A Translational Pathway for Pain and Symptom Treatment in Cancer

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Operational definition

- A symptom is a change in feeling or function *known best by patient report* — for example: pain, fatigue, nausea, neuropathy, disruption in sleep or mood, cognitive dysfunction, poor appetite.
Department of Symptom Research Agenda

- To measure the common symptoms of patients undergoing cancer treatment and to study the trajectory of these symptoms over time
- To look for clinical/biological correlates of symptom change in a trans-disciplinary approach
- To understand the molecular mechanisms of symptom development and identify novel targets for symptom reduction/prevention
- To perform clinical trials to combat treatment-related symptoms
Organization of Department of Symptom Research

- **Clinical Research** – Charles Cleeland, Director
  - Five faculty, (Cleeland, Tito Mendoza, Qiuling Shi, Xin Shelley Wang, Lori Williams)

- **Pre-clinical Research** – Annemieke Kavelaars, Director
  - Three faculty, (Kavelaars, Robert Dantzer, Cobi Heijnen)
Background: Cancer-Related Pain

• Significant pain and other symptoms affect most patients with cancer – hundreds of thousands each year
• Cancer pain is inadequately treated, despite WHO and other treatment guidelines
• Our knowledge about pain is variable
  – Good progress in understanding and treating pain due to bone metastases
  – However, treatment-related pain is becoming more common and is poorly understood
• Treatment-related pain limits treatment tolerability and affects survival
Two Opportunities for Improving Pain and Other Symptoms

• Ensure optimal use of what we know now
  – Use existing guidelines, update guidelines with new evidence
  – Include pain and symptom control in quality assurance, reimbursement review

• Learn more...

• Employ a translational pathway
  – Multi-disciplinary strategy (bench-to-bedside and back)
  – Goal: to develop new treatments for pain and other symptoms
What is a Translational Pathway?

• Strategy to transform scientific discoveries arising from laboratory, clinical, or population studies into clinical applications to reduce cancer incidence, morbidity, and mortality

• Developed by the NCI’s Translational Working Group (TRWG) to speed the steps between basic science and patient use for curative treatments
Translational Symptom Research: Levels of Attack

• Longitudinal patient discovery studies
  – Changes in symptoms and biomarkers over time

• Animal discovery models
  – Animal models of treatment-related symptoms
  – Identification and testing of candidate promoters/inhibitors of symptoms or symptom clusters
Translational Symptom Research: Levels of Attack

• Neuroimaging
  – Functional and molecular imaging of CNS expression of treatment-related symptoms

• Molecular/genetic
  – Longitudinal protein changes that accompany changes in symptom severity
  – Genetic and epigenetic markers of high vs. low vulnerability to expression of treatment-related symptoms

• Phase I/II clinical trials
Symptom Research Translational Pathway


**Problem:**
- Few new/novel agents in use for pain and symptom treatment
- Lack of discovery and preclinical models

**Solution:** Apply TRWG model to symptoms
- Uses wide range of discovery methods
- Identifies mechanisms of action
- Allows for preclinical testing
What We Know Now

• Many different kinds of “pain,” on the basis of underlying mechanisms

• Variations across patients
  – Pain severity (within each type of pain)
  – Response to analgesics and other symptom interventions
  – Only modestly related to such factors as age, sex, socioeconomic status, and even linguistic/cultural background
How Do We Measure Symptoms?
Self-Report Symptom Measures

• Need to be brief
• Need to be phrased in simple and unambiguous wording
• Like any other assay or biomarker, need to meet standards of measurement (valid, stable, sensitive to change, predictive of expected related outcomes)
• Need to exhibit minimal variation in measurement across various languages and cultures
### Brief Pain Inventory (Severity)

2. Please rate your pain by circling the one number that best describes your pain at its WORST in the last 24 hours.

<table>
<thead>
<tr>
<th>No Pain</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Pain as bad as you can imagine</th>
</tr>
</thead>
</table>

### Brief Pain Inventory (Interference)

7. Circle the number that describes how, during the past 24 hours, pain has interfered with your:

<table>
<thead>
<tr>
<th>A. General activity</th>
<th>Does not Interfere</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Completely Interferes</th>
</tr>
</thead>
</table>
## Activities Impaired by Increasing Pain

<table>
<thead>
<tr>
<th>Rating</th>
<th>Enjoyment</th>
<th>Work</th>
<th>Sleep</th>
<th>Active</th>
<th>Mood</th>
<th>Walk</th>
<th>Relate</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Enjoy</td>
<td>Enjoy</td>
<td>Enjoy</td>
<td>Enjoy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
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<td>6</td>
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<td>7</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

> > > > “Pain worst” rating > > > >

Cleeland CS. ??, 1989?
Progress in Three Types of Cancer Pain: How Far Along the Pathway?

- **Bone pain**
  - Good animal models
  - Many molecular mechanisms understood
  - Several existing and potential treatments available

- **Neuropathy**
  - Measurement issues
  - Increasing understanding of mechanisms involved
  - Animal models for some components
  - Few treatments available

- **Arthralgias (joint aches)**
  - No animal models
  - Lack of mechanistic understanding
  - Few treatments available
Bone Pain
Bone Pain: Background

• Prevalence estimates of pain due to bone metastases
  – 67% of patients with metastatic cancer have pain or take daily analgesics
  – 37% have pain that is moderate to severe (greater than 5 on a 0–10 scale)
  – 70 to 80% of those with pain have pain due to metastatic bone disease
  – More than 50% of patients with metastatic disease will have pain due to bone metastases

Cleeland CS et al. Ann Oncol, in press

Do you mean Lancet Oncol? Is this now in press??
Bone Pain: Murine Model

Jimenez-Andrade JM and Mantyh PW. In: *Cancer Symptom Science*, 2011
Treating Pain From Bone Metastases

- Analgesia
- Systemic antitumor therapy
- Orthopedic intervention
  - Surgery
  - Kyphoplasty, vertebroplasty
- Radiation therapy
  - External beam
  - Bone-seeking radionuclides
- Osteoclast inhibition
  - Bisphosphonates
  - RANK-L inhibitors
Bone Pain: Future Directions

• Agents with pre-clinical (murine) data
  – Selective COX-2 inhibitors
  – Selective endothelin inhibitors
  – Kinin inhibitors
  – Anti-NGF (nerve growth factor) therapy

• Developing an understanding of the neuropathic component of bone pain
Translational Pathway

Cleeland, Fisch & Dunn. *Cancer Symptom Science, 2011*

Pain Due to Bone Metastases

- **Status:**
  - Several animal models
  - Pre-clinical tests of effectiveness
  - Pain measures sufficient to assess benefit, perform discovery studies
  - Many candidate agents that are potentially effective

- **Next Steps:**
  - Individual variation in pain expression
  - Pathways of bone destruction to pain transmission

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1. **Identify clinical need**

2. **Measurement strategies appropriate?**

3. **Animal models exist?**
   - NO
   - YES

4. **Candidate mechanisms**

5. **Candidate agents**
   - NO
   - YES

6. **Phase I and/or Animal studies**
   - NO
   - YES

7. **Good results?**
   - NO
   - YES

8. **Prior human use?**
   - NO
   - YES

9. **Phase I/II clinical trials: Symptom/toxicity outcomes**

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**Human studies:** Biomarkers of symptoms (genes/proteins), sensory testing, neuroimaging

**Develop measures**

**Parallel discovery studies**

**Animal models**

**Develop models**
Chemotherapy-Induced Neuropathy
Chemotherapy-Induced Neuropathy (CIPN): More Than Pain

• A major reason for dose reduction or treatment cessation for certain therapies
  – Platinum-based
  – Taxanes
  – Bortezomib
  – Some “targeted” therapies

• Most novel therapy development programs have focused only on painful component

• However, non-painful sensory-motor components may be more disabling than pain
CIPN: Current Trials of Agents

- Vitamins B6, B12, C, D, E
- Calcium glutamate & magnesium sulfate
- D-cycloserine
- N-acetyl cystine
- Acetyl L-carnitine
- Alpha-lipoic acid
- Oxycodone
- Topicals (menthol)
- Duloxetine
- Xaliproden
- MC5-A Scrambler
- GM 1
- Acupuncture
- Amifostine
- Pregabalin
- Gabapentin
- Lamotrigine
- Nabilone
- Dextromethorphan
- Glutamine
- Neotrofin
- Sativex
- NGX-4010 (capsaicin)
- SB-509 (pro VEGF)
- Photobiomodulation
- Venlafaxine

However, few of these agents are based on a mechanistic understanding of neuropathy

Source: Clinicaltrials.gov
CIPN: The Problem

Dougherty PM et al (unpublished data)
CIPN: Do Pain Scales Capture It?

• What is not well measured
  – Hypersensitivity to cold
  – Reduction in tactile sensation
  – Loss of balance
  – Fine eye-hand coordination

• How bothersome are these extra pain symptoms to patients?
CIPN: Treatment-Related Symptoms

Patients with Colorectal Cancer Receiving Oxaliplatin-Based Chemotherapy

Wang XS et al (unpublished data)
CIPN: Post-Treatment Skin Biopsies

Boyette-Davis JA (unpublished data)
CIPN: Mechanical Paw Withdrawal

Withdrawal threshold for animals receiving oxaliplatin with minocycline treatment

<table>
<thead>
<tr>
<th>Time point</th>
<th>Baseline</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 4</th>
<th>Day 6</th>
<th>Day 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold (grams)</td>
<td>0</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>25</td>
</tr>
</tbody>
</table>

- **Mino/Oxali**
- **Mino/vehicle**
- **Vehicle/Oxali**
- **Vehicle/Vehicle**
CIPN: Clinical Example

- Phase II Trial: Minocycline vs. Placebo to Prevent Treatment Induced Neuropathy in Multiple Myeloma
  - PI: Sheeba Thomas, MD
  - Funded by NCI Program Project Grant
- 200 mg orally for one dose, then 100 mg orally every 12 hours for 10 weeks
- Outcomes
  - Primary: touch-detection threshold prior to each cycle
  - Secondary: other treatment-related symptoms by self-report
Translational Pathway


Chemotherapy-induced neuropathic pain

**Status:**
- Clinical measurement issues
- Animal models allow for agents in use for pain and symptom treatment
- Lack of discovery and preclinical models

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**Diagram:**
1. Identify clinical need
2. Measurement strategies appropriate?
   - YES: Parallel discovery studies
   - NO: Develop measures
3. Animal models exist?
   - NO: Develop models
   - YES: Candidate mechanisms
4. Candidate agents
   - NO: Prior human use?
     - NO: Phase I and/or Animal studies
     - YES: Good results?
       - NO: Candidate agents
       - YES: Phase I/II clinical trials: Symptom/toxicity outcomes
   - YES: Human studies: Biomarkers of symptoms (genes/proteins), sensory testing, neuroimaging
Arthralgias
Arthralgias: Treatment Options

• No formal treatment recommendations for aromatase inhibitor (AI)-induced arthralgia
• Various interventions have been tried
  – Most widely used are the non-steroidal anti-inflammatory drugs (NSAIDs)
  – Not clear that any intervention has had a dramatic effect
Arthralgias: Current AI-Targeted Clinical Trials

- Randomized trials of acupuncture for AI-induced joint pain
- Acupuncture for treating with AI-related joint pain
- Androgen and testosterone
- Trial of blue citrus compared to placebo
- Glucosamine and chondroitin
- Pregabalin,
- Vitamin D
- Yoga and exercise

Source: Clinicaltrials.gov
Arthralgias: Group-Based Trajectory

Pain trajectories in patients with early-stage breast cancer during the first year of anastrozole therapy measured by BPI pain worst, N=52

Shi Q et al (2013)
Arthralgias: Mechanisms

• Depletion of estrogen may play a part in AI-induced arthralgias

• Multiple pathways
  – Bone loss: BMD decreases found in patients undergoing AI therapy for 6 months or longer
  – Central nervous system: Anti-nociceptive effect through opioid pain fibers

Smith et al. *J Neurosci*, 2006
Arthralgias: Inflammation

• Expression and secretion of the proinflammatory cytokines IL-1, IL-6, and TNF-α were found to increase with estrogen deficiency in multiple cells.

• Estrogen is able to repress expression of pro-inflammatory cytokine genes, including IL-1, IL-6, and TNF-α.

• Thymosin α1, an anti-inflammation drug, can significantly relieve joint pain and can improve functioning in breast cancer survivors undergoing AI therapy.

Translational Pathway


**Arthralgias due to aromatase inhibitors**

- **Status:**
  - No animal models
  - Few human discovery studies
  - Few agents with established effectiveness

- **Next Steps:**
  - Implement studies at all steps in the pathway

---

**Diagram Details:**

1. **Identify clinical need**
2. **Measurement strategies appropriate?**
   - **NO**
   - **YES**
3. **Candidate mechanisms**
4. **Candidate agents**
   - **NO**
   - **YES**

**Developmental Steps:**

- **Parallel discovery studies**
- **Human studies:** Biomarkers of symptoms (genes/proteins), sensory testing, neuroimaging
- **Animal studies**
- **Biomarkers of symptoms**
- **Sensory testing**
- **Neuroimaging**

**Arthralgias due to aromatase inhibitors**

- **Status:**
  - No animal models
  - Few human discovery studies
  - Few agents with established effectiveness

- **Next Steps:**
  - Implement studies at all steps in the pathway
Does the Pathway Apply to Other Symptoms?
Percent Rating Severe (7–10 on a 0–10 scale) During Treatment (N=527)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>36%</td>
</tr>
<tr>
<td>Weakness</td>
<td>32%</td>
</tr>
<tr>
<td>Poor appetite</td>
<td>25%</td>
</tr>
<tr>
<td>Disturbed sleep</td>
<td>24%</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>24%</td>
</tr>
<tr>
<td>Pain</td>
<td>19%</td>
</tr>
<tr>
<td>Worry</td>
<td>29%</td>
</tr>
<tr>
<td>Distress</td>
<td>26%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>20%</td>
</tr>
<tr>
<td>Sadness</td>
<td>20%</td>
</tr>
</tbody>
</table>
How Symptoms Cluster During Treatment

Cleeland et al. *Cancer*, 2000
IL-6 ($P = 0.001$) and MIP-1α ($P = 0.013$) as the critical inflammatory markers related to the development of the 5 most-severe symptom outcomes during the first 30 days post-AuSCT.

- Fatigue
- Component score of 5 most severe symptoms:
  
  Fatigue
  Pain
  Distress
  Drowsiness
  Disturbed sleep

Fatigue:
  \textbf{sTNF-R1} (P<.001)

Component score:
  \textbf{IL-6} (P<.0001)
  \textbf{sTNF-R1} (P<.0001)

Wang et al, \textit{BBI}, 2012
Sickness Behavior: An Animal Model for Cancer-Related Symptoms?

• Physiological components
  – fever, pain, wasting, increased HPA, autonomic activity

• Behavioral components
  – Somnolence, hyperalgesia, impaired learning, and decreased social interaction, exploration, and eating

• Inflammatory cytokines/chemokines and neurotransmitters may play central mechanistic role
Trajectories Identify Patients in High Symptoms – Symptom Phenotypes

- Patients with head & neck cancer (N=130)
- Radiotherapy or chemo-radiotherapy
- Pain, 0-10 NRS (MDASI-HN)
- Group-based trajectory: responder analysis (McLeod et al. 2011)

Shi et al, Qual Life Res, 2013
Systemic Symptoms – Minocycline vs placebo during XRT for HNC – B Gunn

Composite score of pain, fatigue, lack of appetite, distress, sleep disturbance
100 mg minocycline twice daily vs placebo
## Animal (Murine) Models of Common Cancer-Related Symptoms

<table>
<thead>
<tr>
<th>Reduced energy and activity</th>
<th>Reduced open-field activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased motivation, interest</td>
<td>Loss of sucrose preference, decreased social behavior, sexual behavior, lever pressing for preferred food</td>
</tr>
<tr>
<td>Difficulty in completing tasks</td>
<td>Reduced nest building and burrowing behavior, increased brain “effort” (fMRI)</td>
</tr>
<tr>
<td>Sleep changes</td>
<td>Circadian changes, EEG sleep cycle architecture</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>Novel object recognition, water maze, reversal learning tasks, delayed nonmatching to sample</td>
</tr>
</tbody>
</table>

Meagher M. In: *Cancer Symptom Science*, 2011
• Annemieke Kavelaars, PhD – Professor and Director
• Robert Dantzer, DVM, PhD – Professor
• Cobi Heijnen, PhD - Professor
The anti-diabetic drug Metformin protects against chemotherapy-induced peripheral neuropathy and chemobrain in a mouse model.

Current Funding:
NIH RO1 NS 073939
NIH RO1 NS 074999
TU System: STARS award
Metformin

- Treatment of type 2 diabetes
- Most frequently used prescription drug world wide
- Safe, well-tolerated
- AMP-kinase agonist
- Some evidence for protective effect in surgical models of neuropathic pain
- Anti-inflammatory effects
- Potential anti-tumor effects

Aim:

- To test the hypothesis that metformin protects against chemotherapy-induced neuropathic pain and sensory deficits
Effect of metformin on cisplatin-induced numbness

Adhesive patch on hind paw

Time to respond

Preventive treatment

Mao-Ying et al. PLoSOne 2014
Conclusions

Co-administration of Metformin with chemotherapy:

- Prevents hyperalgesia in mice
- Prevents numbness in mice
- Prevents peripheral neuronal damage
- Clinical translation of these findings could be rapidly achieved
  - Clinical trial under IRB review
Chemobrain

- Cognitive impairment: decreased processing speed, memory, executive functioning and attention
- 69-78% of prospective and cross sectional studies 1995-2012 indicate chemobrain in breast cancer.
- Persists in 17-34% after completion of treatment.
- Neuropsychological tests: decreased processing speed, memory, executive functioning and attention.
- Advanced neuroimaging techniques: structural alterations in white and gray matter; regional changes in brain activity
- Mechanism largely unknown; no preventive or curative treatment

**Treatment-Induced Cognitive Deficit**

**Aims -**
- Develop mouse model of chemobrain with cognitive tasks as outcome
  - Most studies so far: methotrexate, cyclophosphamide,
  - Cisplatin: allows studies on chemobrain, chemopain and chemotherapy-induced sensory loss (numbness)

*Analyze neuro-anatomical changes*

*Investigate mechanisms*

*Test potential interventions*
Cisplatin-induced chemobrain

3 Cycles of cisplatin i.p (5 days cisplatin; 2.3 mg/kg, 5 days rest)
Examine cognitive function one week after last treatment

Social Discrimination

Zhou,...Heijnen 2015 in prep

Total Exploration time

Saline
Cisplatin

No preference
Novel object and Place recognition

3 Cycles of cisplatin i.p (5 days cisplatin; 2.3 mg/kg, 5 days rest)
Examine cognitive function one week after last treatment

No preference

No relation between total interaction time during training and preference
Metformin prevents Chemobrain

3 Cycles of cisplatin i.p (5 days cisplatin; 2.3 mg/kg +/- metformin, 5 days rest)
Examine cognitive function one week after last treatment

Social Discrimination

Novel Object and Place Recognition

Zhou,….Heijnen 2015 in prep
Strategic Points for Implementing a Pain and Symptom Translational Pathway

• Recognition of the high impact of cancer-related symptoms on function and survival
• Development of a strategy to employ “big science” to reduce this impact
• Inclusion of measures of symptom change in oncology clinical trials
• Investment in animal models of symptoms
• Development of funding avenues for pathway research, and training of investigators to implement it