Review

Neurobiology of Cancer Pain: A Narrative Review

Giustino Varrassi , Matteo Luigi Giuseppe Leoni * , Giacomo Farì , Rocìo Guillen

Posted Date: 5 September 2025

doi: 10.20944/preprints202509.0550.v1

Keywords: neurobilogy; cancer; pain

Review

Neurobiology of Cancer Pain: A Narrative Review

Giustino Varrassi [1], Matteo Luigi Giuseppe Leoni [2,*], Giacomo Farì [3] and Rocìo Guillen [4]

[1] Fondazione Paolo Procacci, Roma, Italy
[2] University Sapienza, Roma, Italy
[3] University of Salento, Lecce, Italy
[4] Institute of Cancer, Mexico City, Italy
* Correspondence: matteolg.leoni@gmail.com

Abstract

Cancer pain is a multidimensional phenomenon arising from the convergence of nociceptive, neuropathic, and neuroimmune mechanisms that vary across tumor type, anatomical site, disease stage, and prior anticancer treatments. Recent advances in "cancer neuroscience" have reframed pain as both a symptom and a dynamic outcome of reciprocal tumor–nerve–immune interactions, in which malignant, stromal, and immune cells remodel nociceptive circuits at peripheral and central levels. This narrative review, conducted in accordance with SANRA criteria, synthesizes current mechanistic insights into the neurobiology of cancer pain. At the peripheral level, tumor-derived mediators such as prostaglandins, cytokines, chemokines, glutamate, and endothelin-1 drive nociceptor sensitization via G-protein–coupled and tyrosine kinase pathways. In bone metastases, osteoclast-mediated resorption generates an acidic microenvironment that activates acid-sensing ion channels and transient receptor potential (TRP) channels, linking skeletal destruction with movement-evoked pain. Pathological nerve remodeling and perineural invasion further contribute to neuropathic components and adverse oncological outcomes. Treatment-induced syndromes, notably chemotherapy-induced peripheral neuropathy, result from axonal injury, mitochondrial dysfunction, and neuroinflammation. At the central level, persistent afferent input induces glial activation and chemokine signaling, amplifying synaptic transmission and promoting central sensitization. Emerging evidence also highlights epigenetic regulation, noncoding RNAs, and tumor–immune–neural crosstalk as potential therapeutic targets. Collectively, these findings position cancer pain as a disorder of aberrant tumor–nerve–immune signaling. Effective management requires precision strategies integrating mechanism-guided pharmacology, neuromodulation, and supportive care. This review emphasizes the need for translational research to bridge mechanistic discoveries with personalized, multimodal interventions in oncology.

Keywords: neurobilogy; cancer; pain

Introduction

Cancer pain is a heterogeneous, multidimensional experience driven by converging nociceptive, neuropathic, and neuroimmune mechanisms that vary by tumor type, anatomical site (e.g., bone vs. viscera), disease stage, and prior anticancer treatments. Recent "cancer neuroscience" work has reframed pain as both a symptom and a dynamic product of reciprocal tumor–nerve–immune interactions, in which malignant, stromal, and immune cells remodel peripheral and central nociceptive circuits [1,2]. Appreciating these interactions clarifies why many patients manifest mixed pain phenotypes and why mechanism-guided therapy is needed beyond simple escalation of opioids.

Fundamental insights into cancer pain neurobiology come from seminal reviews demonstrating how tumors provoke nociceptive sensitization via secretion of algogenic mediators (e.g., protons, neurotrophins, cytokines) and by disrupting nerve function, a view grounded in both animal models and clinical observations [3,4]. In bone metastases, tumoral activity stimulates osteoclast-mediated

 doi:10.20944/preprints202509.0550.v1

bone resorption, inducing an acidic microenvironment that activates acid-sensing ion channels and TRPV receptors on peripheral sensory fibers, thereby linking structural destruction with severe, often movement-related pain [5]. Additionally, chemotherapy-induced peripheral neuropathy (CIPN), a common iatrogenic pain phenomenon, derives from cumulative damage to dorsal root ganglia and peripheral axons via microtubule disruption, mitochondrial dysfunction, ion channel dysregulation, and neuroinflammation [6]. This may be particularly disturbing at oral level, where it is very frequent [7].

The neurobiology of cancer pain involves unique features not typically observed in other chronic pain conditions. Tumors secrete neurotrophic factors, cytokines, chemokines, and metabolites such as ATP, glutamate, and protons, which directly excite or sensitize peripheral nociceptors [3,5]. Bone metastases generate a distinctive acidic microenvironment through osteoclast-mediated resorption, activating acid-sensing ion channels and transient receptor potential (TRP) channels on sensory neurons, thereby coupling skeletal destruction with pain [6]. Beyond peripheral mechanisms, cancers promote pathological nerve sprouting and perineural invasion, which contribute to severe neuropathic components of pain and have been linked to disease progression [8].

At the central level, spinal microglia and astrocytes become chronically activated by persistent afferent input, releasing proinflammatory cytokines and chemokines that amplify synaptic transmission and diminish inhibitory control, ultimately driving central sensitization [9,10]. In parallel, supraspinal circuits involved in affect, cognition, and descending modulation undergo maladaptive plasticity, contributing to the emotional and cognitive burden of cancer pain [11].

Importantly, as already mentioned, pain in oncology is not only tumor-driven but also treatment-induced. Chemotherapy, radiotherapy, and surgery can damage peripheral and central neural structures, producing long-lasting neuropathic syndromes such as chemotherapy-induced peripheral neuropathy (CIPN), which substantially affect survivorship [12]. Collectively, these insights highlight cancer pain as a disorder of aberrant tumor–nerve–immune crosstalk, where effective management requires integrating pathophysiological understanding into personalized, multimodal strategies.

The purpose of this narrative review is to synthesize and critically appraise emerging insights into the neurobiology of cancer pain, highlighting how tumor–nerve–immune interactions contribute to its complex and heterogeneous clinical presentation. By integrating mechanistic evidence across peripheral, central, and treatment-induced pathways, this work aims to support the development of more precise, mechanism-guided strategies for effective and personalized pain management in oncology.

Methods

This research was designed as a narrative review, developed in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA), which provides structured criteria to ensure methodological rigor, transparency, and coherence in narrative synthesis [13]. The review adhered to the six SANRA domains, including justification of the review's importance, clarity of aims, appropriate literature search, referencing, scientific reasoning, and appropriate presentation of data.

Literature Search Strategy

A comprehensive, non-systematic search of the literature was conducted between June and August 2025. Major electronic databases, including PubMed/MEDLINE, Scopus, and Web of Science, were queried using a combination of controlled vocabulary and free-text terms. Search strings included: *"cancer pain," "neurobiology," "tumor–nerve interactions," "neuroimmune mechanisms," "bone metastasis pain," "perineural invasion,"* and *"chemotherapy-induced peripheral neuropathy."* Boolean operators and filters were applied to refine results. Only articles published in peer-reviewed journals, in English, and between 2000 and 2025 were considered to ensure both foundational knowledge and the inclusion of contemporary developments in cancer neuroscience.

 doi:10.20944/preprints202509.0550.v1

Eligibility Criteria

Included studies encompassed original experimental research (both preclinical and clinical), systematic and narrative reviews, and clinical guidelines relevant to the neurobiology of cancer pain. Priority was given to publications addressing mechanistic pathways at peripheral, central, or treatment-related levels. Exclusion criteria were articles not directly related to cancer pain mechanisms (e.g., general oncology without a pain component), case reports with insufficient mechanistic focus, and non-peer-reviewed sources.

Data Extraction and Synthesis

Relevant data from eligible studies were extracted narratively, focusing on molecular mediators, cellular interactions, and neuroimmune crosstalk underlying cancer pain. Evidence was organized across major domains: peripheral mechanisms, central sensitization, tumor–nerve–immune crosstalk, translational implications, special context and emerging directions. Reference lists of included articles were also screened for additional relevant sources. No quantitative synthesis (meta-analysis) was attempted, as this work aimed to provide a conceptual integration rather than statistical aggregation.

Quality Assurance

To maintain methodological soundness, the selection of literature and synthesis process were independently cross-checked against SANRA recommendations. Emphasis was placed on scientific reasoning, critical analysis, and balanced reporting, while avoiding selective citation or overinterpretation. Table 1 is better illustrating the used criteria.

Table 1. Compliance of the present review with the SANRA (Scale for the Assessment of Narrative Review Articles) domains.

SANRA Domain	Requirement	Compliance in this Review
1. Justification of the article's importance for the readership	The topic should be relevant and timely.	Cancer pain remains a highly prevalent, multidimensional burden; understanding its neurobiology is crucial for improving mechanism-based treatments.
2. Statement of concrete aims or formulation of questions	Clear articulation of the review's purpose.	Aim explicitly stated: to synthesize current knowledge on neurobiology of cancer pain, focusing on tumor–nerve–immune crosstalk and treatment implications.
3. Description of the literature search	Transparent description of sources and search approach.	Literature searched in PubMed/MEDLINE, Scopus, and Web of Science (2000–2025) using predefined terms related to cancer pain mechanisms; inclusion/exclusion criteria specified.

 doi:10.20944/preprints202509.0550.v1

SANRA Domain	Requirement	Compliance in this Review
4. Referencing	Appropriate, comprehensive, and up-to-date references.	Peer-reviewed primary research, systematic reviews, and guidelines were cited; preference given to high-impact and recent publications.
5. Scientific reasoning	Logical organization and critical interpretation of findings.	Evidence structured by domains (peripheral, central, treatment-related mechanisms); balanced interpretation avoiding overgeneralization.
6. Appropriate presentation of data	Clear structure and synthesis of material.	Findings presented in narrative form, supplemented by structured subheadings; proposal to include schematic figures and summary tables for clarity.

Results

Peripheral Mechanisms

Tumor- and Stroma-Derived Mediators

Malignant cells secrete mediators that directly excite or sensitize primary afferents. Prostaglandins (COX-2/PGE_2), cytokines (IL-1β, TNF-α, IL-6), chemokines (e.g., CCL2), and endothelin-1 lower nociceptor thresholds via G-protein–coupled and tyrosine kinase pathways (including NGF–TrkA), enhancing transducer channel activity and sodium current density [14,15]. In oral and melanoma models, endothelin-1 acting at ETA receptors is a potent peripheral algogen; ETA antagonism can produce morphine-scale antinociception in vivo [16]. Tumor glutamate export through the cystine/glutamate antiporter xCT (SLC7A11) increases extracellular glutamate in tumor beds (including bone), activating peripheral receptors and contributing to ongoing pain; inhibiting xCT with sulfasalazine attenuates pain behaviors in preclinical bone metastasis models [17].

Ion Channels and Nociceptor Sensitization

A hallmark of cancer pain is up-regulated activity in TRP, purinergic, and acid-sensing channels. TRPV1 and TRPA1 are consistently implicated across soft-tissue and bone models; pharmacological blockade or defunctionalization reduces hyperalgesia in animals, and clinical translation of TRPV1-targeting strategies (e.g., resiniferatoxin) is underway. P2X3/P2X2/3 receptors mediate ATP-driven signaling from the tumor microenvironment and bone; selective antagonism or receptor silencing reduces cancer-induced bone pain (CIBP) in animals. [18,19] Tumor- or osteoclast-generated acidosis activates ASIC3 and TRPV1 on bone-innervating afferents, linking osteolysis to spontaneous and movement-evoked pain [20–22].

Nerve Remodeling, Perineural Invasion, and Neurotropism

 doi:10.20944/preprints202509.0550.v1

Cancers foster perineural invasion (PNI) and pathologic nerve sprouting (sensory and sympathetic), driven in part by NGF and other neurotrophic cues [23]. PNI is prevalent in pancreatic and head-and-neck cancers, correlates with severe neuropathic pain, and portends adverse outcomes; mechanistically, cancer–nerve crosstalk (e.g., HGF/c-MET→mTOR→NGF signaling) promotes neuritogenesis and tumor infiltration of nerve sheaths [24,25].

Bone Cancer Pain: A Distinct Microenvironment

Bone is the commonest site of metastatic cancer pain [5,26]. The "vicious cycle" of tumor–bone interaction includes osteoclast-mediated acidification (protons, lactate), release of ATP and growth factors, and exuberant NGF-dependent sprouting of nociceptors [21]. These changes recruit and sensitize bone afferents through ASIC3, TRPV1, and P2X3, driving background pain and movement-evoked flares [27]. Reviews synthesize robust preclinical evidence and the translational signal that targeting osteoclasts (bisphosphonates, denosumab) reduces skeletal events and pain [21,28,29].

Treatment-Induced Neurotoxicity and Pain

Chemotherapy-induced peripheral neuropathy (CIPN), common with platinums, taxanes, vinca alkaloids, and bortezomib, results from combined axonal transport failure, mitochondrial dysfunction, DNA adducts, ion channel remodeling, and neuroinflammation within dorsal root ganglia (DRG) and peripheral nerves. Although mechanistic details differ by agent (e.g., microtubule stabilization with taxanes, proteasome inhibition with bortezomib), the convergent phenotype is distal sensory neuropathy with allodynia and burning pain; duloxetine remains the only guideline-supported analgesic for painful CIPN [30,31].

Central Sensitization

Spinal Neuroinflammation and Disinhibition

Peripheral input from tumor or treatment injury engages microglia and astrocytes in the dorsal horn [32]. Cancer-related models demonstrate hippocampal and spinal cord activation of p38 MAPK in microglia, increased glial cytokines, and chemokine signaling (e.g., CX3CL1/CX3CR1, CCL2/CCR2) that potentiate synaptic transmission and weaken inhibitory control, canonical features of central sensitization. These pathways are consistent with broader neuropathic pain biology and have been directly implicated in CIBP [33,34].

Descending Modulation and Network-Level Changes

Functional alterations in descending inhibitory/excitatory controls and cortical–subcortical circuits (including limbic regions) likely contribute to the affective–cognitive burden of cancer pain and to opioid responsiveness. Although direct cancer-specific imaging evidence remains limited, convergent neuropathic literature and emerging neuromodulation studies suggest supraspinal adaptations relevant to spinal cord stimulation (SCS) targeting [35].

Tumor–Nerve-Immune Crosstalk

Bidirectional signaling between nociceptors, immune cells, and tumor cells is increasingly recognized. Nociceptors can shape tumor progression and immune infiltration in the microenvironment, while tumor-associated immune cells release mediators that sensitize afferents (e.g., IL-6, IL-1β, CCL2) [36]. Recent publication even suggests nociceptor-dependent regulation of myeloid-derived suppressor cells, supporting an integrated model in which analgesic strategies may modify disease biology [2].

Translational Implications

 doi:10.20944/preprints202509.0550.v1

Advances in mechanism-guided pharmacology have expanded therapeutic strategies for cancer-induced bone pain (CIBP). Within the bone microenvironment, anti-resorptive agents play a central role in reducing skeletal-related events (SREs) and alleviating pain. Denosumab has demonstrated superiority over zoledronic acid in delaying the onset of SREs, although both agents remain widely employed in clinical practice, with careful consideration of dental and renal safety precautions. Radiotherapy continues to represent a highly effective modality for painful bone metastases, with both single 8-Gy fractions and short-course regimens providing robust analgesic benefit [29,37].

At the level of peripheral sensitization, several molecular targets have gained prominence. The endothelin axis, particularly ETA receptor antagonism, has emerged as a rational strategy in tumors overexpressing endothelin-1, with preclinical studies showing antinociception comparable to high-dose morphine [16]. Similarly, transient receptor potential (TRP) channels offer therapeutic possibilities, exemplified by resiniferatoxin (RTX), which induces defunctionalization of TRPV1-positive afferents. Translation from companion-dog bone cancer models to first-in-human trials has demonstrated meaningful reductions in pain and opioid use with an acceptable safety profile [38,39]. In addition, purinergic signaling through P2X3 and P2X2/3 receptors has been implicated in CIBP behaviors, with ongoing clinical development in non-cancer conditions suggesting future applicability to oncologic pain [20].

Finally, central neuroinflammatory pathways, particularly chemokine signaling via CX3CL1/CX3CR1 and CCL2/CCR2, alongside microglial p38 MAPK activation, have been strongly validated in preclinical models of neuropathic and bone cancer pain. However, the lack of clinically viable inhibitors capable of penetrating the central nervous system remains a major translational challenge [34].

Neuromodulation and Interventional Approaches

For carefully selected patients with refractory mixed pain, spinal cord stimulation may reduce pain intensity and opioid requirements; mechanistic advances point to both spinal and supraspinal actions [40,41]. Intrathecal drug delivery and sympathetic or splanchnic blocks remain essential for visceral cancer pain syndromes [42].

Special Contexts

Pancreatic and Head-and-Neck Cancers

Severe neuropathic pain often reflects dense PNI and neural remodeling. The HGF/c-MET→mTOR→NGF axis has been implicated in promoting PNI and sensitization; strategies that disrupt this loop may achieve dual analgesic and antitumor benefit [25].

Chemotherapy-Induced Peripheral Neuropathy

Mechanistic heterogeneity argues for agent-specific prevention and treatment trials (e.g., mitochondrial stabilizers for platinums; microtubule-targeted interventions for taxanes). Exercise and behavioral programs show supportive evidence in mitigating symptom burden, but high-quality disease-modifying therapies are lacking [43].

Emerging Directions

Recent advances point toward novel avenues in the mechanistic understanding and treatment of cancer pain. Epigenetic modifications and noncoding RNAs, particularly microRNAs, have emerged as key regulators of neuronal excitability and neuroinflammatory cascades [44]. Preclinical models of bone cancer pain demonstrate that histone acetylation and DNA methylation contribute to persistent nociceptor sensitization, while dysregulated miRNA expression modulates cytokine release and glial activation, suggesting new epigenetic targets for intervention [5,45]. In parallel, efforts to refine clinical phenotyping through the integration of quantitative sensory testing,

 doi:10.20944/preprints202509.0550.v1

inflammatory biomarkers, and neuroimaging hold promise for distinguishing predominant nociceptive, neuropathic, or mixed drivers of cancer pain, thereby informing mechanism-based therapies [46]. Finally, the recognition of a dynamic tumor–nerve–immune triad highlights chemokine signaling pathways such as CCL2/CCR2 and CX3CL1/CX3CR1 as potential dual-action targets that may both attenuate nociceptor sensitization and favorably remodel the tumor microenvironment, offering an attractive strategy for translational research [47–49].

Discussion

The present narrative synthesis highlights the remarkable complexity of cancer pain, in which multiple peripheral and central mechanisms converge to shape a multidimensional clinical phenotype. The evidence reviewed underscores that tumor- and stroma-derived mediators, including prostaglandins, endothelins, cytokines, chemokines, and glutamate, serve as potent drivers of peripheral nociceptor sensitization [50]. These mediators not only lower neuronal thresholds but also promote aberrant ion channel activity, thereby sustaining spontaneous and evoked pain. Importantly, advances in experimental oncology suggest that interfering with these signaling cascades, such as through ETA receptor antagonism or blockade of xCT-mediated glutamate release, may yield analgesic benefits without reliance solely on opioids [4,51].

Ion channel dysregulation emerges as a particularly promising therapeutic target [52]. TRPV1 and TRPA1, along with P2X3 and ASIC3 receptors, link the tumor microenvironment to peripheral hyperexcitability, explaining both the background and movement-evoked components of cancer-induced bone pain. Translational studies with resiniferatoxin and P2X3 antagonists highlight the feasibility of moving from bench to bedside, although challenges remain in balancing efficacy with safety [38,53].

The recognition of pathological nerve remodeling and PNI has deepened understanding of neuropathic elements in cancer pain. PNI, common in pancreatic and head-and-neck cancers, is not only a source of severe pain but also a marker of aggressive disease biology. Pathways such as HGF/c-MET–driven NGF upregulation suggest that interventions disrupting tumor–nerve crosstalk could achieve dual antitumor and analgesic effects, representing a paradigm shift in supportive oncology [47,54].

Equally significant are central mechanisms, where glial activation and chemokine signaling (CX3CL1/CX3CR1, CCL2/CCR2) sustain spinal hyperexcitability and diminish inhibitory tone. These processes resemble established neuropathic pain states but may be amplified by the tumor milieu. While no CNS-penetrant inhibitors are yet approved for clinical use, ongoing preclinical studies strengthen the rationale for targeting glial–neuronal interactions [55,56].

From a translational perspective, therapies that modify the bone microenvironment remain the most mature, as anti-resorptives and radiotherapy are clinically validated to reduce skeletal events and alleviate pain [57]. However, the persistence of CIPN, despite preventive strategies, emphasizes the urgent need for disease-modifying interventions tailored to drug-specific neurotoxic mechanisms [12,58].

Looking forward, integration of epigenetic and biomarker research with refined phenotyping approaches offers the potential to stratify patients by predominant pain mechanisms. This may enable mechanism-guided therapies that not only relieve suffering but also influence tumor-immune dynamics. Ultimately, bridging mechanistic discoveries with precision interventions represents the central challenge (and opportunity) of contemporary cancer pain research.

Limitations: This narrative review is limited by its non-systematic methodology, which may introduce selection bias and restrict comprehensiveness. Although adherence to SANRA guidelines ensured transparency and rigor, the absence of quantitative synthesis prevents formal comparison of effect sizes, and the rapidly evolving literature may render some mechanistic insights preliminary.

Conclusions

 doi:10.20944/preprints202509.0550.v1

Cancer pain arises from a complex interplay between malignant tissue, the skeletal or visceral microenvironment, and the nervous system. Key neurobiological themes include (i) peripheral sensitization by tumor/stromal mediators and acidic/ATP-rich milieus, (ii) pathological nerve remodeling and PNI, (iii) chemotherapy-driven neural injury, and (iv) central glial-chemokine-mediated plasticity. These mechanistic insights already guide practice (e.g., anti-resorptives and radiotherapy in bone pain) and are spawning new approaches, from TRPV1-targeted neuroablatives to chemokine and purinergic antagonists. Future progress hinges on rigorous phenotyping, translational trials that pair mechanism with target, and integrated care pathways that address both pain biology and cancer control.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Mantyh PW. Cancer pain and its impact on diagnosis, survival and quality of life. Nat Rev Neurosci. 2006 Oct;7(10):797-809. doi: 10.1038/nrn1914.
2. de Melo PS, Pacheco-Barrios K, Marduy A, Vasquez-Avila K, Simis M, Imamura M, Cardenas-Rojas A, Navarro-Flores A, Batistella L, Fregni F. The Endogenous Pain Modulatory System as a Healing Mechanism: A Proposal on How to Measure and Modulate It. NeuroSci. 2024 Jul 7;5(3):230-243. doi: 10.3390/neurosci5030018.
3. Mantyh PW, Clohisy DR, Koltzenburg M, Hunt SP. Molecular mechanisms of cancer pain. Nat Rev Cancer. 2002 Mar;2(3):201-9. doi: 10.1038/nrc747.
4. Schmidt BL. The Neurobiology of Cancer Pain. J Oral Maxillofac Surg. 2015 Dec;73(12 Suppl):S132-5. doi: 10.1016/j.joms.2015.04.045.
5. Wang X, Li L, Wang Y. Mechanisms of Cancer-Induced Bone Pain. J Pain Res. 2025 Jan 20;18:315-326. doi: 10.2147/JPR.S498466.
6. Chen X, Gan Y, Au NPB, Ma CHE. Current understanding of the molecular mechanisms of chemotherapy-induced peripheral neuropathy. Front Mol Neurosci. 2024 Apr 10;17:1345811. doi: 10.3389/fnmol.2024.1345811.
7. Kouri M, Rekatsina M, Vadalouca A, Viswanath O, Varrassi G. Oral Neuropathy Associated with Commonly used Chemotherapeutic Agents: A Narrative Review. Curr Pain Headache Rep. 2024 Dec;28(12):1209-1217. doi: 10.1007/s11916-024-01305-8.
8. Nishigami T, Manfuku M, Lahousse A. Central Sensitization in Cancer Survivors and Its Clinical Implications: State of the Art. J Clin Med. 2023 Jul 11;12(14):4606. doi: 10.3390/jcm12144606.
9. Ayala GE, Wheeler TM, Shine HD, Schmelz M, Frolov A, Chakraborty S, Rowley D. In vitro dorsal root ganglia and human prostate cell line interaction: redefining perineural invasion in prostate cancer. Prostate. 2001 Nov 1;49(3):213-23. doi: 10.1002/pros.1137.
10. Ji RR, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and Central Sensitization in Chronic and Widespread Pain. Anesthesiology. 2018 Aug;129(2):343-366. doi: 10.1097/ALN.0000000000002130.
11. Kuner R, Flor H. Structural plasticity and reorganisation in chronic pain. Nat Rev Neurosci. 2017 Jan 20;18(2):113. doi: 10.1038/nrn.2017.5. Erratum for: Nat Rev Neurosci. 2016 Dec 15;18(1):20-30. doi: 10.1038/nrn.2016.162.
12. Starobova H, Vetter I. Pathophysiology of Chemotherapy-Induced Peripheral Neuropathy. Front Mol Neurosci. 2017 May 31;10:174. doi: 10.3389/fnmol.2017.00174.
13. Baethge C, Goldbeck-Wood S, Mertens S. SANRA-a scale for the quality assessment of narrative review articles. Res Integr Peer Rev. 2019 Mar 26;4:5. doi: 10.1186/s41073-019-0064-8.
14. Khosrowshahi D, Lagae L, Bolander J. Decoding Pain: Next-Generation In Vitro Systems for Mechanistic Insights and Drug Discovery. FASEB J. 2025 Aug 31;39(16):e70914. doi: 10.1096/fj.202501025RR.
15. Varrassi g, Leoni MLG, Farì G, Al-Alwany AA, Al Sharie S, Fornasari D. Neuromodulatory signaling in chronic pain patients: A narrative review. *Cells* 2025, *14*(17), 1320. doi.org/10.3390/cells14171320
16. Pickering V, Jay Gupta R, Quang P, Jordan RC, Schmidt BL. Effect of peripheral endothelin-1 concentration on carcinoma-induced pain in mice. Eur J Pain. 2008 Apr;12(3):293-300. doi: 10.1016/j.ejpain.2007.06.001.

 doi:10.20944/preprints202509.0550.v1

17. Slosky LM, BassiriRad NM, Symons AM, Thompson M, Doyle T, Forte BL, Staatz WD, Bui L, Neumann WL, Mantyh PW, Salvemini D, Largent-Milnes TM, Vanderah TW. The cystine/glutamate antiporter system xc- drives breast tumor cell glutamate release and cancer-induced bone pain. Pain. 2016 Nov;157(11):2605-2616. doi: 10.1097/j.pain.0000000000000681.
18. de Almeida AS, Bernardes LB, Trevisan G. TRP channels in cancer pain. Eur J Pharmacol. 2021 Aug 5;904:174185. doi: 10.1016/j.ejphar.2021.174185.
19. Szallasi A. Targeting TRPV1 for Cancer Pain Relief: Can It Work? Cancers (Basel). 2024 Feb 2;16(3):648. doi: 10.3390/cancers16030648.
20. Kaan TK, Yip PK, Patel S, Davies M, Marchand F, Cockayne DA, Nunn PA, Dickenson AH, Ford AP, Zhong Y, Malcangio M, McMahon SB. Systemic blockade of P2X3 and P2X2/3 receptors attenuates bone cancer pain behaviour in rats. Brain. 2010 Sep;133(9):2549-64. doi: 10.1093/brain/awq194.
21. Lu HJ, Wu XB, Wei QQ. Ion channels in cancer-induced bone pain: from molecular mechanisms to clinical applications. Front Mol Neurosci. 2023 Aug 17;16:1239599. doi: 10.3389/fnmol.2023.1239599.
22. Jiang Y, Liu X, Zhang H, Xu L. Targeted therapy: P2X3 receptor silencing in bone cancer pain relief. J Biochem Mol Toxicol. 2024 Nov;38(11):e70026. doi: 10.1002/jbt.70026.
23. Garajová I, Giovannetti E. Targeting Perineural Invasion in Pancreatic Cancer. Cancers (Basel). 2024 Dec 21;16(24):4260. doi: 10.3390/cancers16244260.
24. Shi RJ, Ke BW, Tang YL, Liang XH. Perineural invasion: A potential driver of cancer-induced pain. Biochem Pharmacol. 2023 Sep;215:115692. doi: 10.1016/j.bcp.2023.115692.
25. Qin T, Xiao Y, Qian W, Wang X, Gong M, Wang Q, An R, Han L, Duan W, Ma Q, Wang Z. HGF/c-Met pathway facilitates the perineural invasion of pancreatic cancer by activating the mTOR/NGF axis. Cell Death Dis. 2022 Apr 21;13(4):387. doi: 10.1038/s41419-022-04799-5.
26. Li Q, Liu Q, Yang L, Li Q, Zhang A. Risk factors and clinical significance of refractory pain in patients with bone metastases: a comprehensive meta-analysis. Front Neurol. 2025 Apr 24;16:1517279. doi: 10.3389/fneur.2025.1517279.
27. Coluzzi F, Scerpa MS, Alessandri E, Romualdi P, Rocco M. Role of TRP Channels in Cancer-Induced Bone Pain. Int J Mol Sci. 2025 Jan 30;26(3):1229. doi: 10.3390/ijms26031229.
28. Andriessen AS, Donnelly CR, Ji RR. Reciprocal interactions between osteoclasts and nociceptive sensory neurons in bone cancer pain. Pain Rep. 2021 Mar 9;6(1):e867. doi: 10.1097/PR9.0000000000000867.
29. Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH, Lichinitser M, Fujiwara Y, Yardley DA, Viniegra M, Fan M, Jiang Q, Dansey R, Jun S, Braun A. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol. 2010 Dec 10;28(35):5132-9. doi: 10.1200/JCO.2010.29.7101.
30. Zajączkowska R, Kocot-Kępska M, Leppert W, Wrzosek A, Mika J, Wordliczek J. Mechanisms of Chemotherapy-Induced Peripheral Neuropathy. Int J Mol Sci. 2019 Mar 22;20(6):1451. doi: 10.3390/ijms20061451.
31. Tanay MAL, Armes J, Moss-Morris R, Rafferty AM, Robert G. A systematic review of behavioural and exercise interventions for the prevention and management of chemotherapy-induced peripheral neuropathy symptoms. J Cancer Surviv. 2023 Feb;17(1):254-277. doi: 10.1007/s11764-021-00997-w.
32. Malcangio M, Sideris-Lampretsas G. How microglia contribute to the induction and maintenance of neuropathic pain. Nat Rev Neurosci. 2025 May;26(5):263-275. doi: 10.1038/s41583-025-00914-5.
33. McCaffrey G, Thompson ML, Majuta L, Fealk MN, Chartier S, Longo G, Mantyh PW. NGF blockade at early times during bone cancer development attenuates bone destruction and increases limb use. Cancer Res. 2014 Dec 1;74(23):7014-23. doi: 10.1158/0008-5472.CAN-14-1220.
34. Hu JH, Yang JP, Liu L, Li CF, Wang LN, Ji FH, Cheng H. Involvement of CX3CR1 in bone cancer pain through the activation of microglia p38 MAPK pathway in the spinal cord. Brain Res. 2012 Jul 17;1465:1-9. doi: 10.1016/j.brainres.2012.05.020.
35. Gartner KE, Rustioni S, Vohra A, Almosawi M, Hill N, Stewart T, van Wouwe NC, Zemmar A. A comprehensive review of the supraspinal mechanisms of spinal cord stimulation on chronic pain and cognition. Front Pain Res (Lausanne). 2025 Jul 28;6:1589723. doi: 10.3389/fpain.2025.1589723.

 doi:10.20944/preprints202509.0550.v1

36. Martel Matos AA, Scheff NN. Sensory neurotransmission and pain in solid tumor progression. Trends Cancer. 2025 Apr;11(4):309-320. doi: 10.1016/j.trecan.2025.01.003.
37. Alcorn S, Cortés ÁA, Bradfield L, Brennan M, Dennis K, Diaz DA, Doung YC, Elmore S, Hertan L, Johnstone C, Jones J, Larrier N, Lo SS, Nguyen QN, Tseng YD, Yerramilli D, Zaky S, Balboni T. External Beam Radiation Therapy for Palliation of Symptomatic Bone Metastases: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol. 2024 Sep-Oct;14(5):377-397. doi: 10.1016/j.prro.2024.04.018.
38. Brown DC, Agnello K, Iadarola MJ. Intrathecal resiniferatoxin in a dog model: efficacy in bone cancer pain. Pain. 2015 Jun;156(6):1018-1024. doi: 10.1097/j.pain.0000000000000115.
39. Mannes AJ, Heiss JD, Berger A, Alewine CC, Butman JA, Hughes MS, Rabbee N, Hayes C, Williams TS, Sapio MR, Iadarola MJ. Treatment of Intractable Cancer Pain with Resiniferatoxin - An Interim Study. NEJM Evid. 2025 Jun;4(6):EVIDoa2400423. doi: 10.1056/EVIDoa2400423.
40. Joosten EA, Franken G. Spinal cord stimulation in chronic neuropathic pain: mechanisms of action, new locations, new paradigms. Pain. 2020 Sep;161 Suppl 1(1):S104-S113. doi: 10.1097/j.pain.0000000000001854.
41. Crowther JE, Chen GH, Legler A, Gulati A. Spinal Cord Stimulation in the Treatment of Cancer Pain: A Retrospective Review. Neuromodulation. 2022 Jul;25(5):693-699. doi: 10.1016/j.neurom.2022.01.023.
42. Lor K, Kubrova E, D'Souza RS, Hoffmann C, Banks D, Jin MY, Prokop LJ, Her YF. Interventional Therapies to Treat Cancer Associated Pain. Curr Treat Options Oncol. 2025 Jul;26(7):654-671. doi: 10.1007/s11864-025-01337-1.
43. Huang Y, Tan T, Liu L, Yan Z, Deng Y, Li G, Li M, Xiong J. Exercise for reducing chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis of randomized controlled trials. Front Neurol. 2024 Jan 12;14:1252259. doi: 10.3389/fneur.2023.1252259. Erratum in: Front Neurol. 2024 Mar 07;15:1378461. doi: 10.3389/fneur.2024.1378461. Erratum in: Front Neurol. 2024 Aug 01;15:1460992. doi: 10.3389/fneur.2024.1460992.
44. Chen Y, Mateski J, Gerace L, Wheeler J, Burl J, Prakash B, Svedin C, Amrick R, Adams BD. Non-coding RNAs and neuroinflammation: implications for neurological disorders. Exp Biol Med (Maywood). 2024 Feb 28;249:10120. doi: 10.3389/ebm.2024.10120.
45. Saadh MJ, Rashed AB, Jamal A, Castillo-Acobo RY, Kamal MA, Cotrina-Aliaga JC, Gonzáles JLA, Alothaim AS, Alhoqail WA, Ahmad F, Lakshmaiya N, Amin AH, Younus DG, Rojas GGR, Bahrami A, Akhavan-Sigari R. miR-199a-3p suppresses neuroinflammation by directly targeting MyD88 in a mouse model of bone cancer pain. Life Sci. 2023 Nov 15;333:122139. doi: 10.1016/j.lfs.2023.122139.
46. Martland ME, Rashidi AS, Bennett MI, Fallon M, Jones C, Rolke R, Mulvey MR. The use of quantitative sensory testing in cancer pain assessment: A systematic review. Eur J Pain. 2020 Apr;24(4):669-684. doi: 10.1002/ejp.1520. Epub 2020 Jan 17. Erratum in: Eur J Pain. 2021 Jan;25(1):272. doi: 10.1002/ejp.1667.
47. He S, He S, Chen CH, Deborde S, Bakst RL, Chernichenko N, McNamara WF, Lee SY, Barajas F, Yu Z, Al-Ahmadie HA, Wong RJ. The chemokine (CCL2-CCR2) signaling axis mediates perineural invasion. Mol Cancer Res. 2015 Feb;13(2):380-90. doi: 10.1158/1541-7786.MCR-14-0303.
48. Zhuang Q, Ou J, Zhang S, Ming Y. Crosstalk between the CX3CL1/CX3CR1 Axis and Inflammatory Signaling Pathways in Tissue Injury. Curr Protein Pept Sci. 2019;20(8):844-854. doi: 10.2174/1389203720666190305165722.
49. Hermann DM, Bacigaluppi M, Bassetti CL, Bassotti G, Boltze J, Chan A, Dalkara T, Denes A, Diez-Tejedor E, Dodel R, Doeppner TR, Dzyubenko E, ElAli A, Fulop T, Gerhard A, Giebel B, Gronewold J, Gunzer M, Heinbockel T, Huang K, Iriti M, Karnath HO, Trenite KN, Kilic E, Lanza G, Liesz A, Magnus TU, Mandrioli J, Mohamud-Yusuf A, Müller T, Pan S, Peruzzotti-Jametti L, Pluchino S, Pluta R, Popa-Wagner A, Rezayof A, Seghier ML, Shu X, Singh V, Sipilä J, Slevin M, Tang Y, Tsivgoulis G, Varrassi G, Wang C, Yilmaz B, Zaki MS, Zhang J. Most prominent challenges in translational neuroscience and strategic solutions to bridge the gaps: Perspectives from an editorial board interrogation. Explor Neurosci. 2025;4:1006106. doi: 10.37349/en.2025.1006106.
50. Kaye AD, Perilloux DM, Hawkins AM, Wester GC, Ragaland AR, Hebert SV, Kim J, Heisler M, Kelkar RA, Chami AA, Shekoohi S, Kaye AM. Tumor Necrosis Factor and Interleukin Modulators for Pathologic Pain States: A Narrative Review. Pain Ther. 2024 Jun;13(3):481-493. doi: 10.1007/s40122-024-00603-8.

 doi:10.20944/preprints202509.0550.v1

51. Ungard RG, Linher-Melville K, Nashed MG, Sharma M, Wen J, Singh G. xCT knockdown in human breast cancer cells delays onset of cancer-induced bone pain. Mol Pain. 2019 Jan-Dec;15:1744806918822185. doi: 10.1177/1744806918822185.
52. Shi Q, Yang Z, Yang H, Xu L, Xia J, Gu J, Chen M, Wang Y, Zhao X, Liao Z, Mou Y, Gu X, Xie T, Sui X. Targeting ion channels: innovative approaches to combat cancer drug resistance. Theranostics. 2025 Jan 1;15(2):521-545. doi: 10.7150/thno.103384.
53. Bae J, Kim YO, Han X, Yoon MH, Kim WM, Kim YC. Synthesis and Structure-Activity Relationship Studies of Benzimidazole-4,7-dione-Based P2X3 Receptor Antagonists as Novel Anti-Nociceptive Agents. Molecules. 2022 Feb 16;27(4):1337. doi: 10.3390/molecules27041337.
54. Bakst RL, Wong, RJ. Mechanisms of perineural invasion. J Neurol Surg Part B: Skull Base, 2016, 77.02: 096-106. doi: 10.1055/s-0036-1571835.
55. Qiu X, Yang Y, Da X, Wang Y, Chen Z, Xu C. Satellite glial cells in sensory ganglia play a wider role in chronic pain via multiple mechanisms. Neural Regen Res. 2024 May;19(5):1056-1063. doi: 10.4103/1673-5374.382986.
56. Sun S, Sun Y, Shen J, Mao Z, Zhang T, Gao Y, Yang D, Chen X, Song G. CXCL13/CXCR5: a new target for pain treatment - a review article. Int J Surg. 2025 Jun 20. doi: 10.1097/JS9.0000000000002764.
57. Dalle Carbonare L, Cominacini M, Trabetti E, Bombieri C, Pessoa J, Romanelli MG, Valenti MT. The bone microenvironment: new insights into the role of stem cells and cell communication in bone regeneration. Stem Cell Res Ther. 2025 Apr 12;16(1):169. doi: 10.1186/s13287-025-04288-4.
58. Lee KT, Bulls HW, Hoogland AI, James BW, Colon-Echevarria CB, Jim HSL. Chemotherapy-Induced Peripheral Neuropathy (CIPN): A Narrative Review and Proposed Theoretical Model. Cancers (Basel). 2024 Jul 18;16(14):2571. doi: 10.3390/cancers16142571.