

## Will the Mystery of Pain Ever Be Unraveled?

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## Objectives

- Review current information regarding underlying mechanisms of pain
- Discuss the translation of this knowledge from the laboratory to the clinical setting
- Describe why this is important to palliative care

“For we are born in other’s pain,  
And perish in our own.”  
*Francis Thompson (1859–1907)*

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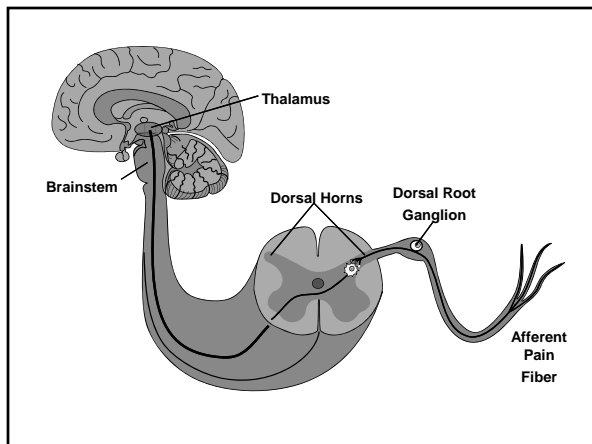
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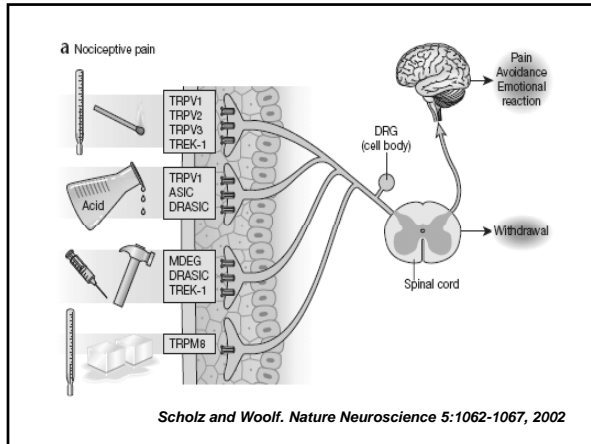
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## Nociceptive Pain

- TRPV1-6: transient receptor potential vanilloid receptor
  - Noxious heat, low pH, capsaicin
- TREK-1: potassium channel
- ASIC: acid sensing ion channel
- DRASIC: dorsal root acid sensing ion channel
- MDEG: degenerin/epithelial (mechanical) Na channel
- TRPM8: transient receptor potential menthol

*Scholz and Woolf. Nature Neuroscience* 5:1062-1067, 2002

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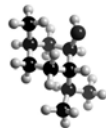
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### From Bench to Bedside: A Case of Rapid Reversal of Bortezomib-Induced Neuropathic Pain by the TRPM8 Activator, Menthol



- Topical 0.5% menthol in calamine cream to feet
- QST changes in 90 m
- After 5 days, improvement in pain, sleep, mobility, mood
- Sustained 2 weeks; no change in hands

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*Marie Fallon*  
Department of Palliative Medicine, Western General Hospital, Edinburgh Cancer Centre, Edinburgh, Scotland

*Colvin LA, et al. J Clin Oncol* 26: 4519-4520, 2008

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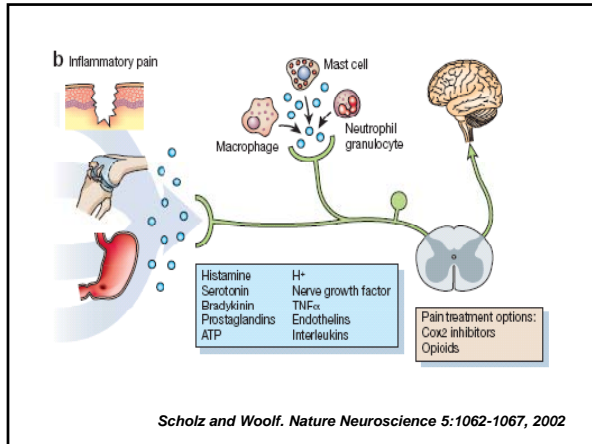
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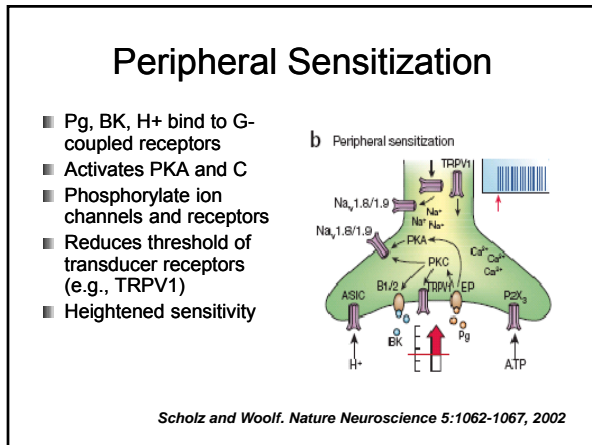
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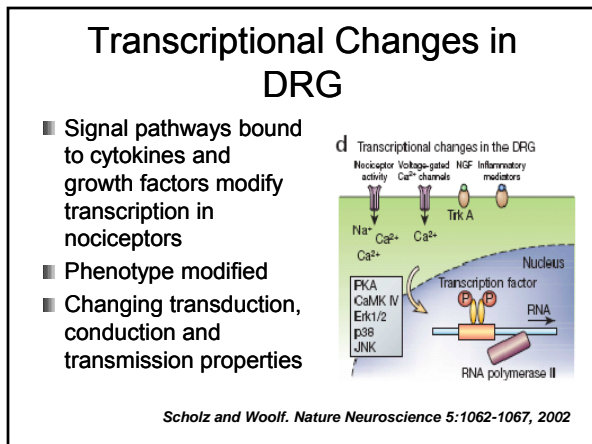
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## Transcriptional Changes

- PKA: protein kinase A
- CaMK IV: camkinase IV
- MAP kinase: mitogen activated kinase
  - Erk 1 / 2: extracellular signal regulated kinase
  - p38: found in glia
  - JNK: jun kinase

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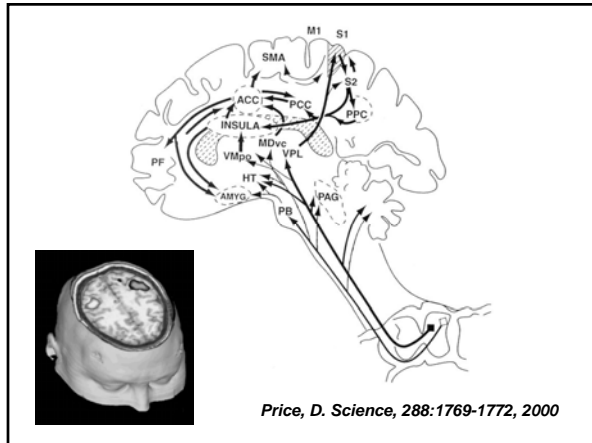
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## Translational Research



■ Bench



■ Bedside



■ Society

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**The American Pain Society and Translational Pain Research**  
*A position statement from the American Pain Society*

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*The statement was prepared by the following members of the APS Translational Task Force: Timothy Ness, MD PhD, Chair; Ursula Wesschnau, MD PhD; Laura Stone, PhD; Patrick Mantyh, PhD JD; John Neubert, DDS PhD.*

*Approved by the APS Board of Directors on March 21, 2007. Copyright ©2007 by the American Pain Society.*

<http://www.ampainsoc.org/advocacy/downloads/translationalpain.pdf>

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### Obstacles to Translational Pain Research

- Funding
- Inadequate clinician-researcher interactions
- Preclinical models of pain ≠ human experience
- Inadequate multicenter coordinating infrastructure
- Inadequate access to clinical databases and tissues

<http://www.ampainsoc.org/advocacy/downloads/translationalpain.pdf>

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### Solutions: Inadequate Funding

- Increase funding
  - Exploratory grants
  - Training grants
  - Evaluate review process
  - Increase expertise on review panels
- Encourage foundations and institutions to support research related to painful diseases

<http://www.ampainsoc.org/advocacy/downloads/translationalpain.pdf>

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## Strategies to Encourage Interaction

- Interdisciplinary professional organizations
- Increase awareness of translation
  - Bench to bedside
  - Bedside to bench
- Provide training opportunities
  - Basic scientists to learn clinical methods
  - Clinicians to learn basic science methods

<http://www.ampainsoc.org/advocacy/downloads/translationalpain.pdf>

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## Improve Preclinical Models

- Need for models that more closely emulate the human experience
- Most studies short term



<http://www.ampainsoc.org/advocacy/downloads/translationalpain.pdf>

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## Solutions

- Establish multicenter collaborative effort
- Establish central registries, data bases, tissue banks related to pain
- Oncology networks serve as a model

<http://www.ampainsoc.org/advocacy/downloads/translationalpain.pdf>

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## Other Challenges to Solving the Mystery – and Relieving Pain

- Issues related to drug addiction – real and perceived
  - Stigma
  - Greater regulatory oversight
  - REMS Risk Evaluation and Mitigation Strategies
  - Abuse deterrent drugs
- Adverse effects of opioid
  - Do opioids worsen cancer pain?



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Pain 132 (2007) 154–158

**PAIN**

[www.elsevier.com/locate/pain](http://www.elsevier.com/locate/pain)

Morphine treatment accelerates sarcoma-induced bone pain, bone loss, and spontaneous fracture in a murine model of bone cancer

Tamara King <sup>a,c</sup>, Anna Vardanyan <sup>a</sup>, Lisa Majumdar <sup>a</sup>, Oshannes Melemedjian <sup>a</sup>, Ray Nagle <sup>a</sup>, Anne E. Cress <sup>b,c</sup>, Todd W. Vanderah <sup>a</sup>, Josephine Lai <sup>a</sup>, Frank Porreca <sup>a,d,e\*</sup>

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Received 14 July 2006; received in revised form 29 March 2007; accepted 20 June 2007

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## Do Opioids Worsen Cancer Pain?

- Murine sarcoma model in mice
- Continuous morphine enhanced spontaneous and evoked pain in dose dependent manner
- ↑ in SP and CGRP staining in DH in morphine group
- ↑ expression of ATF-3 in DRG in morphine group, suggests neuronal damage
- Morphine did not alter tumor growth, but did increase osteolysis

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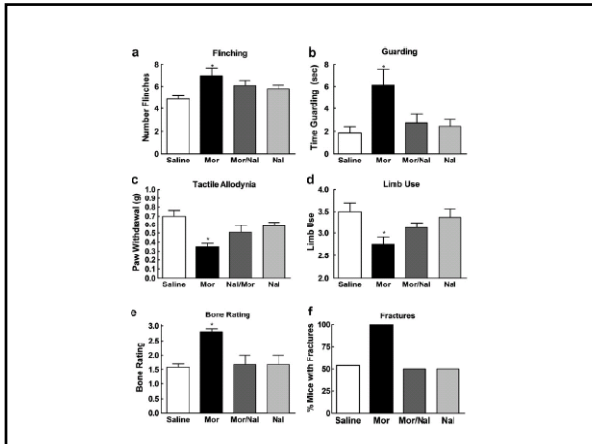
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### The Mystery Unraveled...

- Basic and clinical investigation will result in increased knowledge – but the work must be funded and nurtured
- Interdisciplinary approaches to science are as critical as interdisciplinary approaches to the care of patients

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Never doubt that a small group of thoughtful, committed citizens can change the world. Indeed, it is the only thing that ever has.

*Margaret Mead*

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