Translational research in cancer-induced bone pain

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Outline

- Edinburgh Translational Research Group
- Cancer-induced bone pain (CIBP)
- Animal models
- Preclinical results
  - investigating TRP ion channels in CIBP
- Clinical results
  - sensory responses in CIBP
  - biomarkers to predict response to radiotherapy

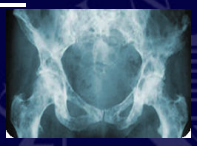
Cancer Pain

Neurobiology
• Peripheral & central changes

Edinburgh Translational Pain Research Group

Clinical issues
• Accurate assessment
• Targeted effective treatment

CIBP – clinical features



Background

Spontaneous

PAIN

Breakthrough pain

Evoked

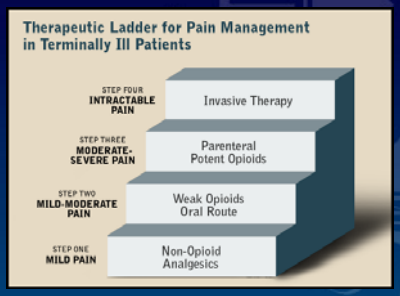
Movement-induced

• Reduced function
• Impaired quality of life

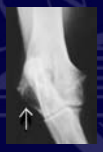
Laird, et al . *Supp Care in Cancer 19:1393-1401, 2011*

CIBP – Challenges

- CIBP affects 75-95% of patients with metastatic or advanced-stage cancer (Mercadante & Arcuri, 1998;Portenoy *et al.*, 1999)
- Current therapeutic regime: Opioids and palliative radiotherapy supplemented with NSAIDs
- Radiotherapy can take up to 6 weeks to work (Tong 1982)
- The current therapeutic regime can leave up to 45% of patients with inadequate pain control (de Wit, 2001; Meuser, 2001)



Lab models of CIBP



- Allow detailed study of pain mechanisms
- Local infusion of cancer cells into mouse femur (Schwei 1999)
- Develop radiological evidence of isolated bone tumour + pain behaviour
  - Parallels clinical course in humans
- Pathophysiology of CIBP
  - Periosteum & mineralised bone richly innervated by primary afferents
  - Tumour cells invade and activate primary afferents, alter osteoblast / osteoclast balance & induce pronounced inflammatory infiltrate

Honore, et al.. *Neurosci* 98:585-598, 2000.

CIBP – central mechanisms

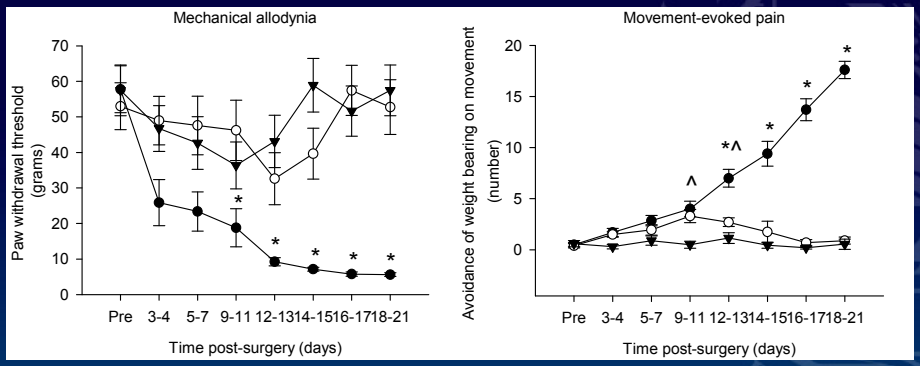
- The dorsal horn of spinal cord undergoes significant alteration in animal models (Honore 2000)
  - Increase in spinal cord neurons expressing c-Fos
  - Expression of dynorphin
  - Massive astrocyte hypertrophy
  - Ratio of wide dynamic range (WDR) neurons to nociceptive specific (NS) increased in CIBP normalised by gabapentin (Urch 2003)
  - Hyperexcitability of spinal cord neurons in CIBP

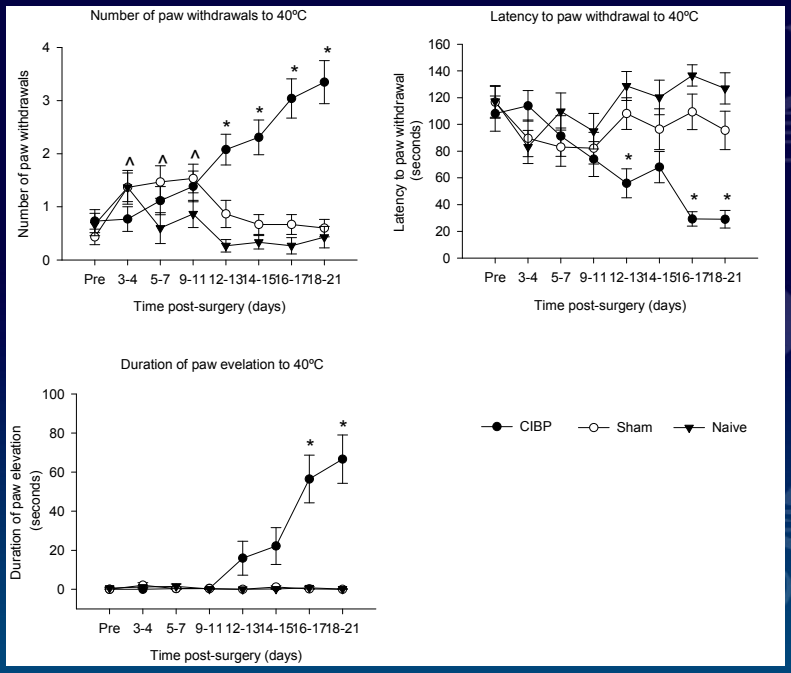
    → allodynia & hyperalgesia

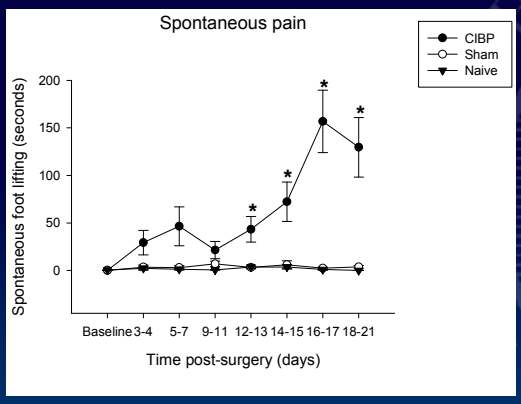
Preclinical Study

- Sprague-Dawley rat model:
  - MRMT-1 rat mammary carcinoma cells injected into intramedullary canal of tibia in anaesthetised rats
- Sensory aspects:
  - Mechanical allodynia by paw withdrawal to von Frey filaments
  - Thermal sensitivity using the thermal foot plate
- Functional impairment / general function & pain:
  - Spontaneous foot lifting (spontaneous pain)
  - Paw guarding behaviour in rotarod test (movement- evoked pain)

CIBP-induced pain-related behaviours







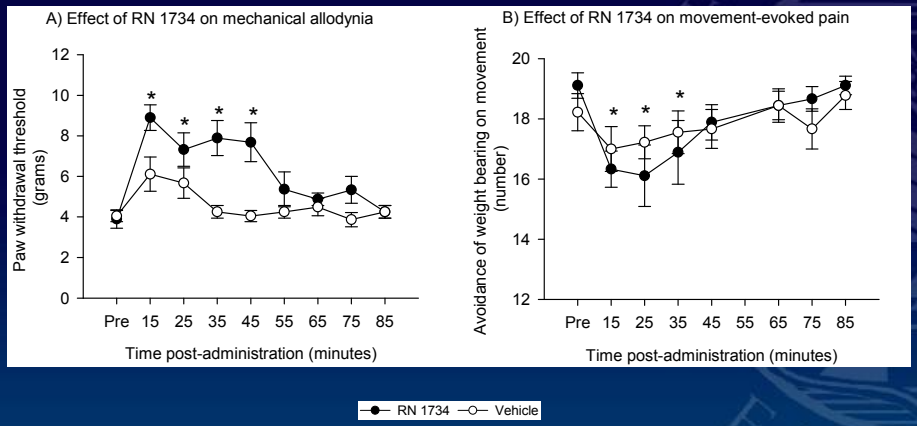
TRP family of ion channels

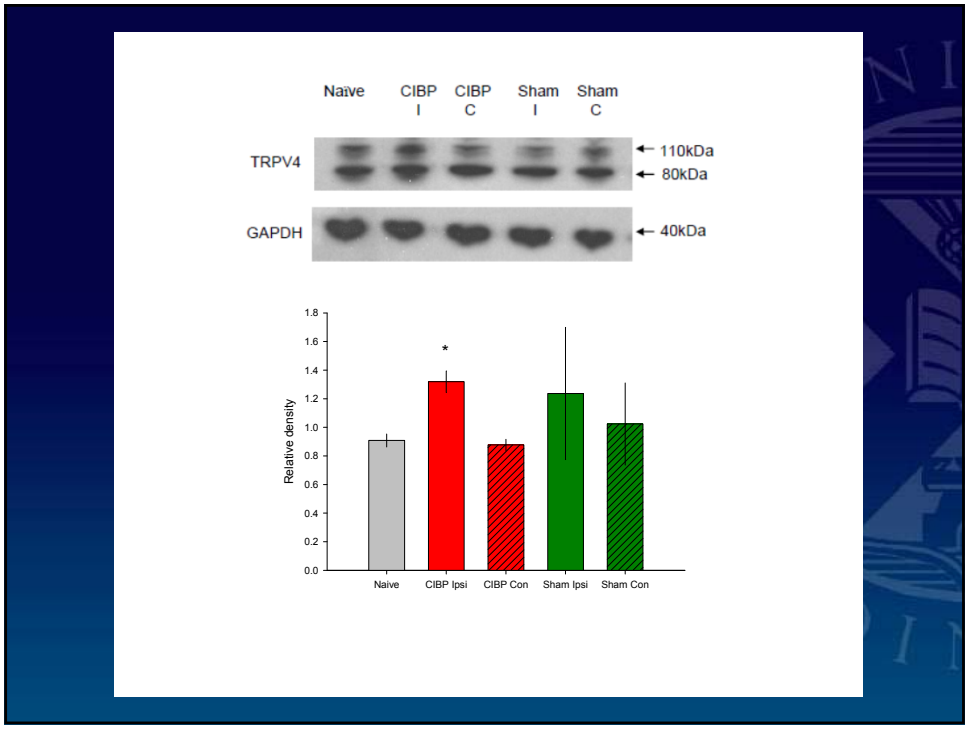
- Thermal sensation
  - TRPV1 – noxious heat
  - TRPA1 – noxious cold
  - TRPM8: cooling sensation
    - Temp (18-24°C)
    - Mint
    - Menthol, icilin and related compounds
  - TRPV3/4 - warm, endogenous substances e.g. arachidonic acid, endocannabinoids

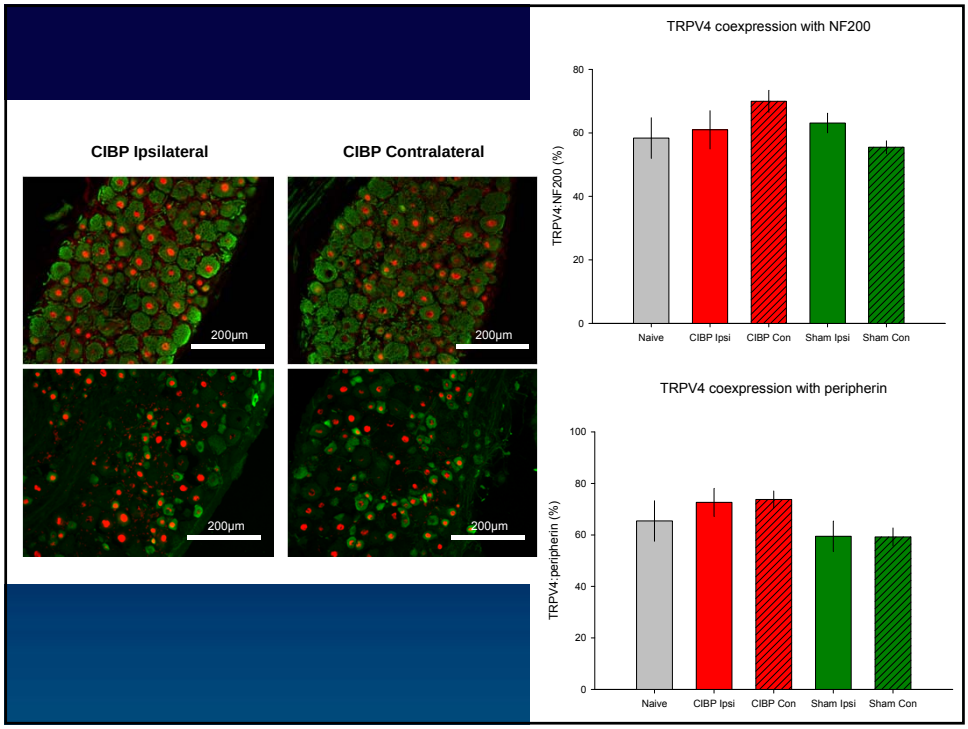
TRPV4

- TRPV4 is expressed in many tissues including epidermal keratinocytes, dorsal root and trigeminal ganglia neurons and cutaneous nerve terminals
- TRPV4 is thought to play many diverse physiological roles including a crucial role in mechanical and thermal nociception
- Several preclinical studies suggest that TRPV4 channels are involved in both inflammatory and neuropathic pain (Todaka 2004, Alessandri-Haber 2004 and Zhang 2008).

TRPV4 antagonist RN 1734




Naïve
CIBP I
CIBP C
Sham I
Sham C
TRPV4
110kDa
80kDa
GAPDH
40kDa
Relative density
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
*
Naive
CIBP Ipsi
CIBP Con
Sham Ipsi
Sham Con


CIBP Ipsilateral
CIBP Contralateral
200µm
200µm
200µm
200µm
TRPV4 coexpression with NF200
TRPV4:NF200 (%)
80
60
40
20
0
Naive
CIBP Ipsi
CIBP Con
Sham Ipsi
Sham Con
TRPV4 coexpression with peripherin
TRPV4:peripherin (%)
100
80
60
40
20
0
Naive
CIBP Ipsi
CIBP Con
Sham Ipsi
Sham Con

Preclinical work conclusions

- Acute administration of a TRPV4 antagonist attenuates mechanical allodynia and movement-evoked pain
- TRPV4 expression increased in CIBP
- TRP channels may be potential targets for improving clinical outcomes

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