Learning objectives

1. Understand the characteristics of breakthrough pain
2. Understand how biological mechanisms underlying breakthrough pain differ from persistent background pain
3. Understand the latest clinical research on management of breakthrough pain

Cancer-induced Pain

- Many cancers are non-painful at the primary site
  Breast, prostate, lung, stomach, colon, brain, melanoma
  However, metastatic cancers to bone are painful
- Some primary tumors are associated with pain
  (e.g. pancreatic, orofacial cancer, sarcoma)
- Bone cancer, both primary and metastatic, are often associated with pain
  Mechanisms underlying cancer-induced bone pain are the most commonly studied
  Some groups are studying pancreatic cancer-induced pain and orofacial pain.
- Breakthrough pain is most commonly reported in patients with bone tumors,
  both primary and skeletal metastases
Cancer-induced Bone Pain

- Primary cancers of bones account for less than 0.2% of all cancers.
- It is estimated that 50 to 95% of all patients who die of cancer have bone involvement.

Cancer is the second leading cause of death in the United States. In 2018, there will be an estimated 1,735,350 new cancer cases diagnosed and 609,640 cancer deaths in the United States.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Lung and bronchus</td>
<td>26%</td>
</tr>
<tr>
<td>Prostate</td>
<td>9%</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>7%</td>
</tr>
</tbody>
</table>

- Of those with bone metastases, approximately 85% experience pain, with resultant immobility and reduced quality of life.

From CDC: Cancer Facts and Figures 2018

Common Comorbidities:

Cancer in bone is associated with:
- **Pain**: Cancer-induced pain is the most feared consequence of the disease.
- **Skeletal related events such as fracture**
- **Decreased mobility**
- **Patients that experience fracture and related decreased mobility have very high mortality rates within the following year.**

The vertebral column is the most common site of skeletal metastases.

- Compression of the spinal cord, nerve roots leading to neuropathic pain
- **Skeletal related events such as fracture**
- **Decreased mobility**

Metastasis to bone compromise patient survival and quality of life:

Advances in cancer therapy are extending the survival times of cancer patients from months to years resulting in chronic pain status.
Breakthrough Pain

- Breakthrough cancer pain occurs despite medication controlling ongoing pain
- Indicates that it is mechanistically distinct
- Suggests individualized treatment strategies are needed

Two Distinctive Pain States

Quest to Improve Cancer Pain Management

- We use preclinical measures of cancer bone pain to learn about mechanisms driving these pain states
- The goal of these endeavors is to guide development of new therapies to better treat the patients.

Neurobiological Mechanisms of Cancer-induced Bone Pain

- Inflammatory Pain
- Neuropathic Pain
- Mechanical Pain
- Medication Issues
- Metastatic Bone Pain
- Persistent Pain
**Rat Model of Cancer Induced Bone Pain**

- Rat mammary adenocarcinoma cells (MATMII) are injected and sealed into the tibia of female Fischer 344 rats.
- Control rats receive 3pl cell-free media (McCoy's 1X).

**Saphenous Nerve Block**

- Diagram showing tracers and dyes indicating nerve block.
- Text: "Di-Labelling from potential of blockade."

**Unmasking Spontaneous/Ongoing Pain**

- Tonic aversive stimuli provide motivation that drives behavior.
- "Taking pain away feels good."

- Pain relief can motivate behavior. Associating a specific event (i.e., taking a medication) with removal of an ongoing stimulus (i.e., pain) will increase the behavior of taking the medication.

**Measuring Ongoing Pain**

- Pre-conditioning phase: Time spent in each chamber analyzed.
- Conditioning phase: Pain alleviating drug is paired with one chamber.
- Testing phase: NO DRUG ADMINISTRATION.

- Graph showing changes in time spent in drug paired chamber.
Cancer Growth in the Tibia Induces Ongoing Pain

- CPP to saphenous nerve block indicates tumor-induced ongoing pain
- Ongoing pain is dependent on sensory input from tumor bearing bone
- Morphine relieves cancer-induced ongoing pain

Movement triggers breakthrough pain

- CPA indicates that movement is followed by a transient increase in pain that is associated with the.
- CPA "breaks through" morphine sufficient to block ongoing pain.
- Consistent with the clinical definition of breakthrough pain.

Neurobiological Mechanisms of Pain

There are multiple subpopulations of nociceptive C-fibers

Neurobiological Mechanisms of Cancer-induced Bone Pain

Do these different fiber populations have distinct roles mediating ongoing and breakthrough pain?
**Targeting TRPV1 and IB4 nociceptive fibers**

- Ablation of IB4 binding fibers blocks movement-induced breakthrough pain.
- Elimination of TRPV1 expressing terminals in the spinal cord fails to block movement-induced breakthrough pain.

**Conclusions**

- Tumor growth within the bone produces 2 distinctive pain states, ongoing and breakthrough pain.
- These pain states can be measured in rats using motivational properties of pain and pain relief.
- IB4 binding, presumably non-peptidergic, fibers selectively mediate breakthrough pain.
- Identification and testing of potential molecular targets specific to this population of nociceptive fibers may allow for development of peripherally restricted analgesics that control breakthrough pain.

**Potential Targets and Tools**

- Bisphosphonates: Blocks bone resorption and delays skeletal related events. In clinical use.
- Anti-NGF (Mantyh): Blocks pain and pathological sprouting, did not alter bone remodeling or tumor growth. In clinical trials for osteoarthritis and cancer pain.
- Resiniferatoxin (Idolora, Brown): Eliminates TRPV1 expressing nerves. Highly effective in canines, in clinical trials.

[https://www.yourTube.com/watch?v=QUBs_WoIP_](https://www.yourTube.com/watch?v=QUBs_WoIP_)

- Under investigation:
  - IL-6 antagonists: Blocks bone remodeling and bone pain in rat model
  - CB2 agonists: Blocks tumor growth, bone remodeling and bone pain in mouse model
  - Endothelin receptor antagonists
  - Others

Selective roles of treatments targeting these mechanisms on different kinds are cancer pain (i.e. ongoing and breakthrough pain) have not been systematically explored.

**Potential Targets and Tool: Medical Marijuana**

- Available in many places, used for many conditions: [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5151254/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5151254/)

**What do we know?** Very little.

**Anecdotal Case reports?**

**Why?** Barriers to research published by the National Academies of Sciences, Engineering and Medicine.

- Regulatory barriers
  - Limit ability (Schedule 1 substance) and
  - Limited funding
  - Sources often have inherent biases
  - Review to be able to do research includes: NIH, FDA, DEA, IACUC/RBB
    - Institution may not support the research

- Barriers to supply
  - "In the United States, cannabis for research purposes is available only through the NIDA Drug Supply Program"

- Methodological issues
  - Drug preparation and delivery
  - The placebo issue
  - Exposure assessment

Over 100 strains with different effects reported
Saphenous Nerve Block Does Not Reverse BTP

Movement-induced BT pain is not reversed by peripheral nerve block.
Indicates that maintenance of breakthrough pain is independent of input from sensory fibers.
Other mechanisms, perhaps at the spinal or supraspinal level maintain breakthrough pain.

Neurobiological Mechanisms of Pain

Cancer-induced bone pain:
- Joshua Havlin
- Ian Pelletier
- Kristina Carlson
- Jonathan Gentry
- Michael (Cory) Dearborn
- Cosmin Jacob
- Ian Imbert, MPH

Cancer Research Institute (CRI) New England Cancer Care Collaborative

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Separate Opioid Receptors for Ongoing & BT Pain?

**Dissociation of the Opioid Receptor Mechanisms that Control Mechanical and Heat Pain**

**Cell**

- Mu opioid and delta opioid receptors are expressed on different sensory fibers.
- MOR are expressed primarily on peptidergic sensory fibers
- DOR are expressed primarily on non-peptidergic sensory fibers
- We have pharmacological agents that selectively target these receptors
- This gives us the tools to examine the relative contribution of different populations of nociceptive fibers to cancer-induced ongoing and breakthrough pain.

**Does DAMGO Block Tumor-induced Ongoing Pain?**

**DAMGO**

A synthetic peptide MOR agonist with low penetration across the blood brain barrier

- Intravenous
  - Morning saline lv.
  - Afternoon DAMGO (MOR) lv

**DAMGO (3 mg/kg, iv) induced CPP**

<table>
<thead>
<tr>
<th>Chamber</th>
<th>Sham</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pairing Chamber 1</td>
<td>0</td>
<td>200</td>
</tr>
<tr>
<td>Unpaired (Neutral)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pairing Chamber 2</td>
<td>0</td>
<td>0</td>
</tr>
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</table>

**Does Deltorphin II block ongoing pain?**

**Deltorphin II**

A synthetic peptide DOR agonist with low penetration across the blood brain barrier

- Intravenous
  - Morning saline lv.
  - Afternoon Deltorphin II (DOR) lv

**Deltorphin II (2 mg/kg, iv) does not induce CPP**

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Does Deltorphin II block ongoing pain?

- Allomone
  - Deltorphin II
  - 10 min

- Shown: Deltorphin II blocks BT Pain
- Deltorphin II (3 mg/kg, iv.)
- Pain: Shown Cancer
- Diminished central effects will improve these patient's quality of life
- Peripheral actions of opioids remain.
- Long term efficacy remains a question with prolonged administration. It is unknown if tolerance or opioid induced hyperalgesia will develop.
- Some studies indicate there may also be unintended enhancement of tumor-induced bone loss with sustained MOR agonist delivery.

Potential of peripheral opioid receptor agonists

- The peptide MOR agonist DAMGO mediates pain through activity at peripheral MORs.
- The peptide DOR agonist Deltorphin II blocks movement-evoked BT pain.
- Targeting different populations of peripheral nociceptive fibers can alleviate different kinds of cancer-induced bone pain.
- Although using peripheral mu opioid receptors is likely not an optimal therapy, this knowledge can provide molecular tools to determine what may work better.

Morphine in a Mouse Model of Bone Cancer Pain

- Osteolytic fibrosarcoma cells are injected into the inflamed mediastinal space of the mouse (C3H mice)
- What is the effect of a background infusion of morphine on cancer pain?
- Is the increase in observed pain behaviors due to opioid-induced hyperalgesia or disease progression?
Morphine in a Mouse Model of Bone Cancer Pain

What is the effect of a background infusion of morphine on cancer pain?

Morphine infusion: Rate - 0.5 μg/kg for 7 days

Day 7: Tumor induction
Day 10: Induction of skeletal and behavioral testing
Day 12: Induction of skeletal and behavioral testing

Bone loss and fracture

Morphine administration accelerated tumor-induced bone loss and fracture, indicating increased pain may be due in part to increased disease progression.

Conclusions

- Opioids are currently our best tool for managing moderate to severe cancer-induced pain.
- Considerations in interpretation of these observations include:
  - Do these effects occur across different cell lines?
  - How “generalizable” are these observations to human cancers?
- Are these effects observed in all patient populations?
  - Multiple drug treatments
  - Adjuvant drugs that may ameliorate these adverse effects
- Much more research is required in clinical and preclinical settings.

Morphine induced increases in pain and bone loss are mediated through activation of opioid receptors.