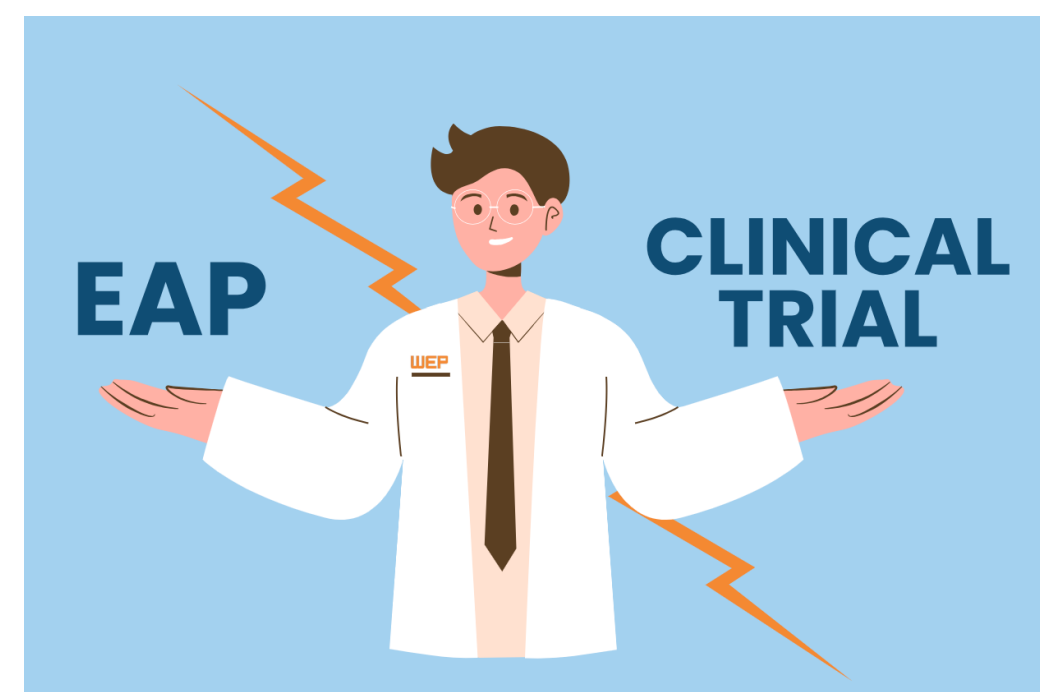
- Evaluate and demonstrate the efficacy and safety in controlled conditions
- Strict framework
- Limited transposability
- Gold standard 

REAL-WORLD EVIDENCE (RWE)



- Explore effectiveness and safety in everyday practice
- Need a rigorous methodology
- Complementary

Expanded Access Programs vs Clinical Trials

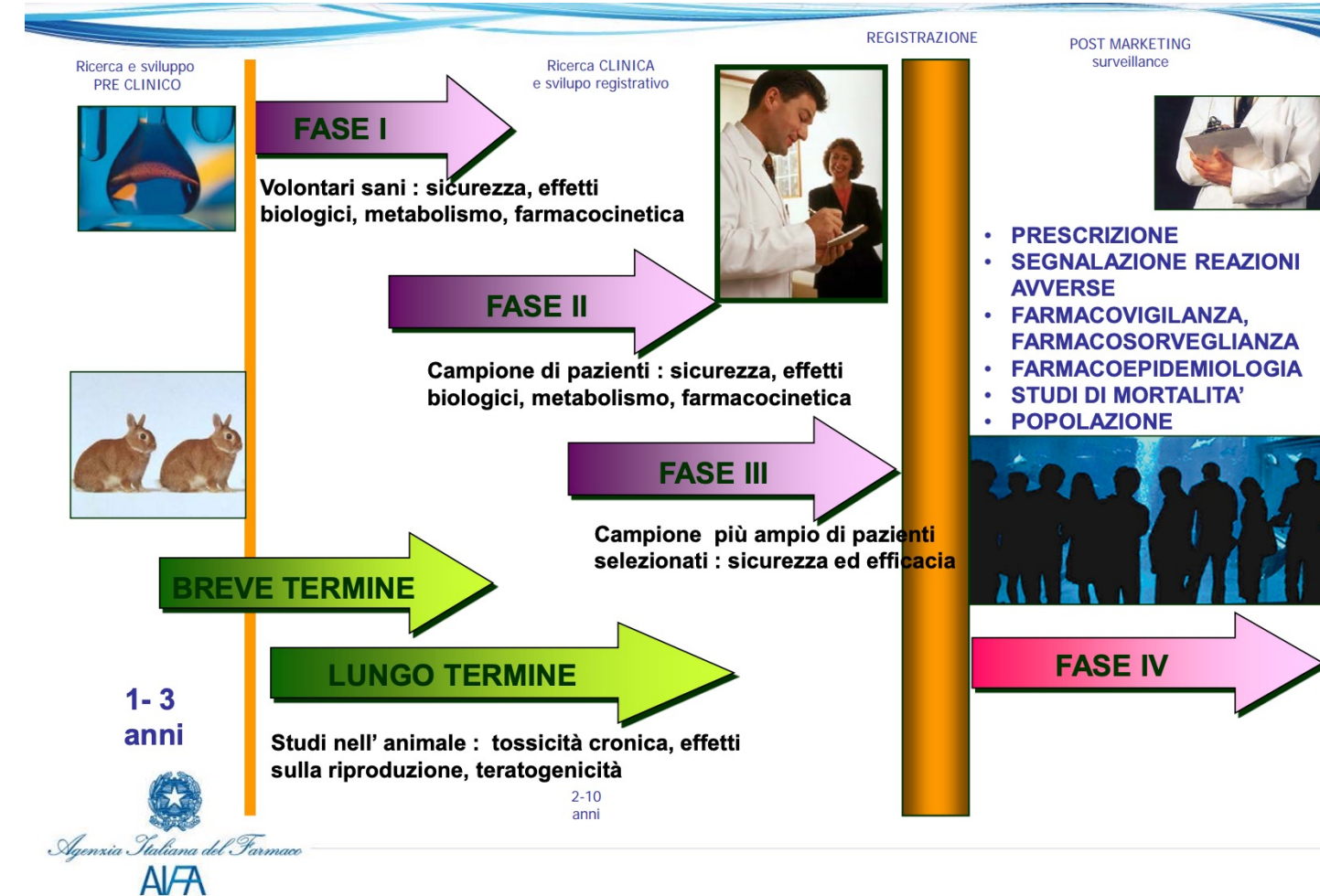


<https://www.wepclinical.com/eap-versus-clinical-trial/>

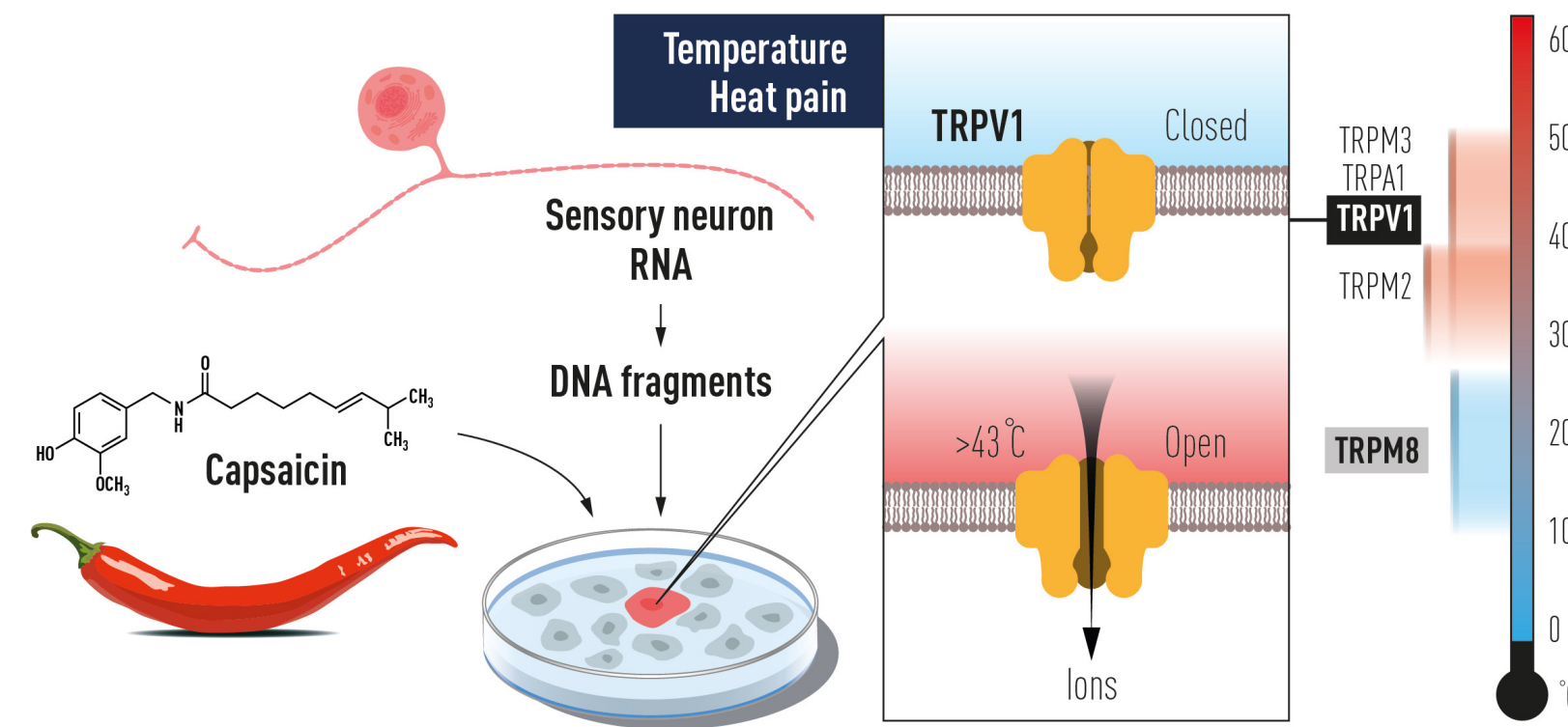
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BACKWARD TRANSLATION

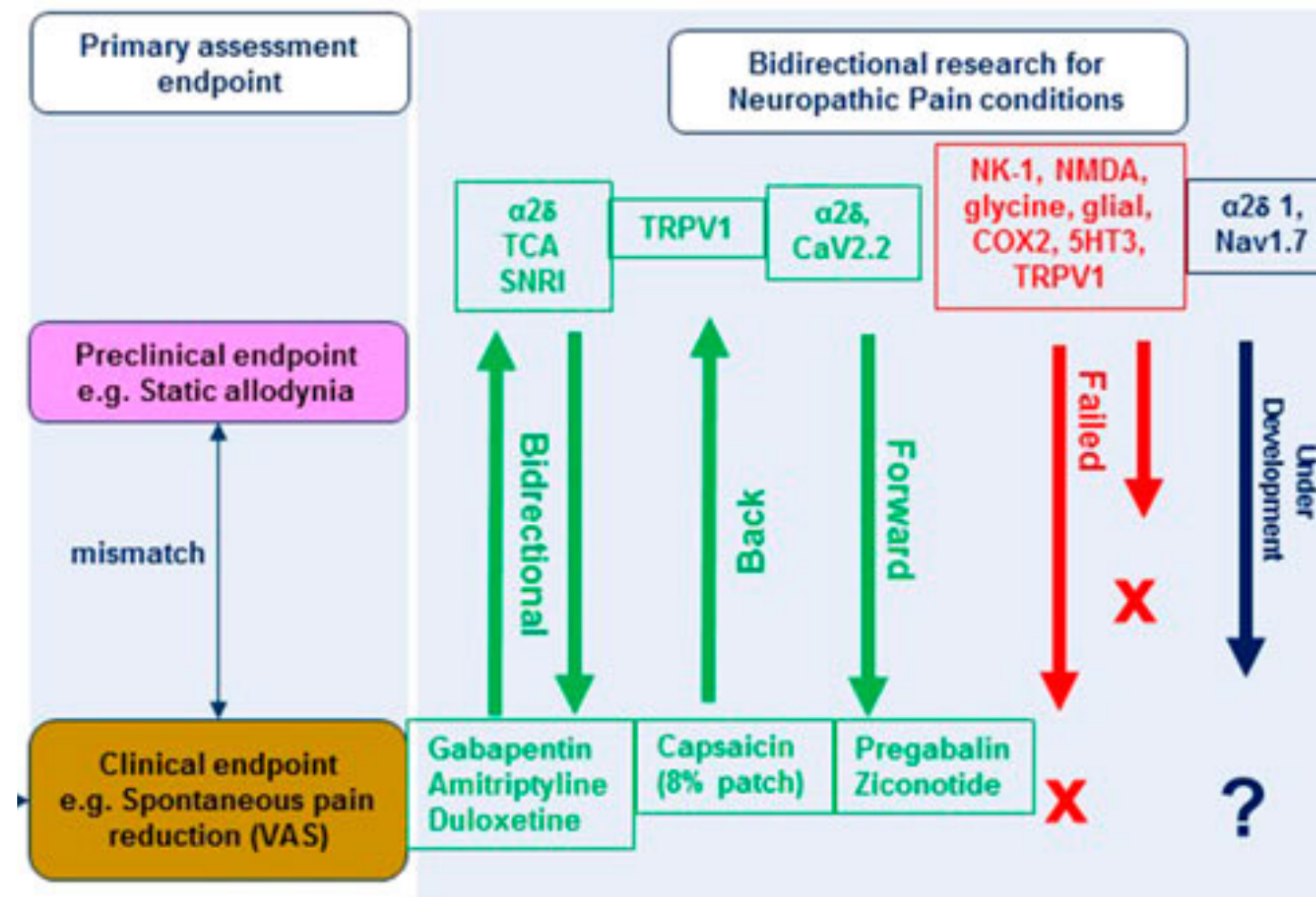


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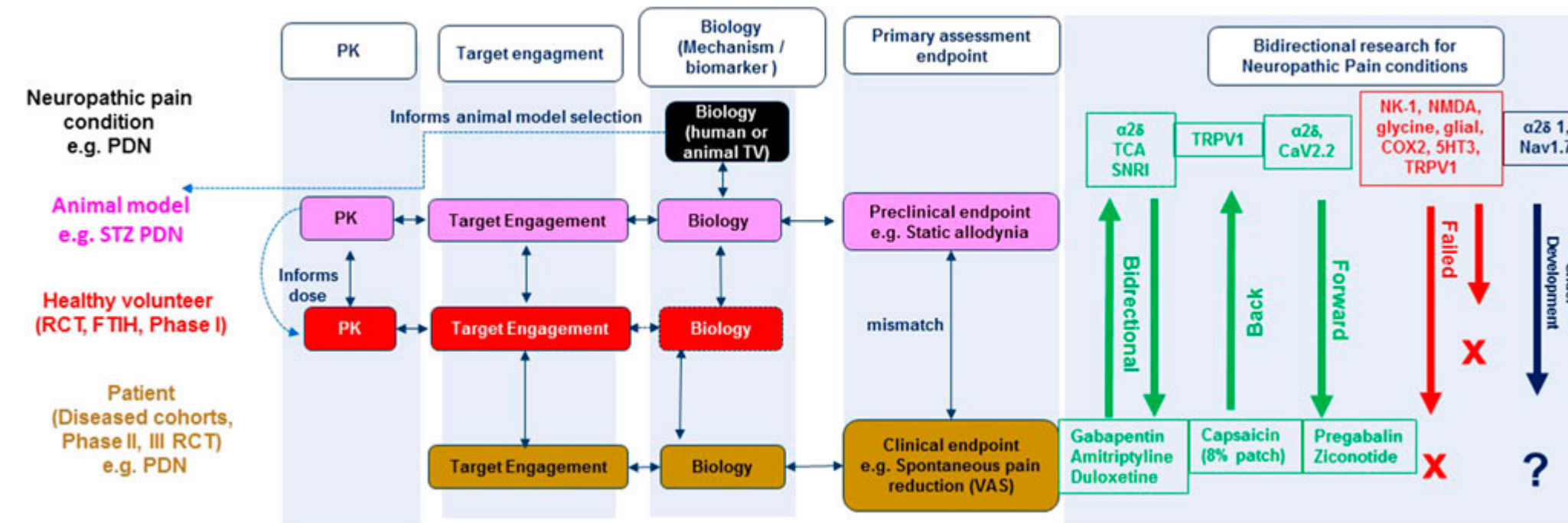
REVIEW
 published: 08 February 2021
 doi: 10.3389/fphar.2020.614990

Preclinical Neuropathic Pain Assessment; the Importance of Translatability and Bidirectional Research

Amy S. Fisher¹, Michael T. Lanigan^{1,2}, Neil Upton¹ and Lisa A. Lione^{2*}

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REVIEW
published: 08 February 2021
doi: 10.3389/fphar.2020.614990



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Methodological mismatch issues

OBSERVATION

Preclinical endpoints	Human RCT endpoints
<p>* Stimulus evoked sensory endpoints</p> <p>Spontaneous pain and Daily living (QoL) Companion animal pain scale ("pets") Pain stimulated and suppressed behaviours e.g. Grimace scales, ultrasonic vocalisation burrowing, hoarding, nesting, gait</p> <p>Affective / Cognitive state depression, anxiety, sucrose preference, sleep Operant place preference/avoidance, self administration</p> <p>Objective markers EEG, microneurography</p>	<p>Reflex QST</p> <p>*Reported pain intensity and Daily living (QoL) (e.g. VAS numerical rating pain scale)</p> <p>Affective / Cognitive state depression, anxiety, motivation, sleep anticipation of pain (preference/avoidance)</p> <p>Objective markers EEG, microneurography, neuroimaging</p>

SELF-REPORTED

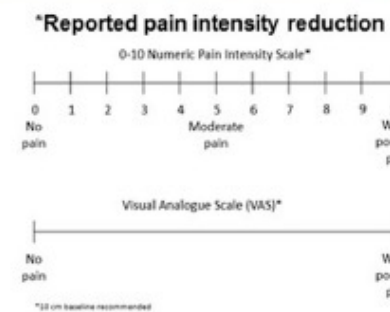


FIGURE 3 | Multiple preclinical neuropathic pain assessment endpoints in development to improve translatability of preclinical to clinical research. *Primary endpoint, RCT (randomised clinical trial), EEG (electroencephalogram), QoL (quality of life).

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Pain Treatment in the Companion Canine Model to Validate Rodent Results and Incentivize the Transition to Human Clinical Trials

Michael J. Iadarola^{1}, Dorothy Cimino Brown², Alexis Nahama³, Matthew R. Sapio¹ and Andrew J. Mannes¹*

What can we learn from osteoarthritis pain in companion animals?

D. Cimino Brown

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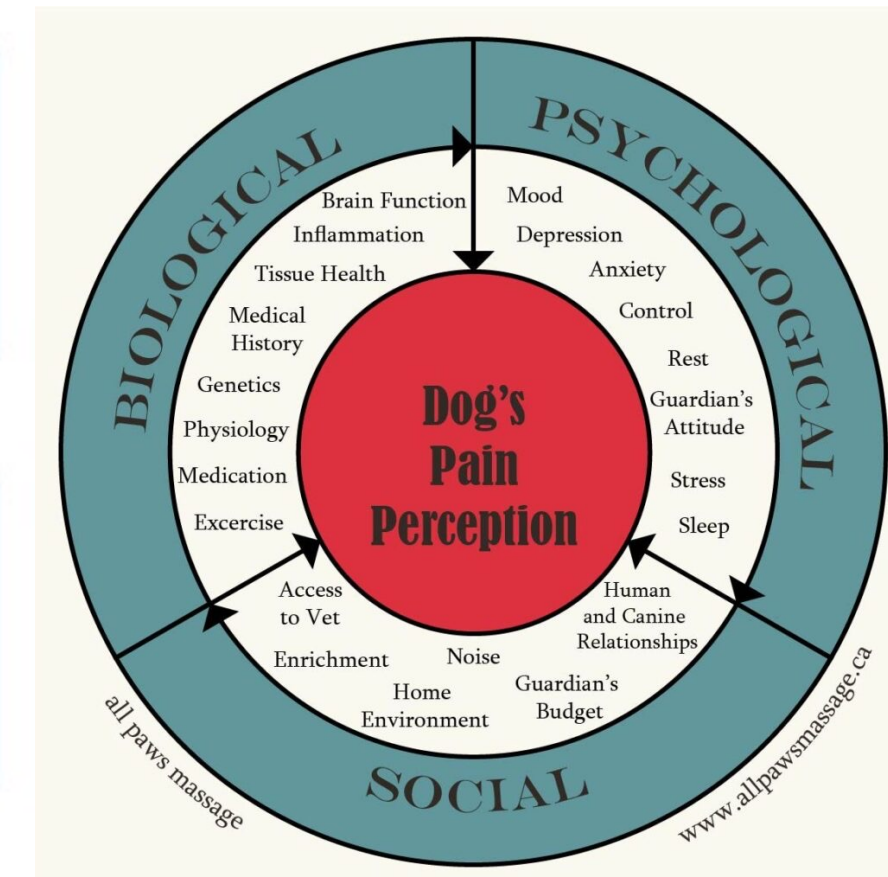
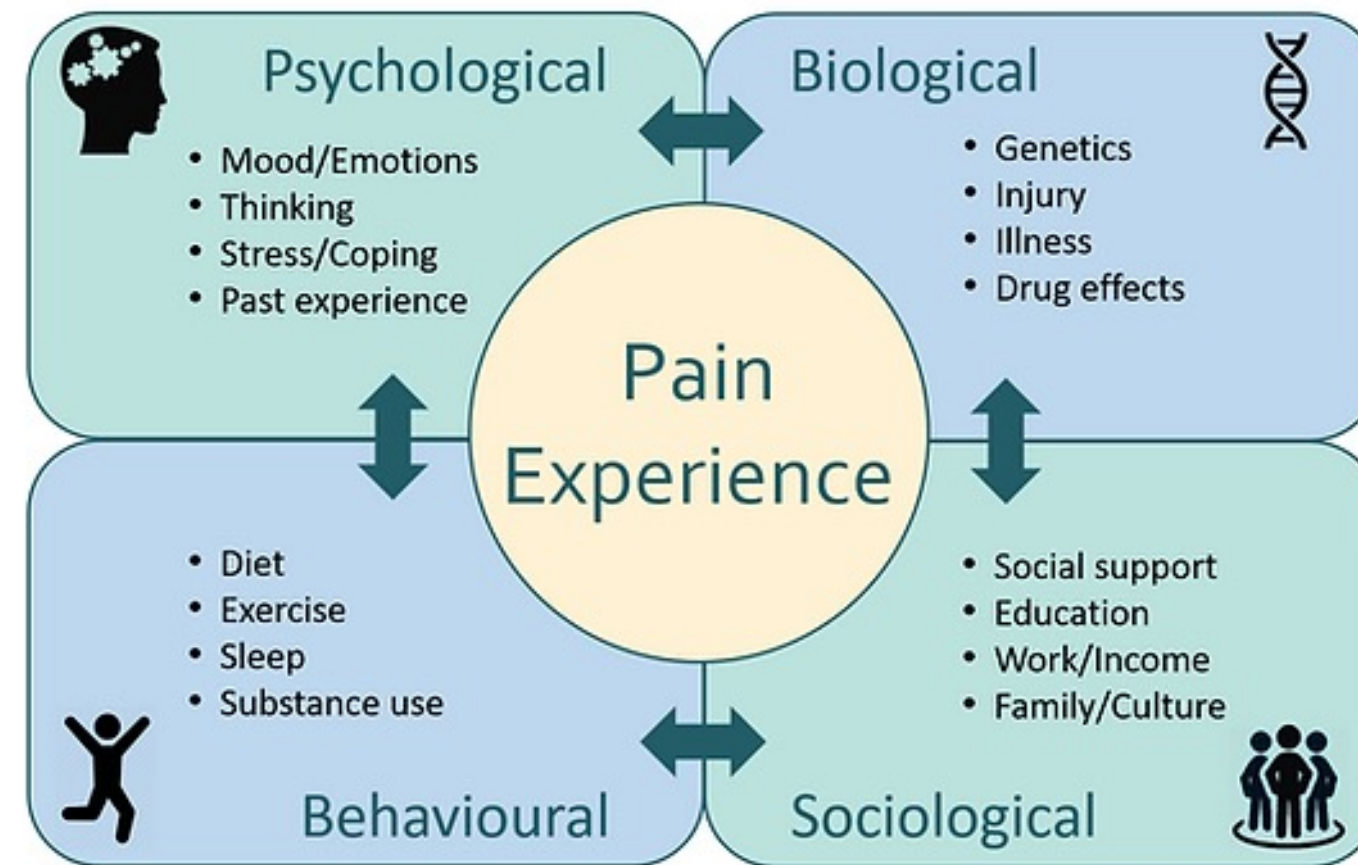
REVIEW
published: 05 August 2021
doi: 10.3389/fphar.2021.705743

Clin Exp Rheumatol 2017; 35 (Suppl. 107): S53-S58.

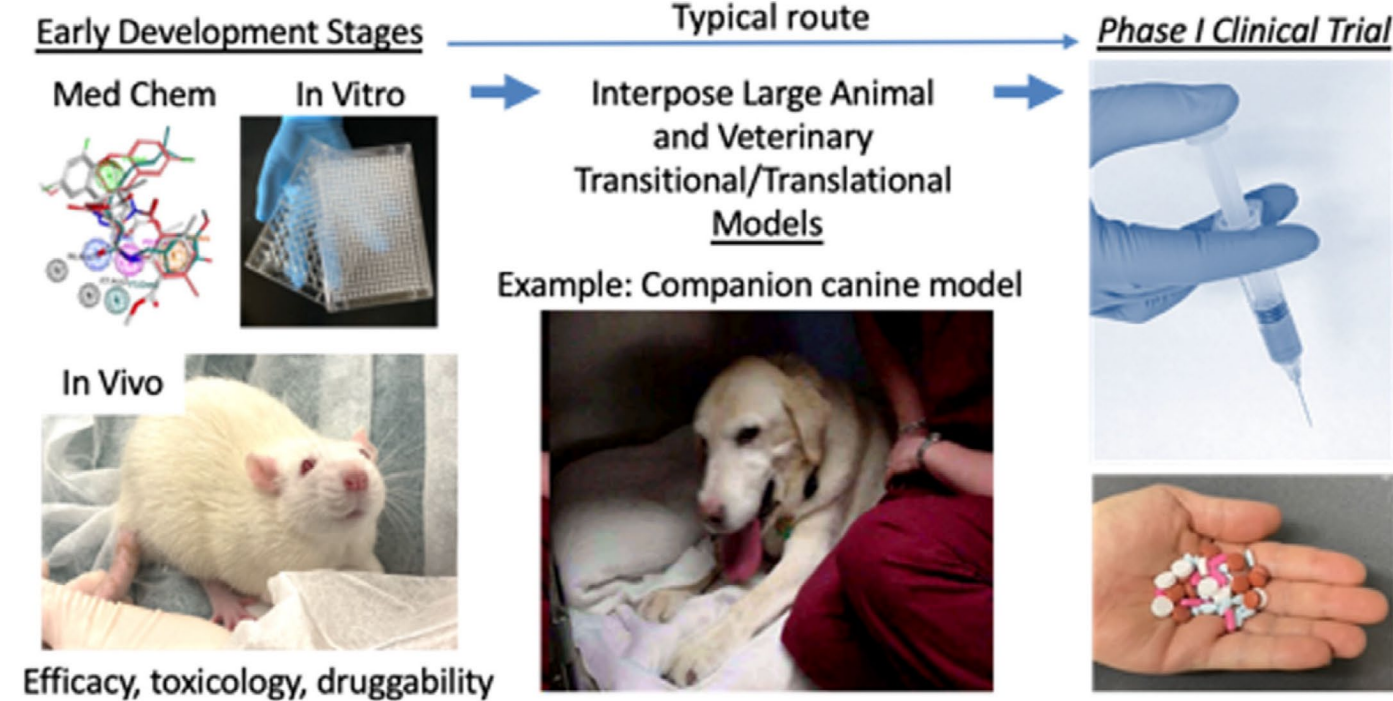
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Role of canine companion model in analgesic drug development



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REVIEW
published: 05 August 2021
doi: 10.3389/fphar.2021.705743

TABLE 1 | Advantages of companion animal models.

Canine model
Owner is familiar with animal's activities of daily living (ADL)
Owner is familiar with animal's "personality"
Naturally occurring diseases (actually not models)
Exhibit complex behaviors spontaneously
Many breeds, genetic diversity
Tissues more similar to human
Efficacy measures can be judged by multiple observers in the home or clinic
Allows better estimation of starting dose in human phase I trial
Positive results provide strong incentive to proceed to human clinical trials or provide an indication for a "no go" signal

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BEDINVETMAB – Canine Ab anti NGF



EUROPEAN MEDICINES AGENCY
 SCIENCE MEDICINES HEALTH

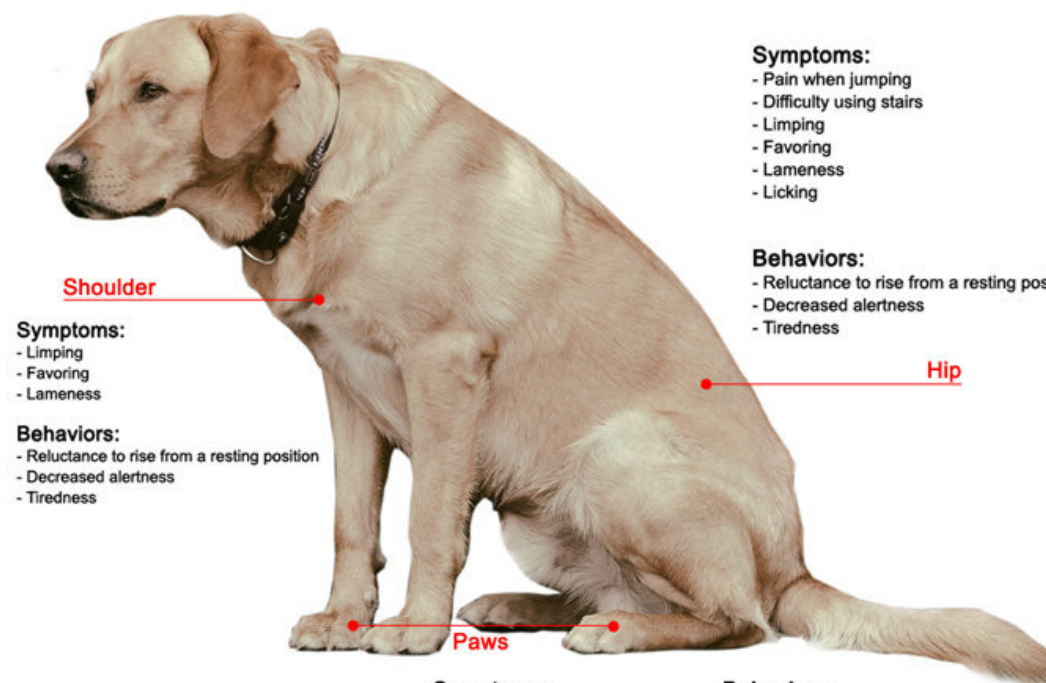
5 January 2021
 EMA/518235/2020
 Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for X X X X
 (EMA/V/C/005180/0000)

Vaccine common name: bedinvetmab

Joint Pain Symptoms



Shoulder
Symptoms:
 - Limping
 - Favoring
 - Lameness

Behaviors:
 - Reluctance to rise from a resting position
 - Decreased alertness
 - Tiredness

Symptoms:
 - Pain when jumping
 - Difficulty using stairs
 - Limping
 - Favoring
 - Lameness
 - Licking

Behaviors:
 - Reluctance to rise from a resting position
 - Decreased alertness
 - Tiredness

Paws
Symptoms:
 - Pain when jumping
 - Difficulty using stairs
 - Limping
 - Favoring
 - Lameness
 - Licking

Hip
Behaviors:
 - Decreased alertness
 - Tiredness
 - Reduced appetite



News

FDA panel votes against Pfizer's tanezumab for osteoarthritis pain

A joint FDA advisory committee has rejected a risk mitigation proposal for Pfizer and Eli Lilly's osteoarthritis (OA) drug tanezumab, concluding that the drug's safety risk to patients is too high.

Darcy Jimenez | March 26, 2021

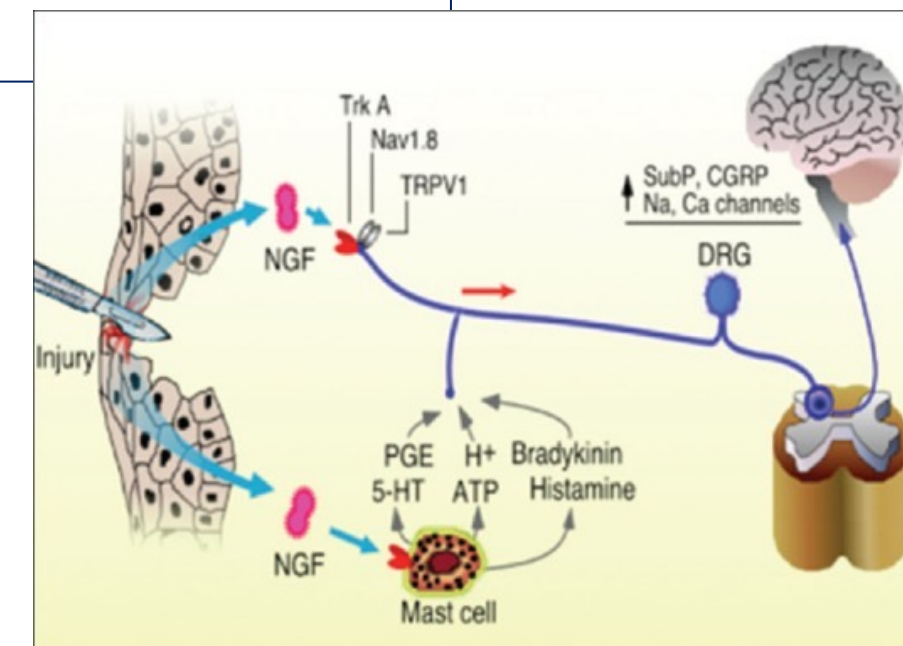
4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Raylumis in the treatment of osteoarthritis, the CHMP considers by consensus that

[a] safety and efficacy of the above-mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the marketing authorisation for the above-mentioned medicinal product. The CHMP considers that:

16 September 2021
 EMA/CHMP/556162/2021
 Committee for Medicinal Products for Human Use (CHMP)



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- Development and Optimization of **Non-Addictive Therapies to Treat Pain**
- Discovery and Validation of Novel Targets for Safe and Effective Treatment of Pain
- Integrated Basic and Clinical Team-Based Research in Pain program
- Preclinical Screening Platform for Pain (PSPP) program
- Restoring Joint Health and Function to Reduce Pain Consortium (Re-JOIN)
- Translating Discoveries into Effective Devices to Treat Pain program
- Translational Research to Advance Testing of Novel Drugs and Human Cell-Based Screening Platforms to Treat Pain and Opioid Use Disorder program

Preclinical and Translational Research in Pain Management

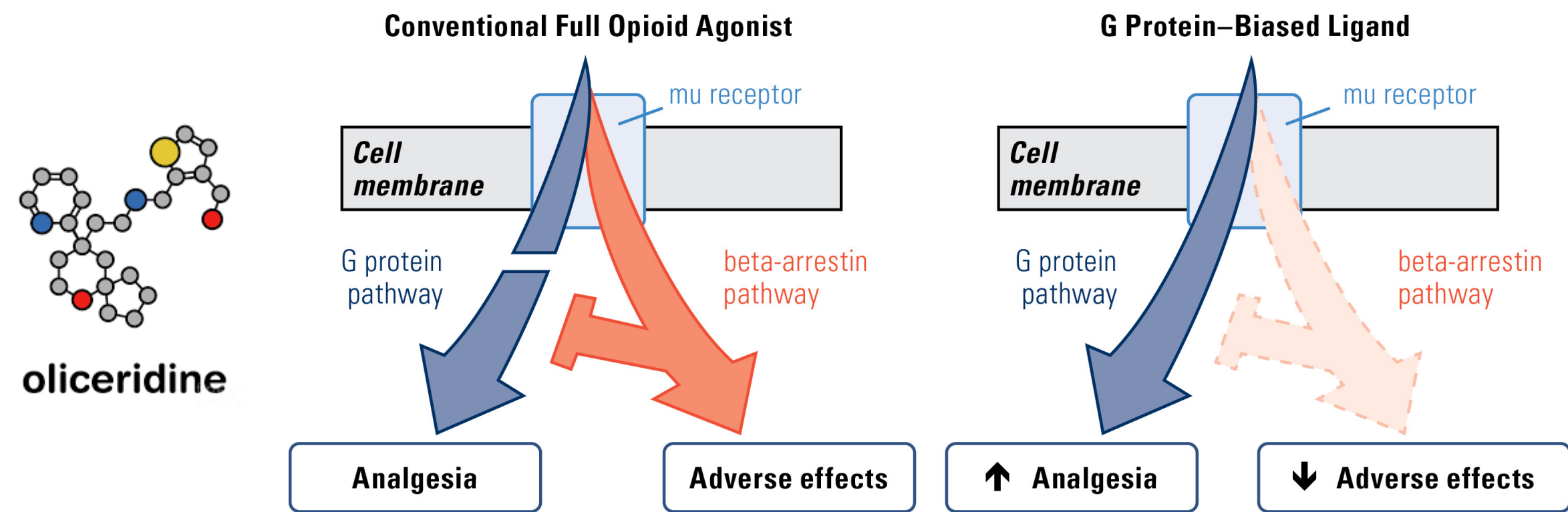
The NIH HEAL Initiative will accelerate the discovery and preclinical development of new medications and devices to treat pain.

**Researchers Developing New Model for Treating,
Managing Chronic Pain **Without Opioids****

Project Is Supported by **\$844,000 Grant from the NIH –
National Institutes of Health**

10/19/2022





The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Selective Inhibition of Na_v1.8 with VX-548 for Acute Pain

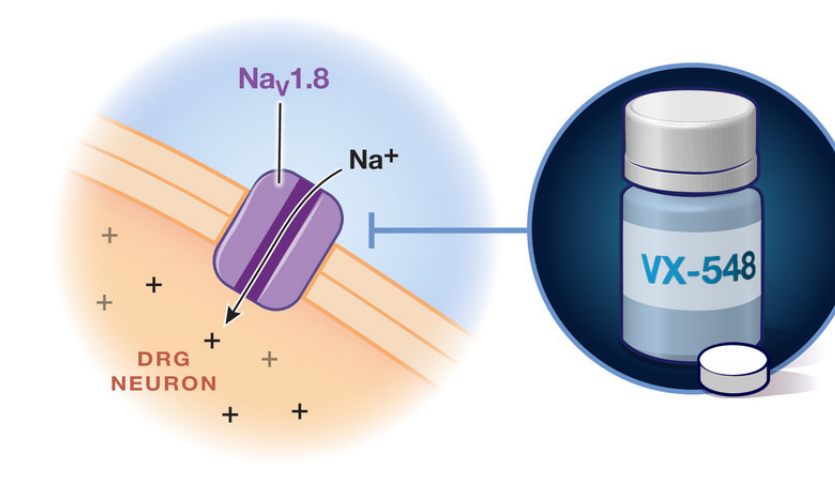
Jones J et al. DOI: 10.1056/NEJMoa2209870

CLINICAL PROBLEM

The sodium channel Na_v1.8 is a target for treatment of pain because of its role in transmitting nociceptive signals and its selective expression in neurons of the dorsal-root ganglia. VX-548, an oral, highly selective inhibitor of Na_v1.8, is under investigation for the treatment of acute pain.

CLINICAL TRIALS

Design: Two phase 2, double-blind, randomized, placebo-controlled clinical trials evaluated the efficacy and safety of VX-548 for the treatment of acute pain after abdominalplasty or bunionectomy.



Basic science and clinical pain research is particularly challenging for several reasons:

- pain is a subjective experience
- the nociceptive system is remarkably redundant and involves diffuse regions of the CNS
- pain is a multi-dimensional experience (cognitive, affective, and sensory-discriminative components)
- pain experiences can be influenced by psychological, socioeconomic, cultural, and genetic predispositions

Delitti in materia di violazione del diritto d'autore (Art. 25-novies, D.Lgs. n. 231/2001) [articolo aggiunto dalla L. n. 99/2009]

- Messa a disposizione del pubblico, in un sistema di reti telematiche, mediante connessioni di qualsiasi genere, di un'opera dell'ingegno protetta, o di parte di essa (art. 171, legge n.633/1941 comma 1 lett. a) bis)
- Reati di cui al punto precedente commessi su opere altrui non destinate alla pubblicazione qualora ne risulti offeso l'onore o la reputazione (art. 171, legge n.633/1941 comma 3)
- Abusiva duplicazione, per trarne profitto, di programmi per elaboratore; importazione, distribuzione, vendita o detenzione a scopo commerciale o imprenditoriale o concessione in locazione di programmi contenuti in supporti non contrassegnati dalla SIAE; predisposizione di mezzi per rimuovere o eludere i dispositivi di protezione di programmi per elaboratori (art. 171-bis legge n.633/1941 comma 1)
- Riproduzione, trasferimento su altro supporto, distribuzione, comunicazione, presentazione o dimostrazione in pubblico, del contenuto di una banca dati; estrazione o reimpiego della banca dati; distribuzione, vendita o concessione in locazione di banche di dati (art. 171-bis legge n.633/1941 comma 2)
- Abusiva duplicazione, riproduzione, trasmissione o diffusione in pubblico con qualsiasi procedimento, in tutto o in parte, di opere dell'ingegno destinate al circuito televisivo, cinematografico, della vendita o del noleggio di dischi, nastri o supporti analoghi o ogni altro supporto contenente fonogrammi o videogrammi di opere musicali, cinematografiche o audiovisive assimilate o sequenze di immagini in movimento; opere letterarie, drammatiche, scientifiche o didattiche, musicali o drammatico musicali, multimediali, anche se inserite in opere collettive o composite o banche dati; riproduzione, duplicazione, trasmissione o diffusione abusiva, vendita o commercio, cessione a qualsiasi titolo o importazione abusiva di oltre cinquanta copie o esemplari di opere tutelate dal diritto d'autore e da diritti connessi; immissione in un sistema di reti telematiche, mediante connessioni di qualsiasi genere, di un'opera dell'ingegno protetta dal diritto d'autore, o parte di essa (art. 171-ter legge n.633/1941)
- Mancata comunicazione alla SIAE dei dati di identificazione dei supporti non soggetti al contrassegno o falsa dichiarazione (art. 171-septies legge n.633/1941)
- Fraudolenta produzione, vendita, importazione, promozione, installazione, modifica, utilizzo per uso pubblico e privato di apparati o parti di apparati atti alla decodificazione di trasmissioni audiovisive ad accesso condizionato effettuate via etere, via satellite, via cavo, in forma sia analogica sia digitale (art. 171-octies legge n.633/1941).

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