Pain and opioids

Pain and Opioids

*NCI Integrative Medicine Course*

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Walter J. Koroshetz, MD
Director, NINDS

DP Mohapatra, PhD
Program Director, NINDS
Opiate history

How did we get here?

- 1805: Friedreich Sertuener isolates morphine from tarry poppy seed juice
  - Physicians believe opium has been tamed
  - Morphine dubbed “God’s own medicine” for long-lasting effects and safety
- 1827: Merck starts commercial manufacture of morphine
- 1843: Dr. Alexander Wood discovers intravenous injection is more powerful and quick
- 1895: Bayer company purifies heroin and used to wean morphine addicts
- 1905: US Congress bans opium
- 1914: US requires doctors prescribing narcotics to register
Treating pain

Balancing act of treating pain

100 million American adults have pain
- 40 million have severe pain
- 25 million report daily pain
- 8 million have pain that interferes with lifestyle

Opioid prescriptions increased through the 1990-2010s

Trends in Annual Opioid Prescribing Rates by Overall and High-Dosage Prescriptions

Source: NIDA, IMS Health, National Prescription Audit, years 1997-2011
Opioid epidemic
Brain regions implicated in pain and reward processing show striking overlap in neuroimaging and electrophysiology studies.

"Nature has placed mankind under the governance of two sovereign masters, Pain and Pleasure" - Jeremy Bentham

Pain and pleasure
Pain versus reward

Shared pathway

Opioid receptor mediates reward and analgesia and other critical functions

NIH Neurological Disorders and Stroke


Pain, 2014 Sep;155(9):1829-35.
Neural circuitry changes
New targets for pain

Advances in pain research: New Targets for Pain

- HSV vector driven expression of analgesic signals in DRG
- Transient receptor potential channels (TRPA1/4)
  - TRPA1 gain of function mutation causes familial episodic pain syndrome
- Voltage activated Ca++ channel blockers
- K+ channels blockers
- Chemokine receptor antagonists
- Tetrahydrobiopterin from GTP release from injured neurons, polymorphisms in BChE enzyme linked to pain vulnerability
- Alpha2 adrenergic agonist
- Bivalent MOR with linked mGluR5 antagonist, CCR5 antagonist, delta OR antagonist,
- Epigenetic mechanisms involved in chronic pain
- microRNA cluster 183
cGRP for migraine

- Calcitonin gene-related peptide (cGRP) levels:
  - rise during spontaneous migraine attacks
  - increased levels in serum in chronic migraine patients
  - decrease in response to triptans in parallel with symptomatic relief
- Kappa Opioid Receptor (KOR) antagonists block increased cGRP
- Anti-cGRP Monoclonal antibodies are in phase 3 clinical trials for migraine prevention
Vagus nerve stimulation

Advances in Pain Research: FDA Approval for Vagus Nerve Stimulation in Headache

gammaCore® Receives FDA Clearance for the Acute Treatment of Pain Associated with Migraine Headache in Adult Patients

First non-invasive vagus nerve stimulation therapy applied at the neck provides new option for Americans living with migrane

FDA Releases gammaCore®, the First Non-Invasive Vagus Nerve Stimulation Therapy Applied at the Neck for Acute Treatment of Pain Associated with Episodic Cluster Headache in Adult Patients
Brain initiative

Translating the BRAIN Initiative to address pain and the opioid crisis

Molecular/Structural Pathology → Circuit Dysfunction → Neuro/Mental/Substance Abuse Functional Disability

First Five Years:
- Emphasize technology development

Second Five Years:
- Emphasize discovery driven science

• One example of BRAIN-funded scientists contributing to understanding of pain as a circuit disorder
• Silencing Basal Lateral Amygdalar (BLA) neurons alleviates pain affective-motivational behaviors without affecting detection of pain stimuli
• Would silencing these BLA neurons in people with chronic pain limit their suffering without affecting their nociceptive sensitivity?

Corder et al., Science, 2019
Neural circuit activity

Tools from the NIH BRAIN Initiative enable precise monitoring and modulation of neural circuit activity

Live cell imaging of GCaMP responses in Nav1.8+ trigeminal ganglion neurons
NIH pain consortium

The NIH Pain Consortium Membership

Mission
To enhance pain research and promote collaboration among researchers across the NIH Institutes and Centers that have programs and activities addressing pain
http://painconsortium.nih.gov/

National Cancer Institute
National Eye Institute
National Institute on Aging
National Institute on Alcohol Abuse and Alcoholism
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Biomedical Imaging and Bioengineering
National Institute of Child Health and Human Development
National Institute on Deafness and Other Communication Disorders
National Institute of Dental and Craniofacial Research
National Institute of Diabetes and Digestive and Kidney Disorders
National Institute on Drug Abuse
National Institute of General Medical Sciences
National Institute of Mental Health

National Institute of Minority Health and Disparities
National Institute of Neurological Disorders and Stroke
National Institute of Nursing Research
National Heart Lung and Blood Institute
National Center for Advancing Translational Science
National Center for Complementary & Integrative Health
John E. Fogarty International Center
Wilmot Grant Magnuson Clinical Center
Office of Science Policy and Analysis
Office of Behavioral and Social Sciences Research
Office of Technology Transfer
Office of Research on Women’s Health
Office of Rare Diseases
Helping end addiction

NIH Helping End Addiction Long-term (HEAL) Initiative

- Mission: scientific solutions to the opioid crisis
- $500M/year Trans-NIH effort
  - Over $945M obligated in FY2019
- 12 NIH Institute and Centers currently leading 26 HEAL research projects
  - Over 20 collaborating Institutes, Centers and Offices
  - From prevention, basic and translational research, clinical trials, to implementation science
- Released 40+ funding announcements in FY2019, issued over 400 awards
HEAL initiative

HEAL Initiative Research Overview

- Pre-Clinical/Translational Research in Pain Management
- Clinical Research in Pain Management
- Novel Medication Options
- Enhanced Outcomes for Affected Newborns
- New Prevention & Treatment Strategies
- Translating Research into Practice

Enhancing Pain Management

Improving Treatments for Opioid Misuse and Addiction
Projects

Pipeline of HEAL Pain Projects

- Discovery
  - Acute to Chronic Pain Signatures
  - Discover and Validate Novel Targets for Safe and Effective Pain Treatment
  - Preclinical Screening Platforms + Novel Drug Development
  - Translating Discoveries into Effective Devices for Pain Treatment
- Preclinical Development
- Clinical Trials
- Implementation/Dissemination
- Back Pain Research Consortium
  - Hemodialysis Pain Management
  - Pain Effectiveness Research Network
  - Pragmatic and Implementation Studies for the Management of Pain
- Data & Asset Sharing Partnership
- Early Phase Pain Investigation Clinical Network
To The Neurobiology of Pain

DP Mohapatra, PhD
Program Director, NINDS
Human pain
What is pain?
Why do I have pain?

A protective mechanism / alarm system in our body to warn about infection/injury and pathological conditions.
Nociception versus pain

**Nociception** vs **Pain**

**Nociception** - The activation of nociceptors by noxious stimuli. *Nociception may or may not be accompanied by the perception of pain.*

**Nociceptor:** Sensory nerve/neuron that responds to damaging or potentially damaging stimuli by sending electrochemical signals to the spinal cord and brain.

**Pain** - The perception of actual or impending tissue damage. In certain pathological conditions, Pain may not be associated with nociception.
Classes of Pain

Nociceptive Pain
Pain originating as a result of activation of nociceptors in response to tissue injury

Neuropathic Pain
Pain originating due to a lesion or disease of the somatosensory, sympathetic or central nervous system

Nociplastic Pain (new class – 2017)
Pain originating from altered nociception despite no clear evidence of
- actual or threatened tissue damage causing activation of peripheral nociceptors or
- disease or lesion of the somatosensory system causing the pain
Cancer cases

Incidences of Major Cancers in the US Facts & Figures – New Cases Predicted for 2019

<table>
<thead>
<tr>
<th>Males</th>
<th>Females</th>
</tr>
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<tbody>
<tr>
<td>Prostate</td>
<td>Breast</td>
</tr>
<tr>
<td>174,650</td>
<td>268,600</td>
</tr>
<tr>
<td>22%</td>
<td>30%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>116,440</td>
<td>111,710</td>
</tr>
<tr>
<td>14%</td>
<td>12%</td>
</tr>
<tr>
<td>Colo-rectum</td>
<td>Colo-rectum</td>
</tr>
<tr>
<td>78,500</td>
<td>67,100</td>
</tr>
<tr>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Uterine corpus and cervix</td>
</tr>
<tr>
<td>61,700</td>
<td>74,050</td>
</tr>
<tr>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>Thyroid</td>
</tr>
<tr>
<td>57,220</td>
<td>37,810</td>
</tr>
<tr>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Non-Hodgkin lymphoma</td>
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<tr>
<td>41,090</td>
<td>33,110</td>
</tr>
<tr>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>Pancreas</td>
</tr>
<tr>
<td>44,120</td>
<td>26,640</td>
</tr>
<tr>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Oral Cavity &amp; pharynx</td>
<td>Leukemia</td>
</tr>
<tr>
<td>38,140</td>
<td>25,860</td>
</tr>
<tr>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Kidney &amp; renal pelvis</td>
</tr>
<tr>
<td>35,920</td>
<td>29,700</td>
</tr>
<tr>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Liver &amp; hepatic bile duct</td>
<td>Ovary</td>
</tr>
<tr>
<td>29,480</td>
<td>22,530</td>
</tr>
<tr>
<td>3-4%</td>
<td>2-3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Bone &amp; joints</td>
</tr>
<tr>
<td>29,340</td>
<td>970</td>
</tr>
<tr>
<td>3-4%</td>
<td>0.11%</td>
</tr>
<tr>
<td>Bone &amp; joints</td>
<td></td>
</tr>
<tr>
<td>2,030</td>
<td></td>
</tr>
<tr>
<td>0.21%</td>
<td></td>
</tr>
</tbody>
</table>

All Sites  870,870  100%

All Sites  881,480  100%

Metastatic bone cancers account for >97% of all bone cancers

The Problem(s) of Chronic Pain

- Over 100 million Americans suffer from chronic pain

66% of patients who have advanced metastatic or terminal cancer experience pain

6-8 out of 10 patients with advanced cancers express major fear of dying due to excruciating/unbearable PAIN

- Associated with multiple chemoRx
  - Platinum drugs (oxaliplatin, cisplatin)
  - Taxanes (paclitaxel, docetaxel)
  - Proteasome inhibitors (bortezomib)
  - Plant alkaloids (vincristine); IMDs (thalidomide)

- Mainly lead to peripheral neuropathy and associated chronic pain

- Annual financial impact of chronic pain in the US
  - $560-635 billion

# Types of cancer pain

## Types of Cancer Pain

<table>
<thead>
<tr>
<th>TYPE</th>
<th>NEURAL MECHANISM</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nociceptive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral</td>
<td>Stimulation of pain receptors on normal sensory nerve endings</td>
<td>Hepatic capsule stretch</td>
</tr>
<tr>
<td>Somatic</td>
<td></td>
<td>Bone metastases</td>
</tr>
<tr>
<td>Nerve compression</td>
<td>Stimulation of nervorum</td>
<td>Sciatica due to vertebral metastasis with compression of L4, L5 or S1 nerve root</td>
</tr>
<tr>
<td>Peripheral</td>
<td>Lowered firing threshold of sensory nerves (deafferentiation pain)</td>
<td>Tumour infiltration or destruction of brachial plexus</td>
</tr>
<tr>
<td>Central</td>
<td>Injury to central nervous system</td>
<td>Spinal cord compression by tumour</td>
</tr>
<tr>
<td>Mixed</td>
<td>Peripheral and central injury</td>
<td>Central sensitization due to unrelieved peripheral neuropathic pain</td>
</tr>
<tr>
<td>Sympathetically maintained</td>
<td>Dysfunction of sympathetic system</td>
<td>Chronic regional pain syndrome following fracture or other trauma</td>
</tr>
</tbody>
</table>

Source: WHO guidelines for the management of cancer pain in adults and adolescents (2019)
Nociceptive pain

Nociceptive Pain

- Postoperative pain
- Arthritis
- Sickle cell disease
- Sports/exercise injuries
- Inflammatory bowel disease
- Primary & metastatic cancers

Inflammatory pain

Inflammatory Pain

- Histamine
- Serotonin
- Bradykinin
- Prostaglandins
- ATP
- H^+
- Nerve growth factor
- TNFα
- Endothelins
- Interleukins

Pain treatment options:
- NSAIDs
- Opioids

Modified from Scholz and Woolf, 2002, Nature Neuroscience
Neuropathic pain

Neuropathic Pain

- Trigeminal neuralgia
- Central post-stroke pain
- Distal polyneuropathy (e.g., Diabetic, HIV, CIPN)
- Spinal tumor-induced nerve compression
- Spinal cord injury-induced pain
- Postherpetic neuralgia / Shingles
- Neuropathic low back pain

Pain treatment options:
- Tricyclic antidepressants
- Anticonvulsants
- Na⁺ channel blockers
- NMDA receptor antagonists
- Opioids

Modified from Scholz and Woolf, 2002, Nature Neuroscience
Nociplastic pain

Nociplastic Pain

- Fibromyalgia
- Complex regional pain syndrome (CRPS)
- Pain in irritable bowel syndrome
- Chronic low back pain
- Bladder pain syndrome
- Spinal tumor-induced nerve compression
Sensory subtypes

Functionally distinct sensory subtypes in DRG

Musculoskeletal sensory nerves

Musculoskeletal Sensory Nerves and Circuit
Visceral sensory nerves

Visceral Sensory Nerves and Circuit

From: Neuroscience Online Text Book, UTHSCCH
Classification of sensory fibers

- **A fibers** – myelinated (multiple extent) → High conduction velocity.
- **C fibers** – unmyelinated → low conduction velocity.
Nociceptor fiber types

Nociceptor Fiber Types
Classes of nociceptors

**Classes of Nociceptors**

**Thermal Nociceptors**
- Respond to extreme temperatures (>43°C or <5°C)
- Thin, sparsely myelinated Aδ fibers that conduct at 5-30m/s

**Mechanical Nociceptors**
- Respond to intense pressure
- Also Aδ fibers

**Polymodal Nociceptors**
- These fibers respond to extreme temperatures, pressure, and noxious chemicals
- Aδ and C fibers that conduct at ~1m/sec

<table>
<thead>
<tr>
<th>Modality</th>
<th>Sub Modality</th>
<th>Sensory Fiber</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temp.</td>
<td>Warm/Hot</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Cool/Cold</td>
<td>Aδ/C</td>
</tr>
<tr>
<td>Pain</td>
<td>Sharp cutting pain</td>
<td>Aδ</td>
</tr>
<tr>
<td></td>
<td>Dull burning pain</td>
<td>C, Aδ(??)</td>
</tr>
<tr>
<td></td>
<td>Deep aching pain</td>
<td>C, Aδ(??)</td>
</tr>
<tr>
<td></td>
<td>Chemical pain (acid)</td>
<td>C</td>
</tr>
</tbody>
</table>
Receptors

Contribution of Specific Receptors in Nociceptor Excitation

Physiological Initiators
- Activate receptors or ion channels (sensory transducers) that are Primary Transducers
- Depolarize the membrane potential, which generates action potential by activating voltage-gated ion channels that are Secondary Transducers (or signal propagators)

Modified from Marchand et al., Nat Rev Neurosci (2005)
Sensory TRP channels

Sensory TRP Channels: Major Nociceptive Receptors

(Modified from: Jacobs, J., Shepherd, G. & Edgell, L. Progress in Molecular Biology and Translational Science (2019).)
Noxious stimuli

Detection of Noxious Stimuli → Action Potential Generation

a. Primary Transducers
   b. Sodium channels
   b-c. Calcium channels
   c. Potassium channels

- Repolarization begins
- Threshold, action potential begins
- Ions due to stimulus activation of channels
Nociceptors

Distribution of Receptors/Ion Channels in the Peripheral and Central Axons of Nociceptors

Nociceptive inputs

Nociceptor Inputs to the Spinal Cord Dorsal Horn

Adapted from Kandel, Schwartz, and Jessell (2012)
Nociceptive signal transmission

Nociceptive Signal Transmission in the Spinal Cord Dorsal Horn

Adapted from Univ. Wisconsin Pain Management Project
Nociceptive information

Multiple areas in the brainstem, mid- and fore-brain process nociceptive information

Descending pain modulatory pathways
- Facilitatory
- Inhibitory

Endogenous opioids (endorphins) - analgesic

Adapted from Zhou (2008), Trend Neurosci
Pain measurement

How Pain is Measured or Assessed?

0-10 SCALE OF PAIN SEVERITY

<table>
<thead>
<tr>
<th>Severity</th>
<th>Description of Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Unable to Move</td>
</tr>
<tr>
<td>9</td>
<td>Severe</td>
</tr>
<tr>
<td>8</td>
<td>Intense</td>
</tr>
<tr>
<td>7</td>
<td>Unmanageable</td>
</tr>
<tr>
<td>6</td>
<td>Distressing</td>
</tr>
<tr>
<td>5</td>
<td>Distracting</td>
</tr>
<tr>
<td>4</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Uncomfortable</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
</tr>
<tr>
<td>1</td>
<td>Minimal</td>
</tr>
<tr>
<td>0</td>
<td>No Pain</td>
</tr>
</tbody>
</table>

Universal Pain Assessment Tool

This pain assessment tool is intended to help patient care providers assess pain according to individual patient needs. Explain and use this scale for patient self-assessment. Use the faces or behavioral observations to interpret experienced pain when patient cannot communicate his/her pain intensity.
Sensory testing

Quantitative Sensory Testing for Pain

http://www.youtube.com/watch?v=fSrecWPY132c
Mechanical nociception

Mechanical Nociception

A. Probe with blunt object

B. Pinprick

C. Pinch with serrated forceps

Adapted from Kandel, Schwartz, and Jessell (2012)
Pain testing

Quantitative Sensory Testing for Pain
Quantitative testing

Quantitative Sensory Testing for Pain

https://www.youtube.com/watch?v=ArulkS2D0Y
Animal pain

Assessing Pain in Animals
Stimulus-response

Nociceptor Sensitization Shift Pain Stimulus-Response

Worse Possible Pain

Very Severe

Severe

Moderate

Mild

No Pain

Pathological

Physiological

No Pain

Low

Stimulus Intensity

High

Alloynxia

Hyperalgesia

Stimulus Response

Worse Possible Pain

Physiological

Noxious Stimulus
Peripheral nociceptor

Peripheral Nociceptor Sensitization

Purves et al., (2013)
Nociceptor sensitization

Peripheral Nociceceptor Sensitization

Constitutive activation of TRPV1, ASICs and TRPA1 channels

Central sensitization

Primary afferents innervating the site of secondary hyperalgesia are not sensitized in response to inflammation. Thus, there must be some change in the spinal cord or brain that mediates secondary hyperalgesia/allodynia. These changes are known as **Central Sensitization**

From work by LaMotte and others
Central sensitization

Inflammation-Induced Central Sensitization

Central sensitization serves as an amplifier of nociceptive input to the CNS → pain out of proportion to input intensity

Modified from Iadarola and Caudle, 1997, Science
Spinal cord

Central Sensitization in the Spinal Cord: Anatomical Mechanisms

Changes in synaptic connectivity

Loss of inhibition

Pain

Modified from Scholz and Woolf, 2002, Nature Neuroscience
Central and peripheral sensitization

Peripheral & Central Sensitization

Brain
- Inflammatory mediator release
- Glial cell activation
- Cortical remodeling
- ↑ descending facilitation
- ↓ descending inhibition

Spinal Cord
- Inflammatory mediator release
- Glial cell activation
- ↑ synaptic efficacy
- ↓ inhibitory tone

Dorsal Root Ganglia
- ↑ excitability
- Altered gene expression
- Ectopic firing

Peripheral fibers
- ↑ nociceptor sensitivity
- Ectopic firing
- Altered signal transmission
Pain modulation

Descending Pain Modulation

Anterior cingulate gyrus
Periaqueductal gray
Rostral ventromedial medulla
Dorsal horn

Dopamine
Norepinephrine
Serotonin
A11
A5
Monoamine pathways

Monoamine Pathways in Descending Pain Modulation

Monoaminergic pathways

Nociceptor afferent

SERT

NET

α₃A

D₂

5-HT₁₆

D₁

D₂

5-HT₁₅

Ca²⁺

Norepinephrine

Dopamine

Serootonin

Glutamate Substance P

GABA

Spinothalamic neuron

Local inhibitory neuron

α₁
## Pharmacological Management of Cancer Pain

<table>
<thead>
<tr>
<th>MEDICINE GROUP</th>
<th>MEDICINE CLASS</th>
<th>EXAMPLE MEDICINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-opioids</td>
<td>Paracetamol</td>
<td>Paracetamol oral tablets and liquid. Rectal suppositories, injectable</td>
</tr>
<tr>
<td></td>
<td>NSAIDs</td>
<td>Ibuprofen oral tablets and liquid, Ketorolac oral tablets and injectable, Acetylsalicylic acid oral tablets and rectal suppositories</td>
</tr>
<tr>
<td>Opioids</td>
<td>Weak opioids</td>
<td>Codeine oral tablets and liquid and injectable</td>
</tr>
<tr>
<td></td>
<td>Strong opioids</td>
<td>Morphine oral tablet and liquid and injectable, Hydromorphone oral tablets and liquid and injectable, Oxycodone oral tablets and liquid, Fentanyl injectable, transdermal patch, transmucosal lozenge, Methadone oral tablet, liquid, injectable</td>
</tr>
<tr>
<td>Adjuvants</td>
<td>Steroids</td>
<td>Dexamethasone oral tablet and injectable, Methylprednisolone oral tablets and injectable, Prednisolone oral tablets</td>
</tr>
<tr>
<td></td>
<td>Antidepressants</td>
<td>Amitriptyline oral tablets, Venlafaxine oral tablets</td>
</tr>
<tr>
<td></td>
<td>Anticonvulsants</td>
<td>Carbamazepine oral tablets and injectable</td>
</tr>
<tr>
<td></td>
<td>Bisphosphonates</td>
<td>Zoledronate injectable</td>
</tr>
</tbody>
</table>

Source: WHO guidelines for the management of cancer pain in adults and adolescents (2010)
Cancer pain management

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Psychological      | • Hypnosis
                     • Relaxation
                     • Cognitive Behavioral Therapy (CBT) |
| Physical           | • Acupuncture
                     • Transcutaneous Electrical Nerve Stimulation (TENS)
                     • Healing touch and massage
                     • Yoga
                     • Occupational therapy |
| Clinical Process   | • Specific Pain Assessment
                     • Physical Advice and Communication
                     • Education (including family) |
Other roles

Other Roles of Nociceptive Sensory System in Cancers

- Perineural Invasion (PNI) High prevalence in prostate and pancreatic cancers
- Cancer cells penetrate inside perineurium and migrate to sympathetic, nodose and dorsal root ganglia, and spinal cord
- Utilize nociceptive sensory neurons for tumor growth, aggression and metastasis
- Ablation of nociceptive afferents in mice \(\rightarrow\) significantly reduced pancreatic tumor growth, and prolonged survival (Saloman et al 2016, PNAS)
Cancer pain

Cancer Pain: Controversies and Gaps in Knowledge

- Chronic opioid use correlated with cancer aggressiveness (in certain cancers) – only few studies

- In cellular and preclinical studies opioids shown to enhance cancer cell proliferation, tumor growth & metastasis

- Mechanisms (clinically-relevant) underlying peripheral & central pain sensitization and central modulation in primary and metastatic cancers
  - A lack in relevant animal models
  - Difficulty in assessing ongoing cancer-related pain in animals

- Neuropathies associated with cancer chemotherapy
  - A lack of relevant animal models of CIPN
  - Difficulties in studying heterogeneous nature of CIPN