THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

A Translational Pathway for Pain and Symptom Treatment in Cancer

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The University of Texas MD Anderson Cancer Center

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

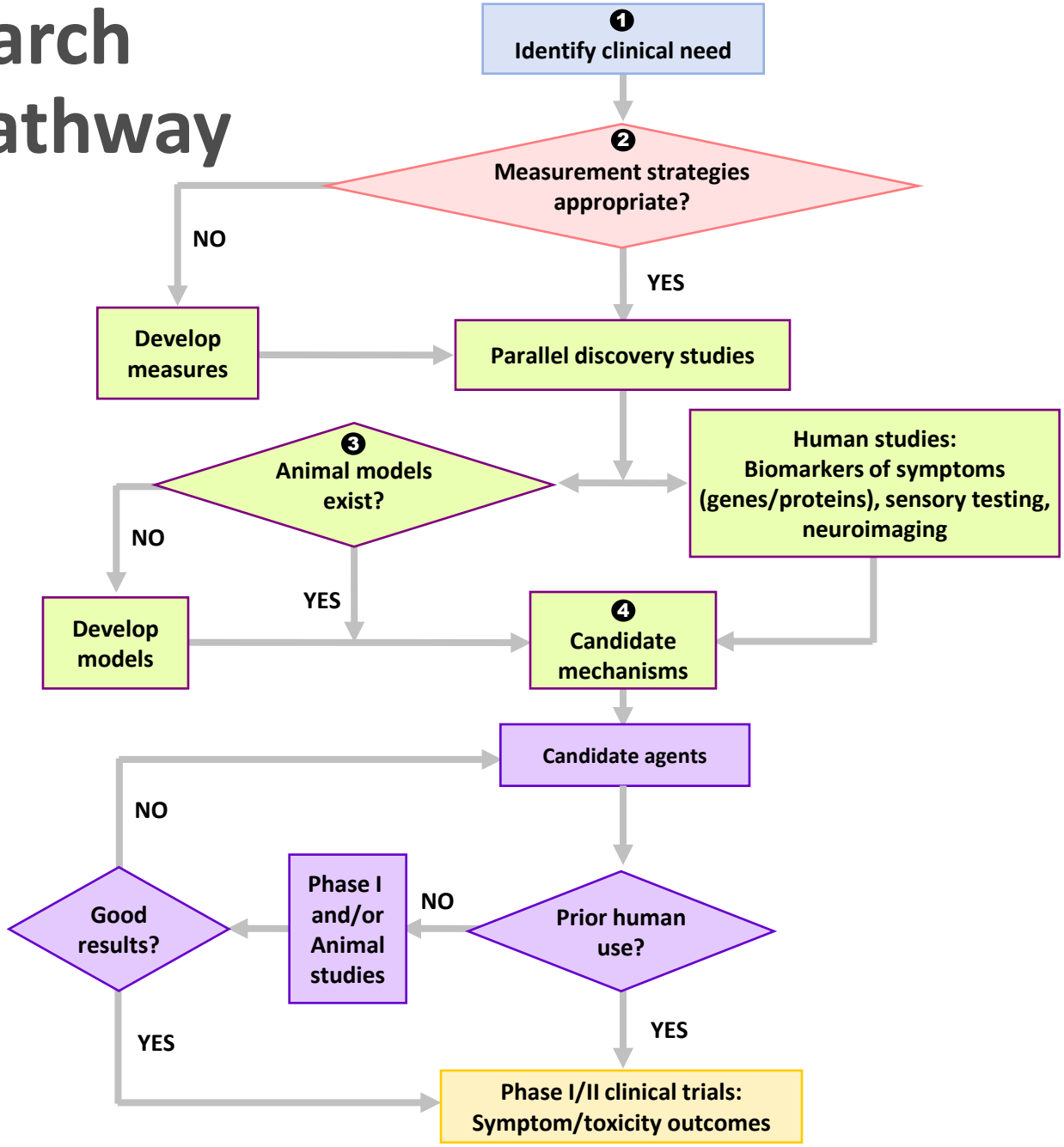
Translational Symptom Research: Levels of Attack

- 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

Cleeland, Fisch & Dunn.
Cancer Symptom Science, 2011

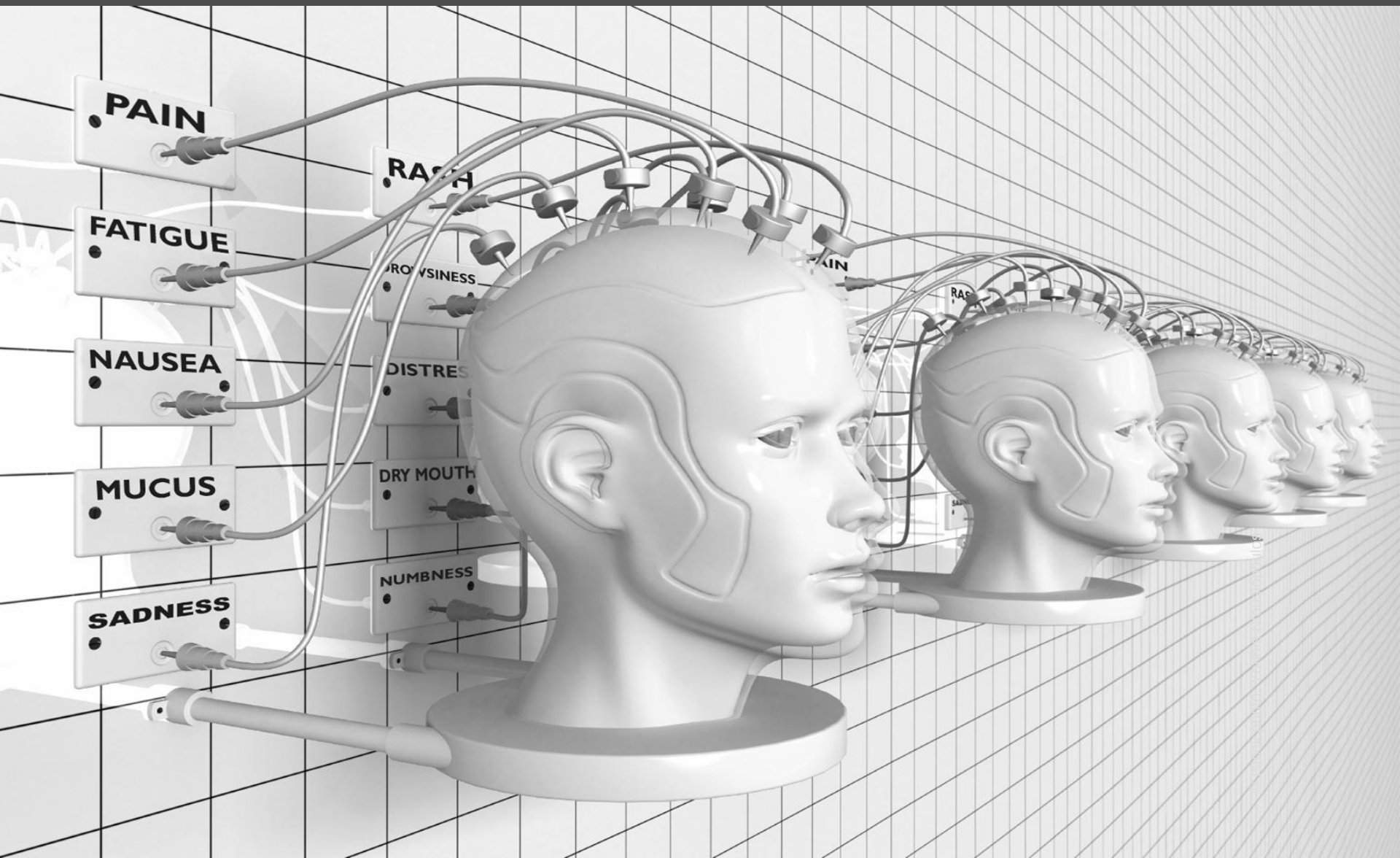
- **Problem:**
  - Few new/novel agents in use for pain and symptom treatment
  - Lack of discovery and preclinical models
- **Solution:** Apply TRWG model to symptoms
  - Uses wide range of discovery methods
  - Identifies mechanisms of action
  - Allows for preclinical testing



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

The Emergence of Patient Report

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.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Brief Pain Inventory (Interference)

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

A. General activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Activities Impaired by Increasing Pain

3	4	5	6	7	8
					relate
				walk	walk
		sleep	sleep	sleep	sleep
		active	active	active	active
		mood	mood	mood	mood
	work	work	work	work	work
enjoy	enjoy	enjoy	enjoy	enjoy	enjoy

> > > > “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

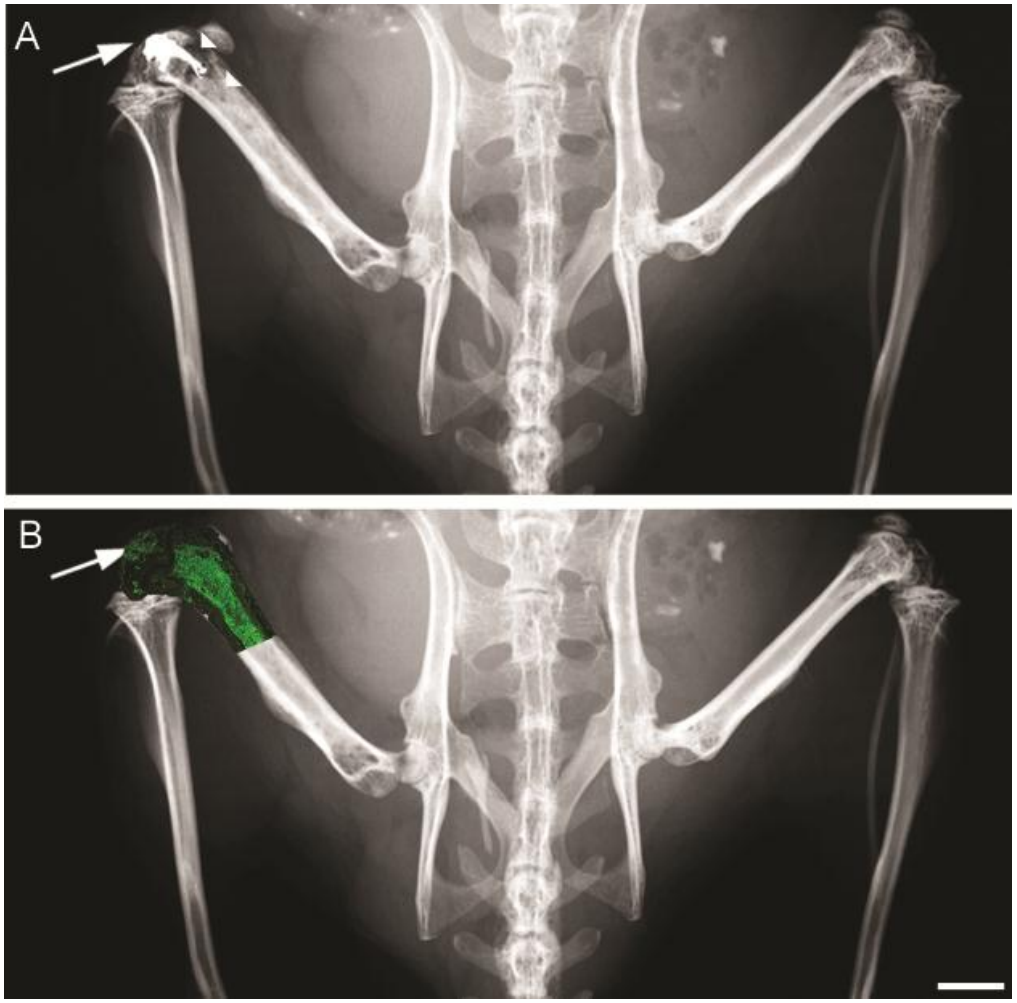
Bone Pain

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. *New Engl J Med*, 1994
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

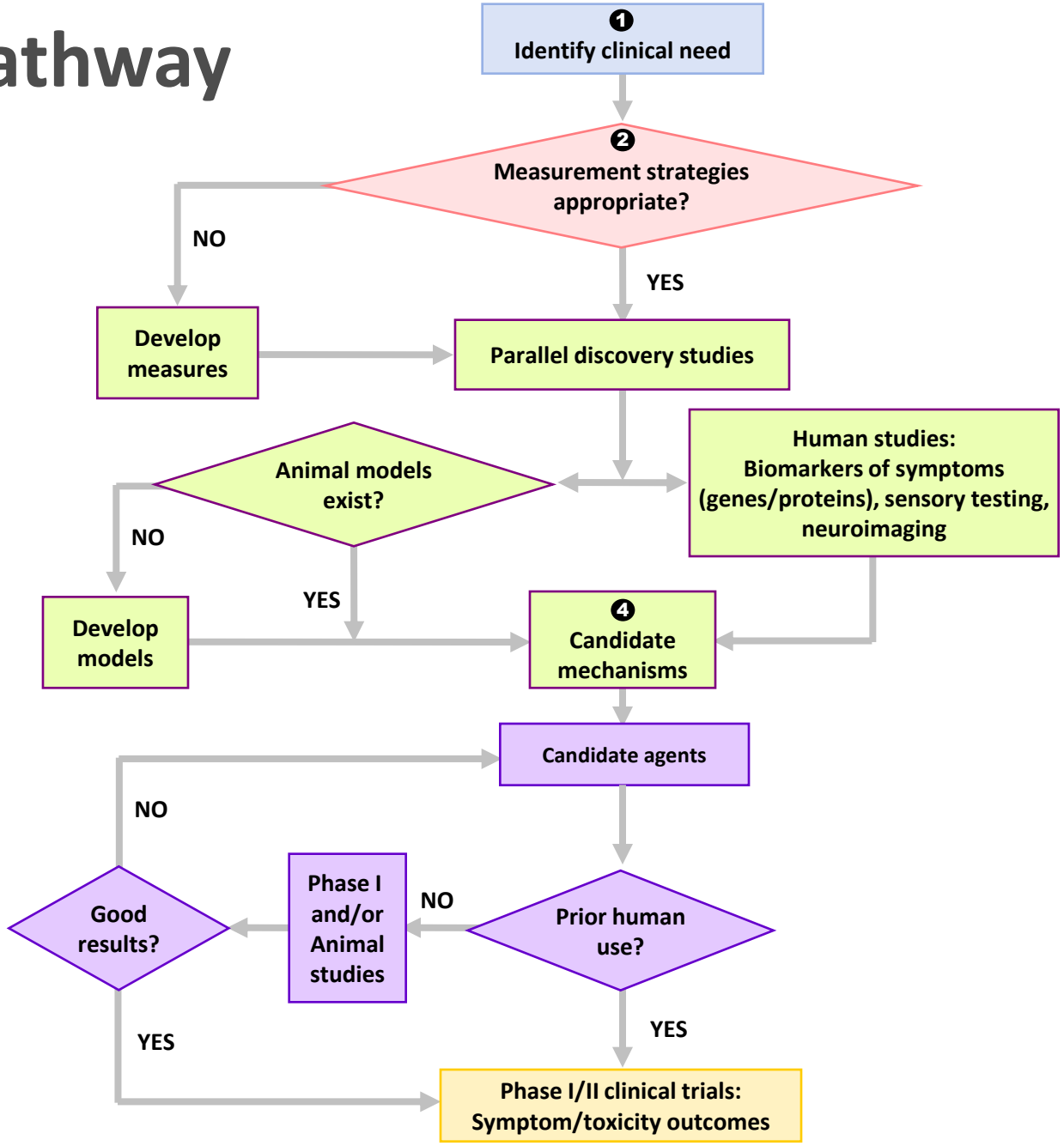
Jimenez-Andrade JM and Mantyh PW. In: *Cancer Symptom Science*, 2011

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



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

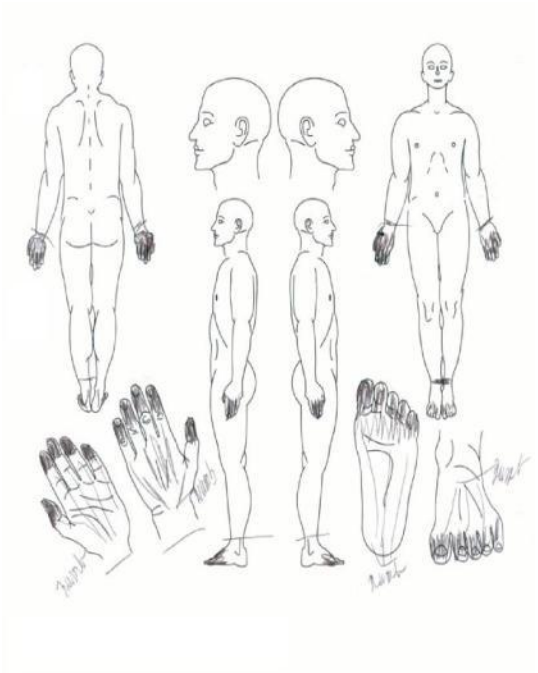
Vitamins B6, B12, C, D, E
Calcium glutamate & magnesium sulfate
D-cycloserine
N-acetyl cystine
Acetyl L-carnitine
Alpha-lipoic acid
Oxycodone
Topicals (menthol)
Duloxetine
Xaliproden
MC5-A Scrambler
GM 1
Acupuncture

Amifostine
Pregabalin
Gabapentin
Lamotrigine
Nabilone
Dextromethorphan
Glutamine
Neotrofin
Sativex
NGX-4010 (capsaicin)
SB-509 (pro VEGF)
Photobiomodulation
Venlafaxine

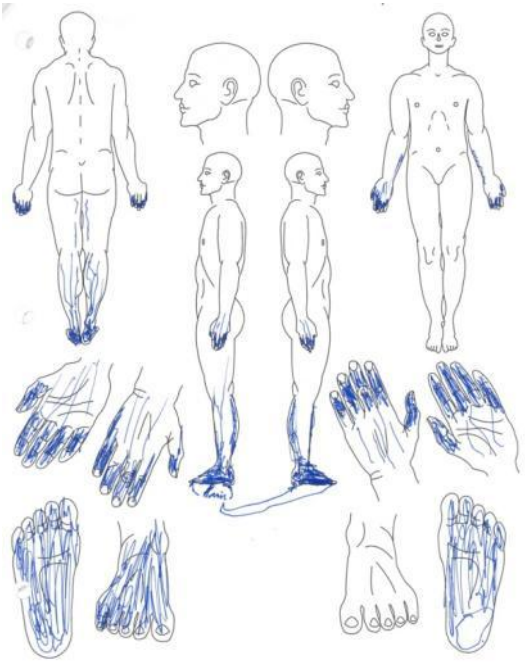
However, few of these agents are based on a mechanistic understanding of neuropathy

Source: *Clinicaltrials.gov*

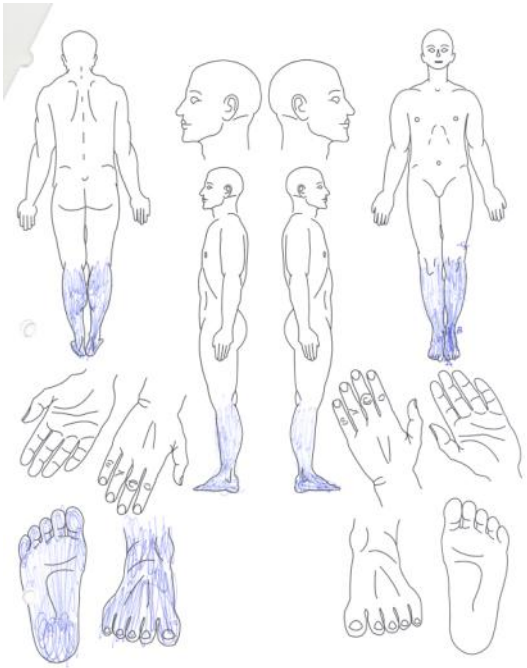
CIPN: The Problem



Taxol



Velcade



Cisplatin

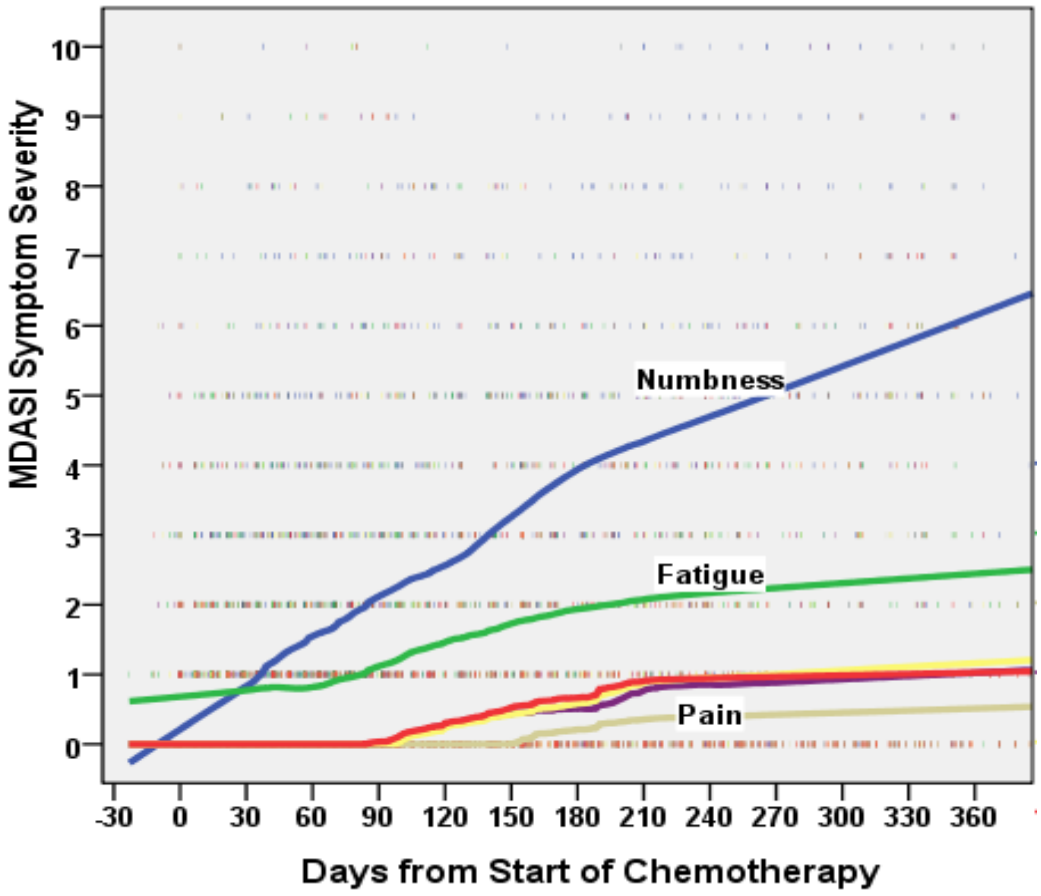
Dougherty PM et al (unpublished data)

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?

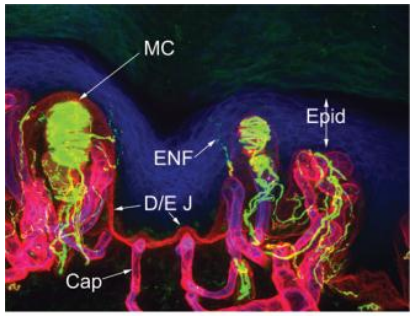
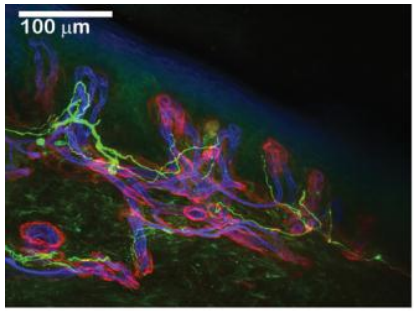
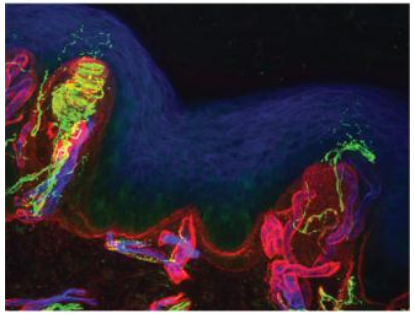
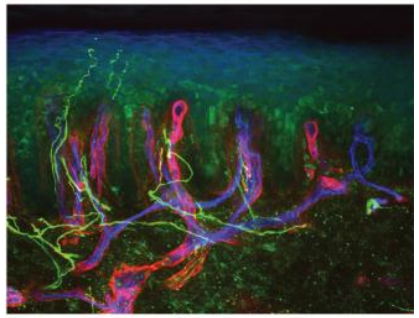
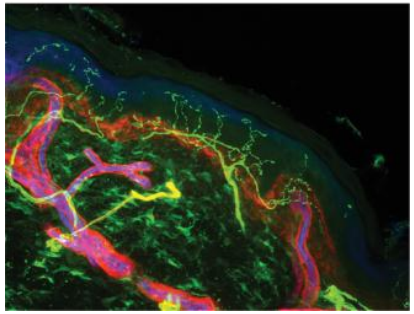
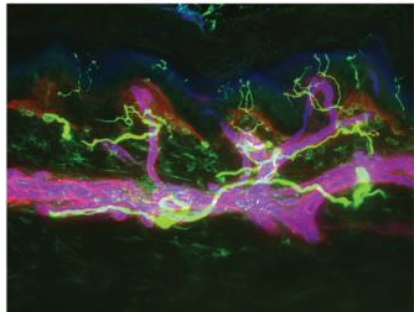
CIPN: Treatment-Related Symptoms

Patients with Colorectal Cancer Receiving Oxaliplatin-Based Chemotherapy

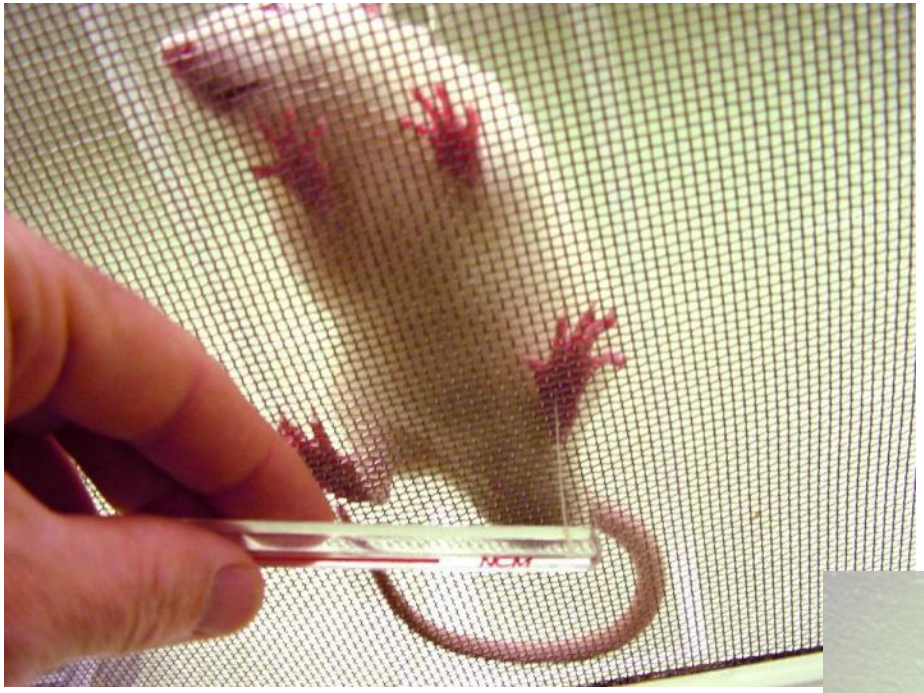


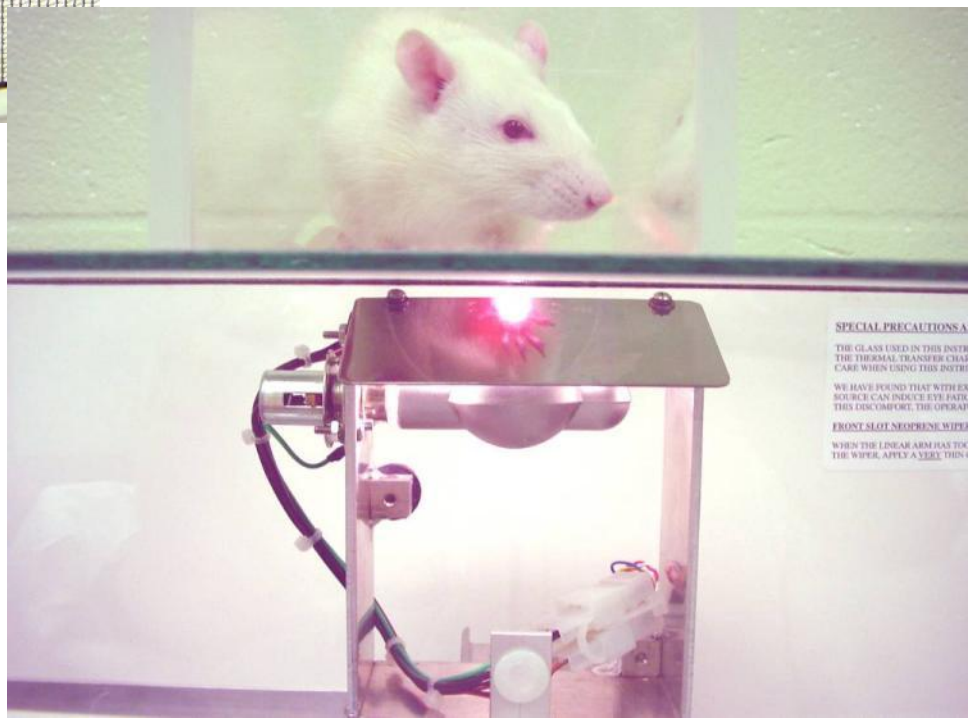
Wang XS et al (unpublished data)

CIPN: Post-Treatment Skin Biopsies

	Normal	Chemo neuropathy
Fingertip		
Palm		
Forearm		

Boyette-Davis JA (unpublished data)

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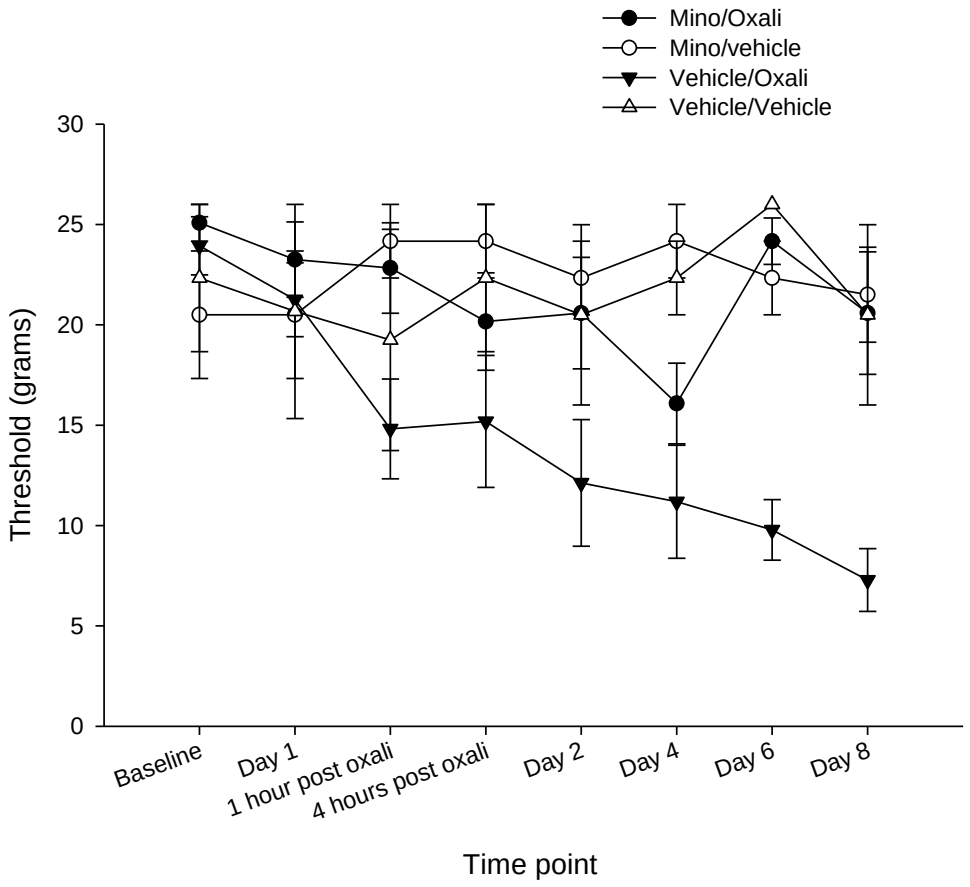
THE WIPER, APPLY A VERY THIN

CIPN: Mechanical Paw Withdrawal

Withdrawal threshold for animals receiving oxaliplatin with minocycline treatment



Dougherty PM et al (unpublished data)

CIPN: Clinical Example

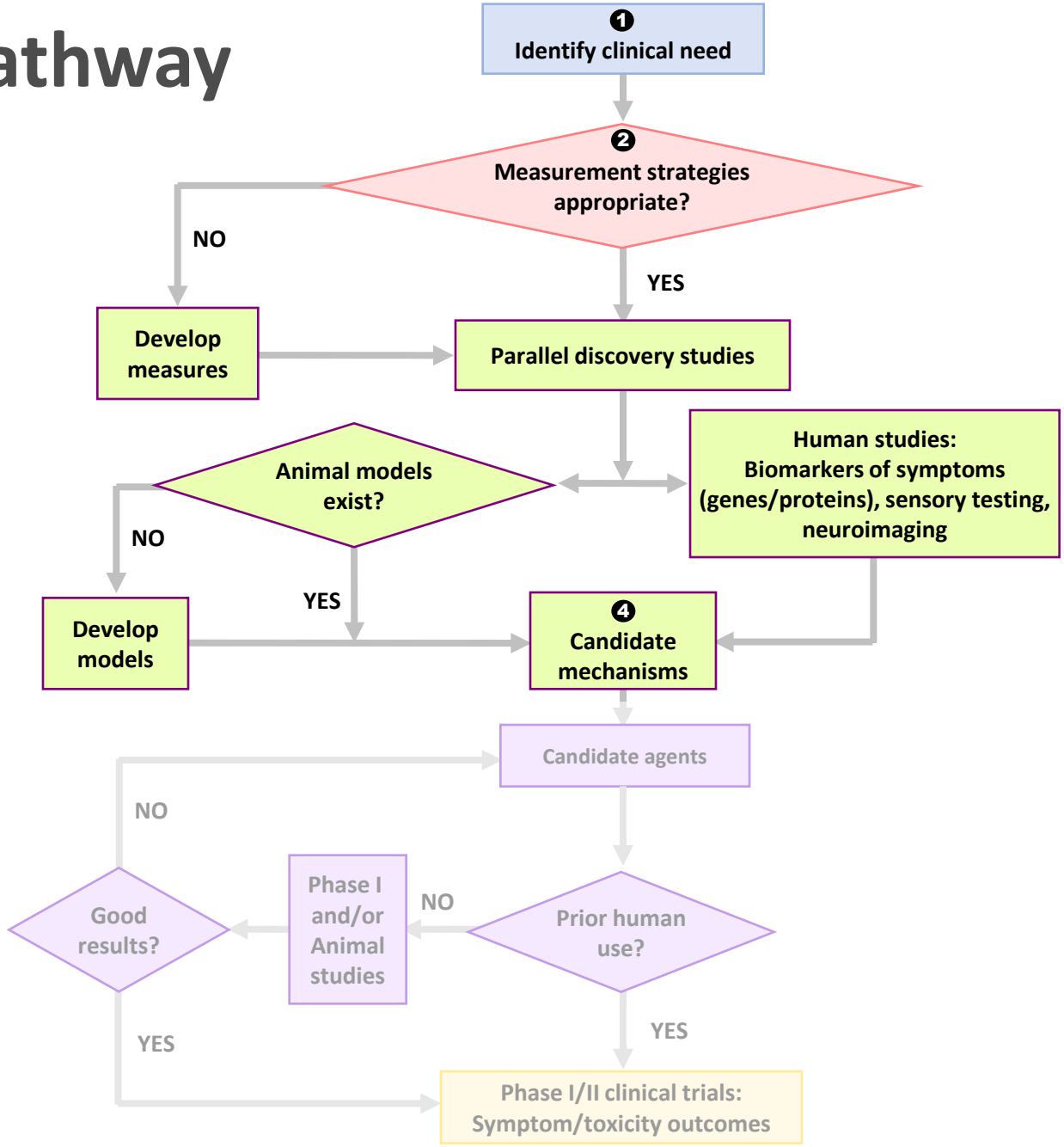
- Phase II Trial: Minocycline vs. Placebo to Prevent Treatment Induced Neuropathy in Multiple Myeloma
  - PI: Sheeba Thomas, MD
  - Funded by NCI Program Project Grant
- 200 mg orally for one dose, then 100 mg orally every 12 hours for 10 weeks
- Outcomes
  - Primary: touch-detection threshold prior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

Translational Pathway

Cleeland, Fisch & Dunn.
Cancer Symptom Science, 2011

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



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

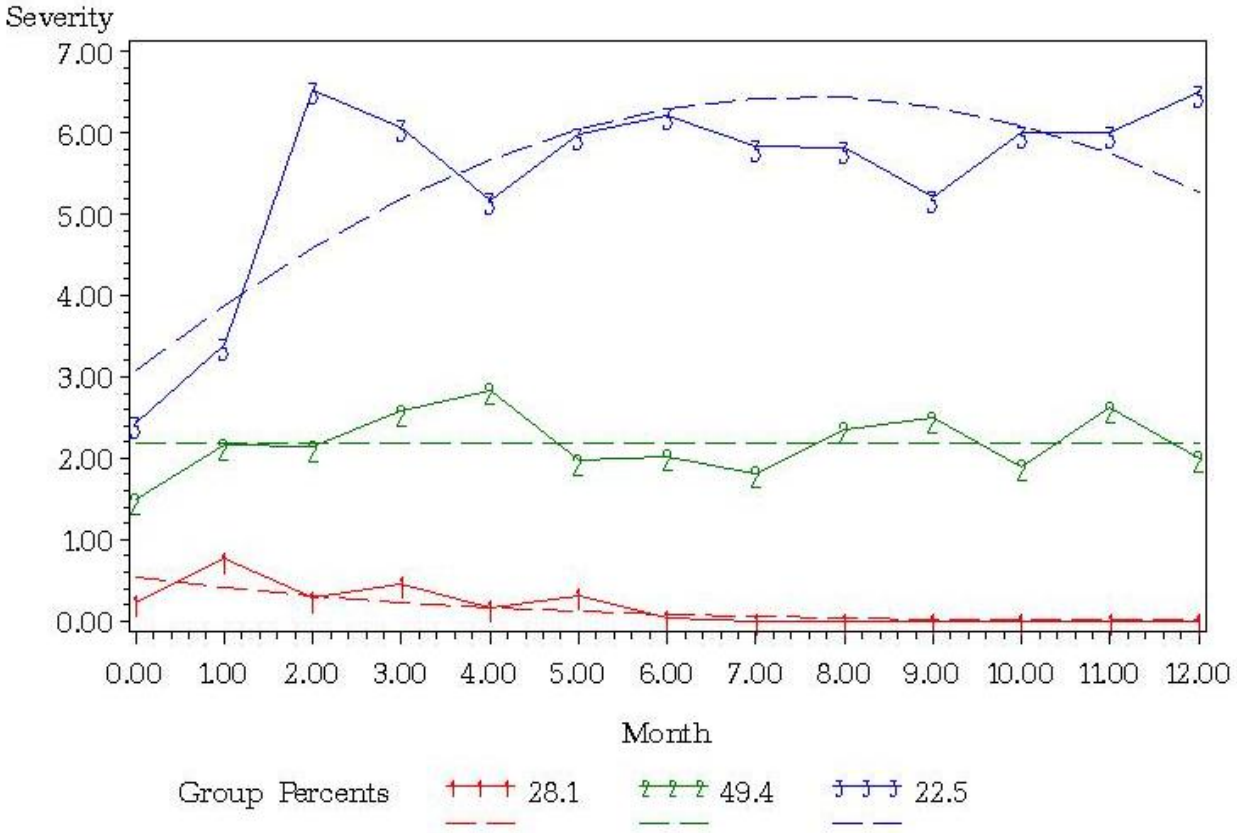
Arthralgias: Current AI-Targeted Clinical Trials

- 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

Eastell et al. *J Clin Oncol*, 2008
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

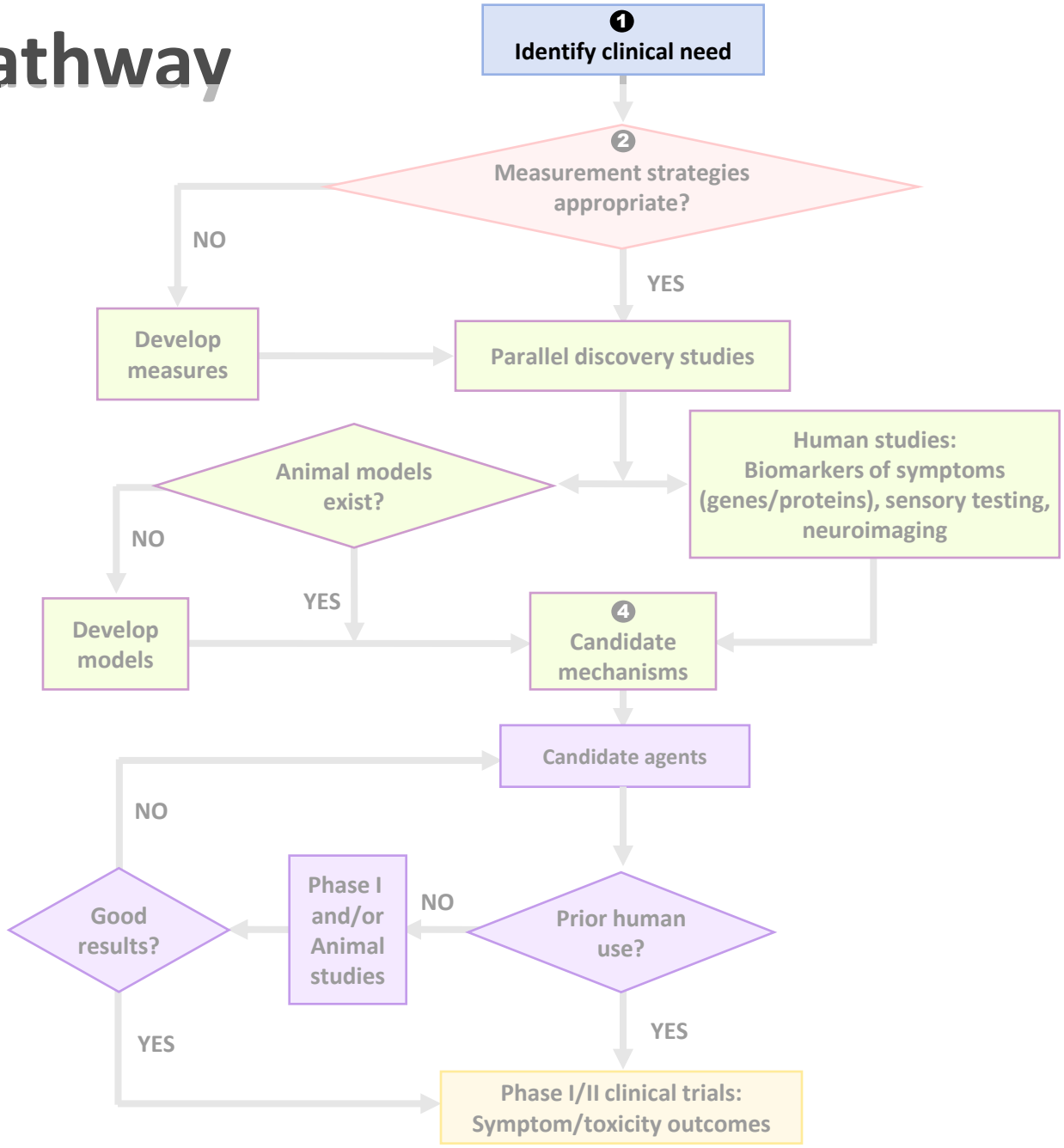
Cohen and Cohen. *Am J Clin Pathol*, 1996
Cvoro et al. *J Immunol*, 2008
Zhang et al. *Am J Clin Oncol*, 2010

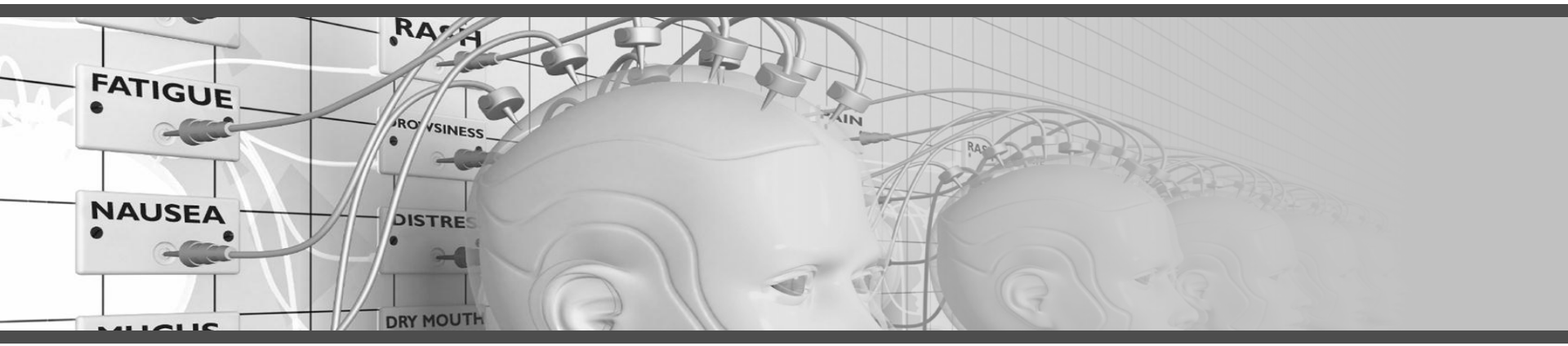
Translational Pathway

Cleeland, Fisch & Dunn.
Cancer Symptom Science, 2011

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?

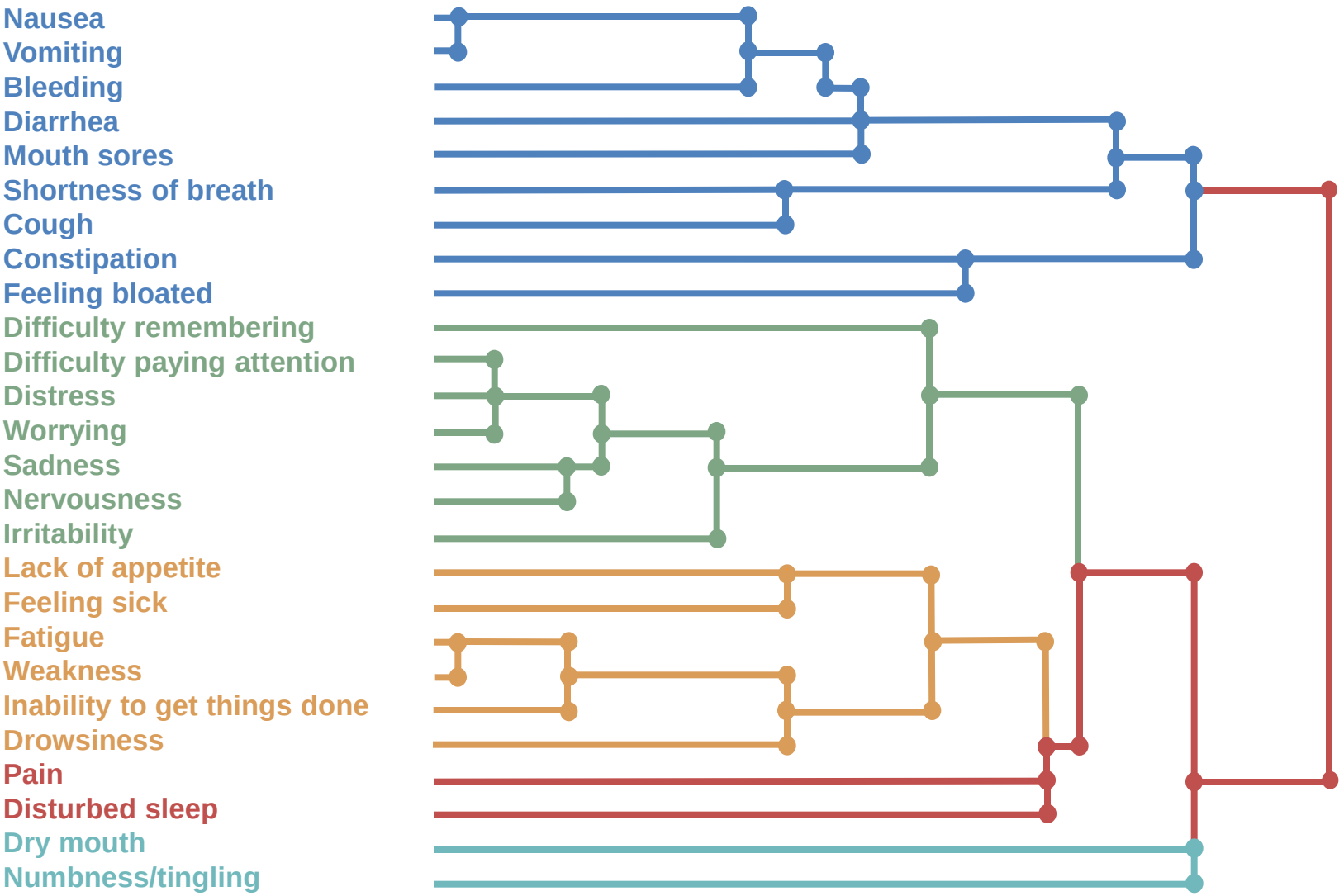
Percent Rating Severe (7–10 on a 0–10 scale) During Treatment (N=527)

- Fatigue 36%
- Weakness 32%

- Poor appetite 25%
- Disturbed sleep 24%
- Drowsiness 24%
- Pain 19%

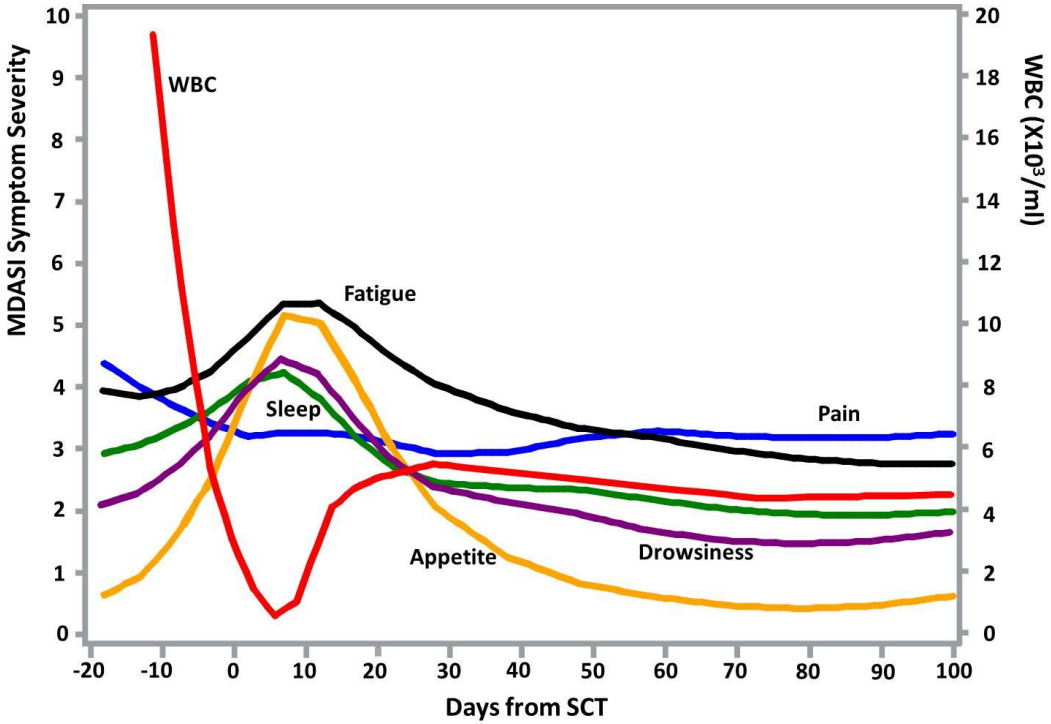
- Worry 29%
- Distress 26%
- Nervousness 20%
- Sadness 20%

How Symptoms Cluster During Treatment



Cleeland et al. *Cancer,* 2000

Most Severe Symptoms and WBC Count during 100 days AuSCT for MM



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.

Wang et al, *Cli Can Rec*, 2014

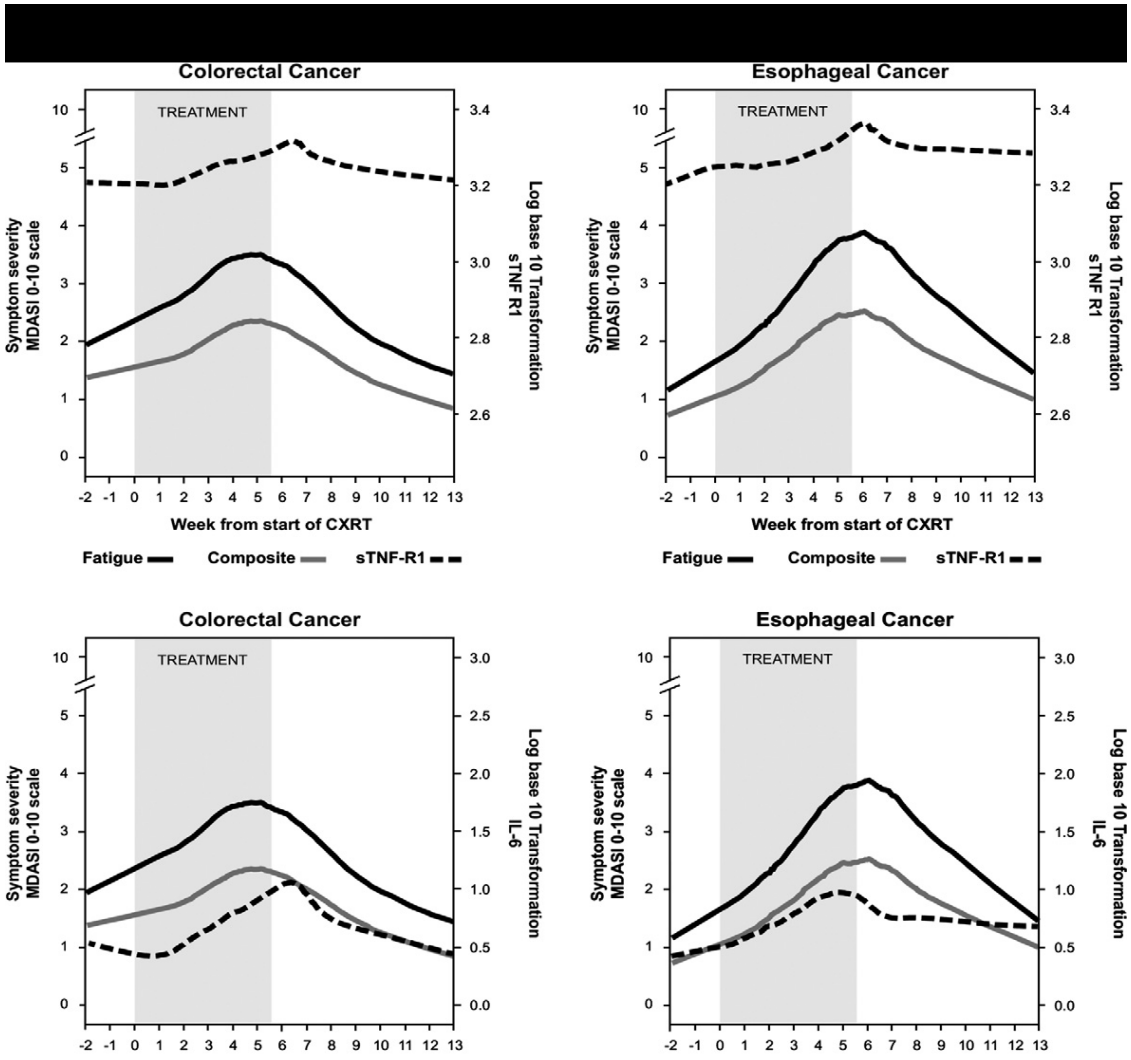
Colorectal & Esophagus Cancer: IL-6, sTNF-R1, Symptoms Over Time

- Fatigue
- Component score of 5 most severe symptoms:

  Fatigue
  Pain
  Distress
  Drowsiness
  Disturbed sleep

Fatigue:
  sTNF-R1 (P<.001)

Component score:
  IL-6 (P<.0001)
  sTNF-R1 (P<.0001)

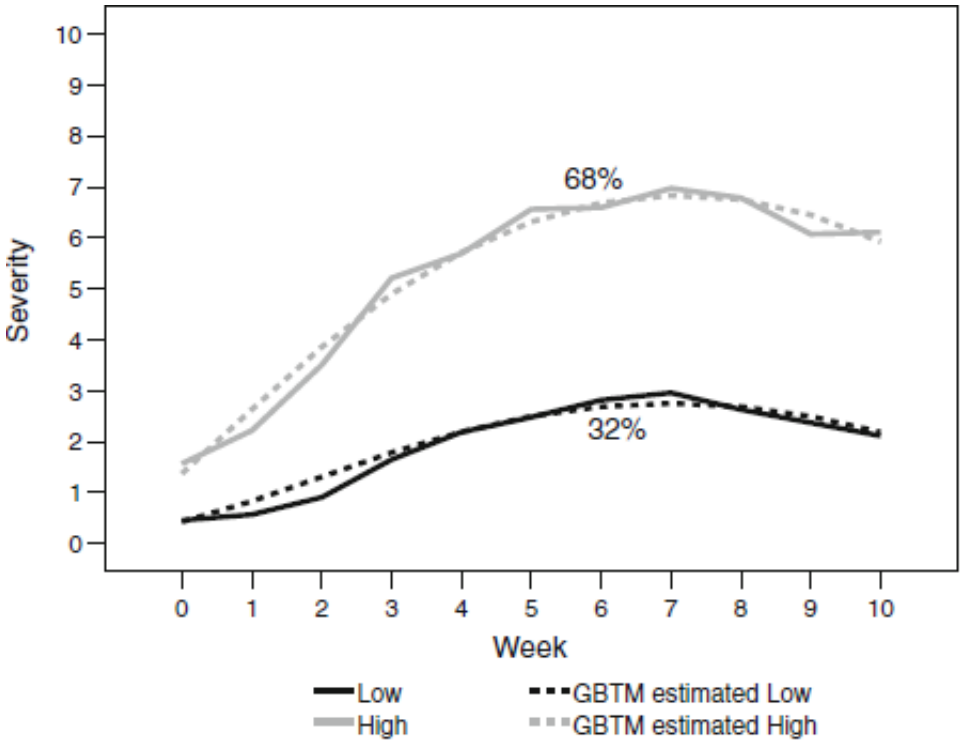


Wang et al, *BBI,* 2012

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

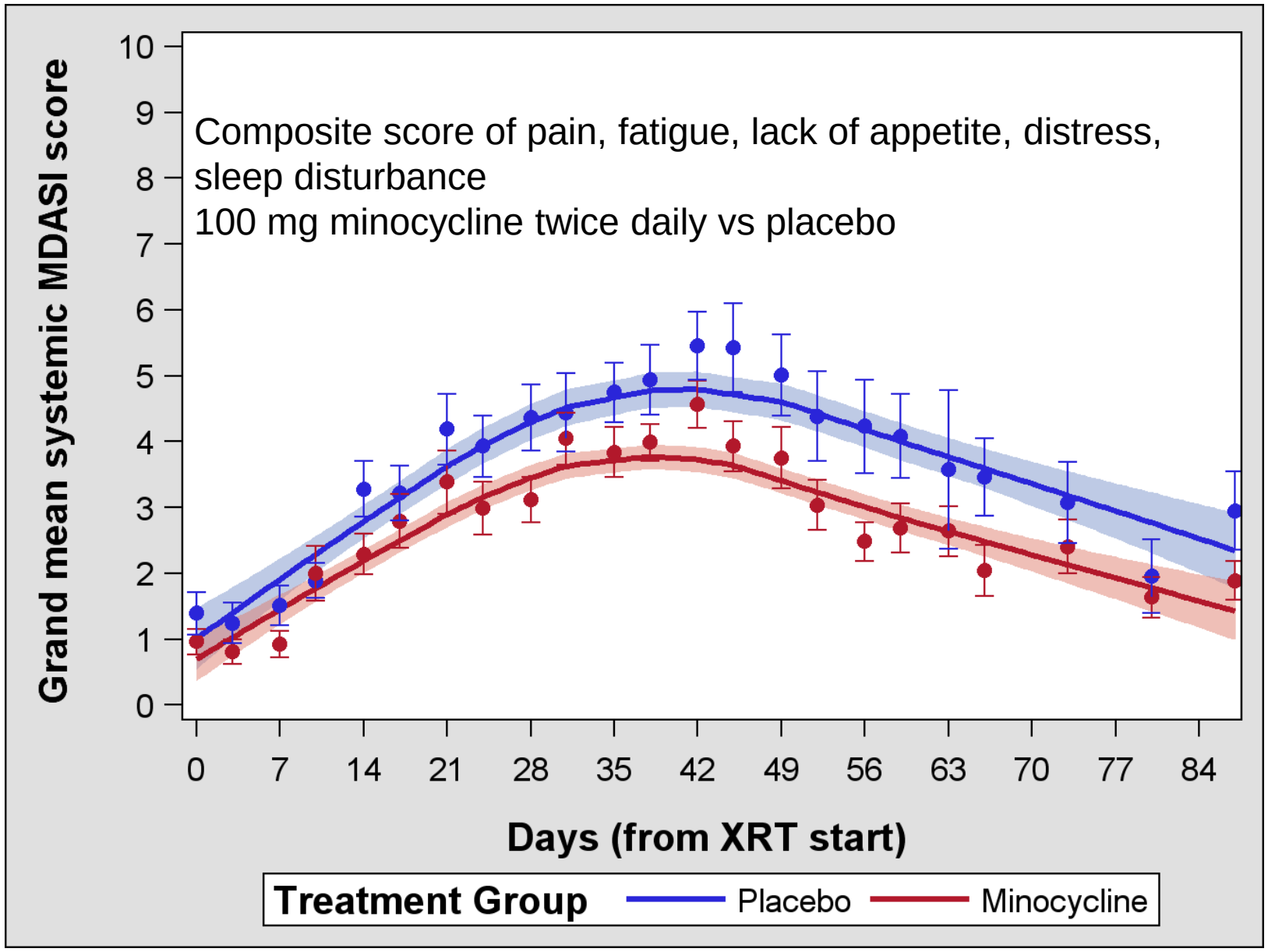
Trajectories Identify Patients in High Symptoms – Symptom Phenotypes



- 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



Animal (Murine) Models of Common Cancer-Related Symptoms

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

Meagher M. In: *Cancer Symptom Science*, 2011

Laboratory of Neuroimmunology – Department of Symptom Research - 2012

- 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

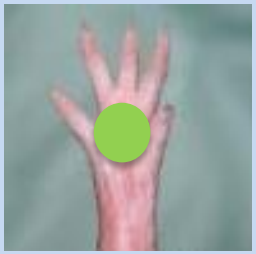
Metformin

- 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

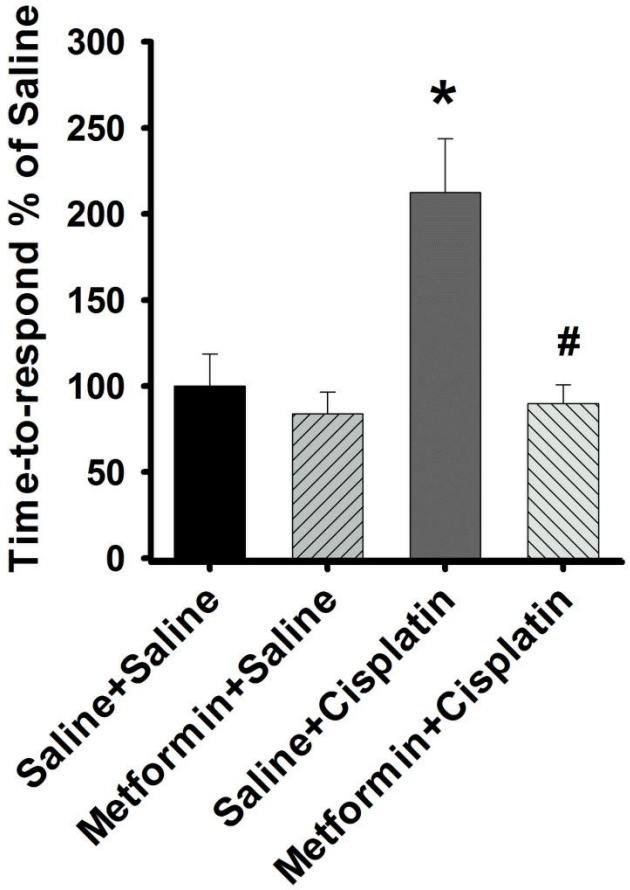
Effect of metformin on cisplatin-induced *numbness*



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

NYTimes.com

- 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

Wefel JS, Schagen SB. Curr. Neurol. Neurosc. Rep. 2012;12:267; Ahles TA, Saykin AJ. Nature Rev. Cancer. 2007;7:192-201;O'Farrell E et al. Curr. Oncol. Rep. 2013;15:260; Simo M et al. Neurosci. Biobehav. Rev. 2013;37:1311; Kesler SR et al. Proc. Natl. Acad. Sci. USA 2013;110:11600

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

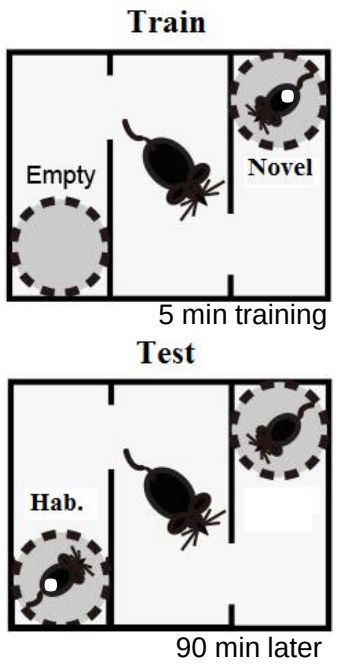
Investigate mechanisms

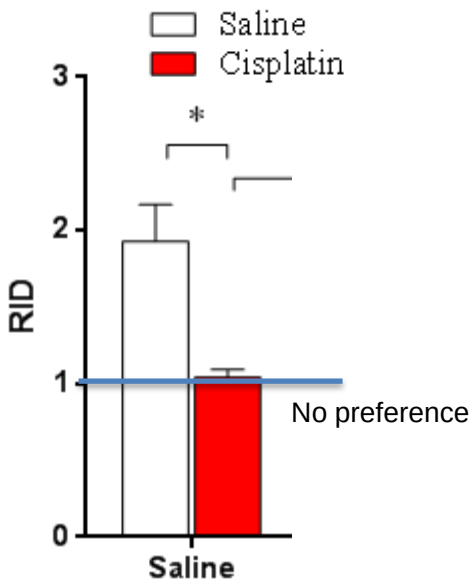
Test potential interventions

Cisplatin-induced chemobrain

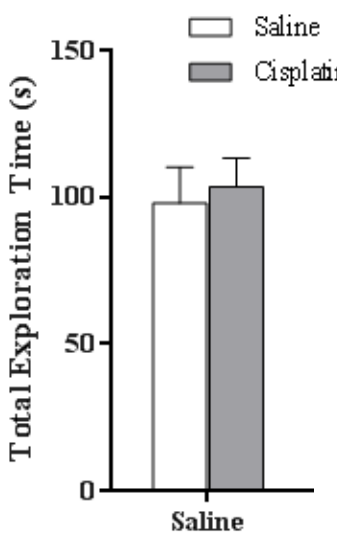
3 Cycles of cisplatin i.p (5 days cisplatin; 2.3 mg/kg, 5 days rest)
Examine cognitive function one week after last treatment

Social Discrimination





Total Exploration time



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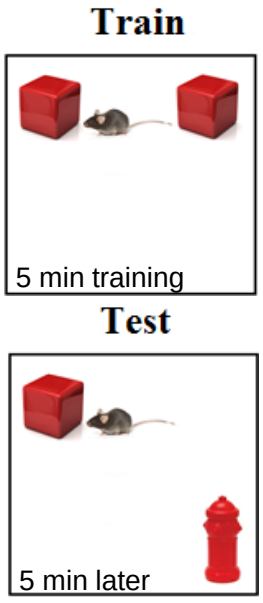
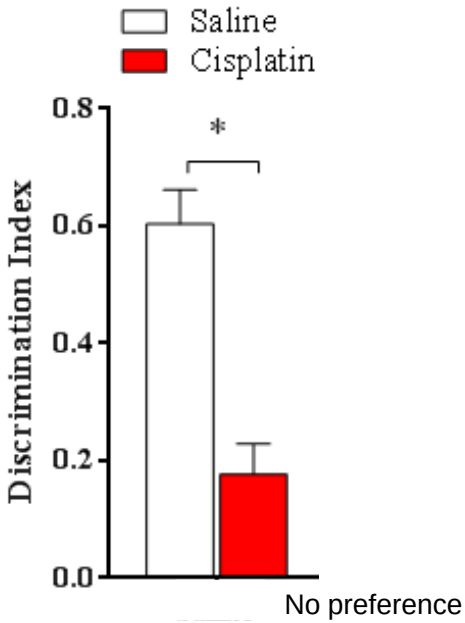
Novel object and Place recognition

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

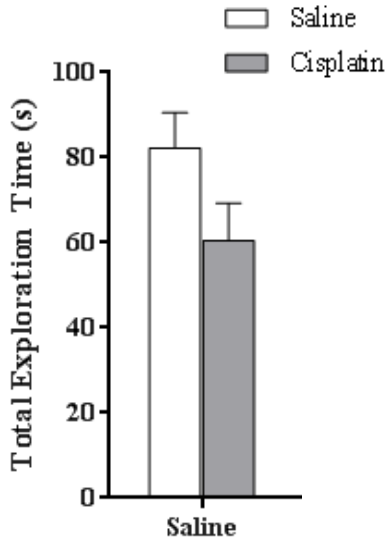
Novel Object and Place Recognition





No preference

Total Exploration time



No relation between total interaction time during training and preference

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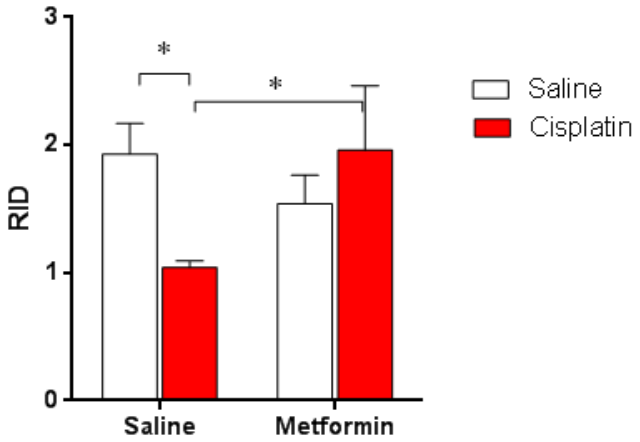
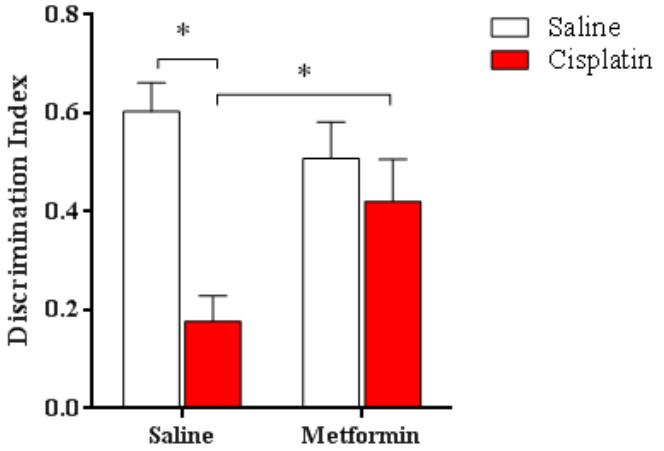
Metformin prevents Chemobrain

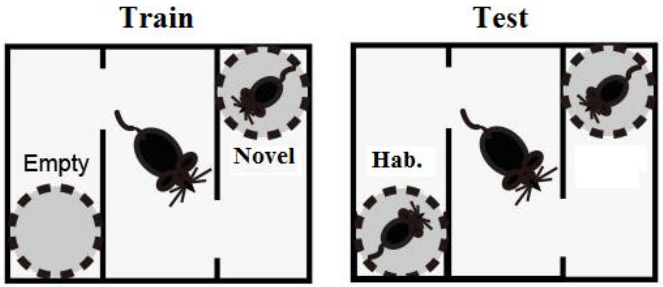
3 Cycles of cisplatin i.p (5 days cisplatin; 2.3 mg/kg +/- metformin, 5 days rest)
Examine cognitive function one week after last treatment

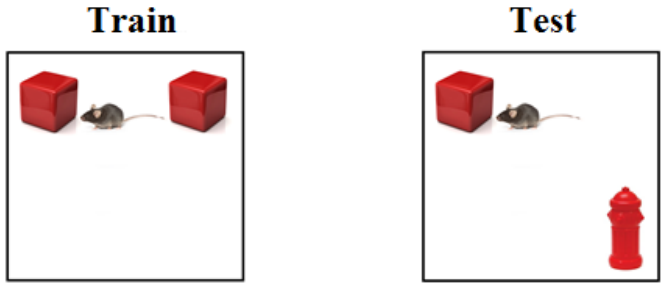
Social Discrimination



Novel Object and Place Recognition







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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

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