Mechanisms of Cancer Induced Bone Pain (CIBP) using animal models and relevant clinical paradigms

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Companies we have collaborated with on CIBP:

• Abbott
• Amgen
• Array
• Johnson & Johnson
• Lilly
• Merck
• Pfizer
• Plexxikon
• Rinat
• Roche
• Sanofi-Aventis
ECOG attribution of Cancer Pain study

255 cancer patients with metastatic lung, prostate, breast, and myeloma reporting pain intensity > 4 (Visual Analog Score 0 - 10)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>84.0%</td>
</tr>
<tr>
<td>Neural involvement</td>
<td>12.0%</td>
</tr>
<tr>
<td>Pleuritic</td>
<td>11.1%</td>
</tr>
<tr>
<td>Visceral</td>
<td>11.1%</td>
</tr>
<tr>
<td>Headache</td>
<td>4.9%</td>
</tr>
<tr>
<td>Postoperative</td>
<td>3.1%</td>
</tr>
<tr>
<td>“Pure neural”</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

*ECOG=Eastern Cooperative Oncology Group Study (E4Z93)*
Development of metastatic bone cancer

Bone Scintigraphy (Tc-99m)

Breast Cancer
- S = Scapula (Shoulder blade)
- St = Sternum
- H = Humerus

Female, 52 yrs

Lung Cancer
- V = Vertebrae
- R = Rib

Male, 60 yrs

Prostate Cancer
- V = Vertebrae
- R = Rib
- P = Pelvis

Male, 77 yrs
Mouse model of bone cancer

In same animal can measure: pain, tumor growth, bone remodeling and tumor metastasis to other organs.
Fig 2

Spontaneous Nocifensive Behavior (sec)

Bone Cancer Pain

Surgical Pain

Day (Post-Tumor Cell Injection)

- O Sarcoma
- ▼ Sham
- □ Naive

Values in parentheses indicate sample sizes.
<table>
<thead>
<tr>
<th>Preclinical Measures</th>
<th>Human Clinical Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocifensive behavior</td>
<td>Spontaneous pain</td>
</tr>
<tr>
<td>Dynamic Weight Bearing</td>
<td>Ability to load tumor-bearing limb</td>
</tr>
<tr>
<td>Limb Use</td>
<td>Gait and spontaneous use of limb</td>
</tr>
<tr>
<td>Hind limb rears</td>
<td>Frequency of spontaneous loading and use of tumor bearing limb</td>
</tr>
<tr>
<td>Weight</td>
<td>Weight gain or loss with CIBP</td>
</tr>
<tr>
<td>Time to Bone Fracture</td>
<td>Bone fractures / SREs</td>
</tr>
<tr>
<td>Bone Destruction/Formation</td>
<td>X-ray and serum markers of bone destruction/formation</td>
</tr>
<tr>
<td>Tumor Burden</td>
<td>Local and total tumor burden</td>
</tr>
</tbody>
</table>
Cancer Induced Bone Pain (CIBP)

• Nociceptive component

• Neuropathic component

• Analgesic agents can have disease modifying effects

• Rapid translation into human clinical treatments / trials
Nociceptive component of CIBP?

Bisphosphonate, Denosumab, radiation

[diagram showing inflammatory cells, osteoclasts, bone, sensory neurons, and spinal cord, with arrows indicating pathways]
Cancer Induced Bone Pain (CIBP)

- Nociceptive component
- Neuropathic component
- Analgesic agents can have disease modifying effects
- Rapid translation into human clinical treatments / trials
Sensory nerve fibers in normal bone marrow and bone marrow with early and late prostate cancer.
Sensory nerve fibers in normal bone marrow and bone marrow with early and late prostate cancer

Normal          Early              Late
Do sprouting axons revert to a "developmental state?"

GAP-43
Inositol signaling (PI3K, IMPA1)
Na\textsubscript{v} channels (Na\textsubscript{v}1.3)
p75 and TrkA
Number of flinches in a 2-min period

- Sham
- Prostate + vehicle (days 14-70)
- Prostate + anti-NGF (days 35-70)

*p < 0.05 vs sham
#p < 0.05 vs prostate + vehicle

Days post-cell injection

14 21 28 35 42 49 56 63 70
Cancer Induced Bone Pain (CIBP)

• Nociceptive component

• Neuropathic component

• Agents given as analgesics can have disease modifying effects

• Translation of preclinical results into human clinical treatments / trials
Disease modifying effects of Denosumab in mouse and humans

Bisphosphonate, Denosumab (OPG)
Kaplan-Meier estimates of time to first and subsequent SREs (multiple event analysis) in humans with breast cancer metastases to bone

Adapted from: Stopeck A T et al. JCO 2010;28:5132-5139
Translational of preclinical results into human clinical trials

Pharmacological therapies currently used to manage CIBP
(Non-NSAID and non-opiate pharmacological therapies for CIBP)

- **Xgeva (Denosumab) 2010**
- **Zometa (Zolendronic Acid [bis]) 2002**
- **Gabapentin**

Ongoing clinical trials for CIBP

- **Anti-NGF monoclonal antibody**
- **CSFR1 antagonists**
- **Cannabinoid agonists**
- **Resniferatoxin**
- **mTOR inhibitor**
- **Endothelin-A antagonists**
- **Anti-sclerostin monoclonal antibody**
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