6 Treatment of Established Chemotherapy-Induced Peripheral Neuropathy: Basic Science and Animal Models

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Abstract

Advancement of effective therapies to treat established CIPN will require a deeper understanding of CIPN pathomechanisms. Simplified models of CIPN have been developed using whole-animal systems, primary cultures, and immortalized cell lines to allow for detailed mechanistic studies. Recently, human stem-cell derived neuronal cultures have also allowed new opportunities to study CIPN. In this chapter, we provide an overview of studies that used model systems to investigate the treatment of established CIPN. We have divided the chapter into two main areas. First, there are studies that investigate CIPN-related nerve damage through the lens of neurogenesis, Schwann cells, and axonal regrowth. Next, we review model approaches to treat CIPN-related pain that have focused on voltage-gated ion channels, neuroinflammation, sphingosine metabolism, and endocannabinoids. The broad approaches that are being employed to study the treatment of established CIPN in model systems provide hope for future beneficial therapeutics.

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6.1 Introduction

Despite a growing understanding of the pathophysiology of CIPN few therapies have shown success in humans. Only the antidepressant medication duloxetine has shown moderate efficacy to treat established pain due to CIPN [1]. Animal models appear to be important for identifying appropriate therapies for treating established CIPN. Experimental models of CIPN can be induced in different strains of rats or mice through intraperitoneal (ip), subcutaneous (sc), or intravenous (iv) administration of the desired drug [2]. "In vitro" studies are also important to further study the effects of the different drugs at the cellular level and for the search of potential therapy targets against CIPN. These studies can be performed with cultures of dorsal root ganglion (DRG)-neurons obtained from rats or mice [3] or with immortalized and commercially available murine sensory neurons cell lines [4, 5]. Nonetheless "in vitro" studies have limitations due to the biologic differences between humans versus mice or rats. To overcome this problem, sensory neurons can be induced from human skin fibroblasts or multipotential $CD34^+$ hematopoietic stem cells obtained from peripheral blood [6, 7].

6.2 Models of CIPN

6.2.1 In Vivo Animal Models of CIPN

About 70% of in vivo animal studies are conducted with rats and 30% with mice, the drugs commonly used to induce CIPN are oxaliplatin, paclitaxel, vincristine, cisplatin, and bortezomib [8]. The doses and schedules of the different chemotherapy agents for the induction of CIPN in rodents are listed in Table 6.1.

After the administration of the drug in the required dosage, behavioral tests are performed to assess the establishment of neuropathy. These tests are directed to test motor coordination, mechanical allodynia, and thermal sensitivity. Neuromuscular coordination is assessed with the rotarod test, which consists of a circular rod turning at different speeds. The amount of time in which an animal stays on the rotating rod is related to its motor coordination. Mechanical allodynia is measured with the electronic von Frey hair test, placing the mouse or rat in an inverted plastic cage with a wire-mesh floor. Semiflexible filaments are then applied to the center of the hind paws, gradually increasing the pressure for 5 s, in order to establish a pain threshold [18]. Cold hyperalgesia and alterations in thermal sensibility are tested with the acetone test and the hot plate test, respectively. The acetone test consists of touching the plantar skin of a hind paw with a 100 μl droplet of acetone from a syringe, while the hot plate test is performed by placing animals on an aluminum plate which is uniformly heated. For the hot plate a cut-off time of 30 s is used, to prevent damage [19].

Table 6.1 Doses and schedules for experimental models of CIPN in mice and rats

Drug	Animal	Dose	Route	Schedule	References
Oxaliplatin	Rat	4 mg/kg	Ip	Twice a week × 4	[9]
	Rat	5 mg/kg	Ip	Days 0, 3, 6, and 9	[10]
	Mouse	4 mg/kg	Ip	Days 0, 2, 4, and 6	[10]
Paclitaxel	Rat	2 m/kg	Ip	Days 0, 2,4, and 6	[11]
	Mouse	4 mg/kg	Ip	Days 0, 2, 4, and 6	[12]
Vincristine	Rat	200 μg/kg	Iv	Single dose	[13]
	Mouse	200 μg/kg	Ip	Single dose	
Cisplatin	Rat	2 mg/kg	Ip	4 consecutive days	[14]
	Mouse	2.3 mg/kg	Ip	2 cycles of 5 consecutive days with 5 days rest in between.	[15]
Bortezomib	Rat	0.1–0.2 mg/kg	Ip	Days 0, 3, 7, and 10	[16]
	Mouse	400 μg/kg	Ip	3 days /week × 4 weeks	[17]

6.2.2 In Vitro Models of CIPN

The difficulties in obtaining human neurons for study make cell culture models an important tool for CIPN pathophysiological and pharmacological research. The commercially available rat PC12 pheochromocytoma cell line differentiates to neurons in the presence of forskolin, stimulating neurite outgrowth [20]. Forskolin is a diterpenoid obtained from the plant *Coleus forskohlii* that penetrates cell membranes and increases the levels of adenylyl cyclase (cAMP), which is involved in many transduction pathways [21]. The 50B11 neuronal cell line is another commercially available cell line derived from rat DRG [4].

Primary cell cultures can be performed with DRG neurons obtained from embryonic or early-postnatal rats after surgical removal, cultivation with collagenase I, centrifugation and seeding in neurobasal medium [3]. Schwann cells derived from the sciatic nerves of neonatal rats are also used for primary culture [22].

The biologic differences between mice or rats and humans limit the extrapolation of results. To overcome this problem, sensory neurons can be induced from human embryonic fibroblasts, through the transfection with lentiviral vectors of the transcription factor *Brn3a* with either *Ngn1* or *Ngn2* [23]. The pluripotent hematopoietic CD34+ stem cells are also a source for the induction of sensory neurons, which can be available from blood banks or from peripheral blood sampling. The isolated CD34+ stem cells are cultured in the required media and transfected with the lentivirus OCT4 delivery system to produce induced neural progenitor cells (iNPCs). The iNPCs are then cultured in a sensory neuron specification medium, supplemented with brain derived neurotrophic factor, glial derived neurotrophic factor, nerve growth factor, neurotrophin-3 and forskolin, until the desired maturation stage [7]. Likewise, sensory neurons can be differentiated from human induced pluripotent stem cells [6], which has been also utilized as a model for CIPN [24–27].

These "in vitro" models enable the study of the cellular effects of the different cytotoxic drugs and of the effects of potential products directed to protect the neurons of the cytotoxic damage. For this purpose, the cells are cultured with different concentrations of the chemotherapy agent to be studied; after an established incubation period, biochemical and morphological testing can be performed to assess its effects on the concrete functions or structures to which the experiment is directed. These cell cultures enable the study of drugs or natural products with potential properties in reversing the effects of the drugs causing CIPN or with the capability of inducing neuronal regeneration.

6.3 Treatment of CIPN-Related Nerve Damage

At the moment the only clinically available treatments for CIPN are only symptomatic [1], so there is an urgent need for the development of treatments aimed to revert or reduce the neuronal damage. The different cytotoxic drugs causing CIPN affect different cells, organelles, or pathways within the sensory nerve system, resulting in mitochondrial dysfunction, oxidative stress, inflammation, microtubule damage, and alterations in ion channels, along with other effects [10], making the search to uncover CIPN treatments a great challenge. Research can be aimed at a common pathomechanism of damage shared with different drugs or directed to revert the changes induced by a specific drug.

6.3.1 Categorized by Pathomechanism

As chemotherapy targets fast dividing cells and not all chemotherapy agents produce CIPN, there may be additional effects of the cytotoxic drugs on the non-dividing neurons [28]. Most chemotherapy agents do not cross the blood–brain barrier, but they may accumulate in the DRG and nerve terminals, resulting in neuronal body, axonal, or myelin sheath injury [29]. The research toward therapies is aimed at reversing the pathogenic mechanism of the different drugs or in inducing the regeneration of neurons, Schwann cells, or axons.

6.3.1.1 Neurogenesis

The sensory neurons and the supporting glial cells that form the DRG arise from a sub-population of trunk neural crest cell progenitors and the *Notch* signaling pathway is involved in its final differentiation. Some of these cells remain in the undifferentiated stage [30] and express the neural stem cells markers nestin and p75 neurotrophin receptor (p75NTR). The transcription factors involved in its differentiation to neurons or glia could be potential targets in neurogenesis [31]. As seen in the experimental model of peripheral nerve crush injury, the number of DRG neurons increase up to 42%, compared to controls [32]. Alternatively, survival pathways could be activated, as evidenced by the fact that DRG neurons expressing *ptv1* oncogene (plasmacytoma variant translocation 1), a long

non-coding RNA gene, are protected from apoptosis through the activation of the PI3K/AKT pathway [33].

6.3.1.2 Schwann Cell Mechanisms

Schwann cells are essential for the regeneration of peripheral nerves after an injury. In this process Schwann cells halt the production of myelin, digest myelin debris, and facilitate a process of dedifferentiation. These dedifferentiated Schwann cells guide the axon's growth until its completion. After this, the Schwann cells differentiate again and restart the production of myelin [34]. Dynein is a motor protein and regulator of microtubule dynamics, axonal transport, and membrane trafficking. Dynein is essential for the process of Schwann cell dedifferentiation and, consequently, for axon regeneration [35]. Following nerve injury, several pathways are activated in Schwann cells, such as p38, JNK, and ERK, which are involved in the acquisition of the dedifferentiated phenotype of the Schwann cells to start axon recovery [36], resulting in the upregulation of proteins C-Jun and p75NTR, whereas the myelination associated protein EGR2 (early growth response protein 2) becomes downregulated [37]. The involvement of signaling pathways involved in these mechanisms is another focus of research.

6.3.1.3 Axonal Regrowth

The peripheral nervous system, in contrast with the central nervous system, has a capacity to recover after traumatic or toxic injuries. This process involves a series of changes that provides the neuron with the capacity to growth. Axon regeneration is regulated through the activation of several transcription factors, epigenetic changes of chromatin and microRNAs (miRNAs) [38]. Some of the transcribed mRNAs are transported to distal parts of the axon where the translation into proteins occurs, preventing both axon degeneration and neuron apoptosis. One of these retrograde response genes is *Bclw* (*Bcl2l2*), which belongs to the *Bcl2*- family and induces axon survival [39]. Following peripheral nerve injury, the activation of the JNK signaling pathway increases the expression of transcription factors JUN and ATF3, in DRG neurons starting axon regeneration. Other transcription factors induced by peripheral axon injury are members of the SMAD family and STAT3 [38]. Activation of STAT3 happens in DRG neurons after nerve injury by being phosphorylated by cyclin-dependent kinase 5 (Cdk5) [40].

6.3.2 Categorized by Drug

The fact that anticancer chemotherapy targets rapid dividing cells but not all agents produce CIPN supports that different drugs have their own mechanisms of causing neuronal damage [28]. The different gene expression induced by different chemotherapy drugs in normal cells can help in the search for targets in the development of therapies to treat CIPN [41]. As oxaliplatin, paclitaxel, vincristine, cisplatin, and bortezomib are the drugs that commonly cause CIPN in clinical practice, many studies are related to them [42].

6.3.2.1 Oxaliplatin

Animal and "in vitro" studies have shown that the nuclear factor-erythroid-2-related factor 2 (Nrf2) pathway protects from oxaliplatin-induced axonal damage, by stimulating the synthesis of proteins with antioxidant activity. Dimethyl fumarate is a drug used in the treatment of multiple sclerosis that exerts a neuroprotective effect through Nrf2-mediated reduction in oxidative stress. Recent work demonstrated functional and structural improvements with dimethyl fumarate treatment in the rat model of oxaliplatin-induced neuropathy [43]. Another neuroprotective agent, donepezil, an inhibitor of acetylcholinesterase and used for the treatment of Alzheimer's disease, reduced sciatic nerve degeneration and improved mechanical allodynia in rats treated with oxaliplatin, without a reduction in the antitumor efficacy [20]. Oxaliplatin and paclitaxel produce an inflammatory response in DRGs and spinal cord astrocytes with an increased production of inflammatory cytokines (CCL2, CCL3, TNF-α, IL-6, IL1β, and IL-8) and a reduction in the anti-inflammatory cytokines (IL-10 and IL-4). In a rat model of oxaliplatin-induced neuropathy, the selective inhibition of IL-8 receptors improved the results of the behavioral test and reduced the expression of the proteins JAK2 and STAT3, which are associated with oxaliplatin damage [44].

6.3.2.2 Paclitaxel

Oxidative stress produced by the effect of paclitaxel on the mitochondria of DRG neurons and peripheral nerves is one of the pathophysiological mechanisms of CIPN. Melatonin has been shown to be a potent antioxidant that enters the mitochondria. "In vitro" studies showed that melatonin reduces paclitaxel-induced mitochondrial damage. Using the rat model of paclitaxel-induced neuropathy, co-treatment with melatonin improved the results of the behavioral tests and reduced the C-fiber activity-dependent slowing [45]. Paclitaxel-induced apoptosis of DRG neurons is another mechanism involved in CIPN and the tumor suppressor gene *p53* appears to play an essential role in pathways related with DNA-damage and apoptosis. In an "in vitro" study with DRG neurons obtained from neonatal rats treated with paclitaxel and in a mice model of paclitaxel-induced CIPN, duloxetine reduced the expression of p53 and improved thermal and mechanical allodynia. The effect of duloxetine on p53 is through the reduction of oxidative stress [3]. As with oxaliplatin, inflammation in DRGs plays an important role in paclitaxel-induced neuropathy. Pretreatment with an IL-6 neutralizing antibody protects mice from such neuropathy [18].

Membrane drug transporter proteins are also involved in CIPN. These proteins such as ABCB1 and ABCC1 regulate uptake and efflux of drugs and are expressed in the peripheral nervous system [46]. Organic anion-transporting polypeptides (OATPs) are related with the accumulation of paclitaxel in DRG. OATP1B2 knockout mice have a decreased uptake of paclitaxel in DRG. The tyrosine kinase inhibitor nilotinib is a potent inhibitor of OATP1B1 and OATP1B2, protecting mice of paclitaxel induced neuropathy without impairing antitumor activity [47].

6.3.2.3 Vincristine

Axonal degeneration is an active process that is triggered by several transcription factors after a traumatic or toxic lesion. Sterile alpha and TIR motif-containing protein 1 (SARM1) is one of its components. *Sarm1*-knockout mice are protected from vincristine induced neuropathy, when compared with wild-type mice. SARM1 or its down-stream effectors could be potential therapeutic targets for reducing neuropathy [48]. Vincristine also stimulates the immune system, resulting in the consequent release of pro-inflammatory cytokines and neuroinflammation [28]. The anti-diabetes drug metformin reduces the levels of TNF-α, IL-6 and suppress the macrophage activation through the adenosine monophosphate activated protein kinase (AMPK) pathway, preventing mechanical allodynia and numbness in CIPN mice models [29].

6.3.2.4 Cisplatin

Cisplatin targets nuclear and mitochondrial DNA of DRG neurons, causing inter- and intra-strand adducts, inducing DGR-neurons apoptosis and mitochondrial disfunction, with the consequent generation of oxidative stress [49]. Peroxisome proliferator-activated receptor-α (PPAR-α) is a ligand-activated transcription factor of the nuclear hormone receptor superfamily expressed in several cells, including microglia and astroglia. PPAR-α increases mitochondrial and peroxisomal β-oxidation of fatty acids and thus has an important role in oxidation/antioxidant pathway [50]. Stimulation of PPAR-α could increase the levels of endogenous antioxidants reducing the oxidative stress. One stimulator of PPAR-α, undergoing CIPN animal studies, is the endogenous fatty acid, palmitoylethanolamide [49]. "In vitro" studies have shown that cisplatin mediated DRG neurons apoptosis can be prevented with phenoxodiol, an isoflavone analogue, that upregulates the cell-cycle regulator *p21 Waf1/Cip1* stimulating neurite growth [5]. The *sirt2* gene encodes the enzyme NAD-dependent deacetylase sirtuin 2, which results in neurite growth and protects mice from cisplatin-induced neural damage [51].

6.3.2.5 Bortezomib

As described earlier, the drug dimethyl fumarate, used in the treatment of multiple sclerosis, is an antioxidant and neuroprotective agent whose effect is mediated through the upregulation of *Nfr2*. "In vitro" studies using PC12 and rat DRG neurons showed that it reduces the effect of bortezomib, oxaliplatin, and cisplatin on neurite outgrowth, but lacks any protection against apoptosis [52]. Bortezomib alters the energetic metabolism of DRG-neurons, shifting the mitochondrial oxidation to aerobic glycolysis, the so-called Warburg effect. This aerobic glycolysis-phenotype with the consequent overexpression of lactate dehydrogenase A (LDHA) and pyruvate dehydrogenase kinase 1 (PDHK1) contributes to development of CIPN. Studies with a mouse model of bortezomib-induced neuropathy demonstrated that, by inhibition of LDHA and PDHK1 with oxamate and dichloroacetate, respectively, an improvement in the behavioral tests was achieved together with the reversal of the metabolic phenotype [53].

6.4 Treatment of CIPN-Related Pain

There are number of approaches that have been taken to treat CIPN-related pain in animal model systems. Overall, studies suggest that while initial neuropathic pain in CIPN is due to damage to the peripheral sensory nerve fibers, persistent CIPN-related pain is likely due to a combination of peripheral and central pathomechanisms. Supporting this idea is that duloxetine (which appears to act in central nervous system) is the only medication to be shown to be effective in reducing pain from established CIPN in double-blind placebo controlled human clinical trials [54, 55]. Many of the other off-label use of neuropathic pain medications have been tested and shown to provide relief in animal models [56]. The disconnect between successful treatment of CIPN-related pain in animal models versus the failure in human clinical trials is an important point that deserves careful attention.

6.4.1 Categorized by Pathomechanism

The study of pathomechanisms of CIPN-related pain reflects the study of neuropathic pain more broadly. As such, many of the pathways discussed below have broad implications for neuropathic pain; however, there are some pathomechanisms that are specific to the CIPN realm, which will be explicitly highlighted. While most of the studies below focused on specific neurotoxic chemotherapy agents, it is unclear how chemotherapy-specific any of the mechanisms below are. For example, a given paper may study a treatment mechanism in cisplatin-induced peripheral neuropathy, but does not explicitly test whether or not the same mechanism is at play in CIPN from other medications. Furthermore the majority of papers either used paclitaxel-, oxaliplatin-, or cisplatin-induced peripheral neuropathy models; bortezomib and vinca alkaloid models are far less represented.

6.4.1.1 Voltage-Gated Ion Channels

Voltage-gated ion channels are a prominent target for CIPN-related pain. Multiple models of CIPN have demonstrated altered voltage-gated ion channel expression that leads to neuronal hyperexcitability and correlates with pain behaviors. Voltage-gated sodium channels have shown increased expression in CIPN [57], especially the Nav1.7-mediated sodium current; blockade of this channel reverses hyperalgesia in a rat model of oxaliplatin-induced peripheral neuropathy [58]. Reduced expression of potassium channels occurs in CIPN models [57, 59, 60], which has been shown to be counteracted by the voltage-gated potassium channel activator retigabine (an FDA-approved epilepsy medication that targets the Kv7 channel) [61]. Voltage-gated T-type calcium channel Cav3.2 expression is increased in paclitaxel-induced peripheral neuropathy models [62]; blockade of this channel or the N-type (Cav2.2) can alleviate CIPN-related pain behaviors [63, 64]. The alpha-2-delta-1 auxiliary subunit for voltage-gated calcium channels, the target of pregabalin and gabapentin, is also upregulated by paclitaxel (PMID

17084535). Finally, the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels have been shown to be upregulated in a rat model of paclitaxel- or oxaliplatin-induced neuropathy [57, 60], and blockade of these channels reduces hyperalgesia and allodynia [60].

6.4.1.2 Neuroinflammation

Neuroinflammation is an often-used, but somewhat nebulous, term that typically refers to the deleterious effects of non-neuronal cells (e.g., immune cells, cytokines, and glial cells) to a neuropathological process (in this case CIPN). Extensive data have established neuroinflammation as playing an important role in CIPN and CIPN-related pain. CIPN is associated with changes in the peripheral immune system, seen as increases in CD4+ and CD8 T-cells [65]. Astrocytosis is seen in the central nervous system with CIPN, which, in part, appears to be mediated by heme oxygenase-1 expression [66], but there are no documented significant changes in microglial activation [65, 67]. Alterations in cytokine levels have been observed in CIPN models, with increased CNS levels of TNF-alpha, IFN-gamma, CCL11, CCL4, CCL3, IL-12p70, and GM-CSF [65]. Blockade of CXCR pathways [68, 69] or MCP-1 [70] can decrease CIPN-related pain behaviors. Increasing evidence also implicates toll-like receptor family activation (a component of the innate immune system) as playing a key role in CIPN-related pain, which can also be beneficially targeted [71–73], noting that data points to sexual dimorphism in this response [71].

6.4.1.3 Sphingosine Metabolism

Sphingosine 1-phosphate is generated via sphingolipid and ceramide metabolism, which can be activated via a number of mechanisms, including bortezomib and paclitaxel. Activation of the sphingosine 1-phosphate receptor in astrocytes has been shown to be important in establishing and maintaining bortezomib and paclitaxel-induced neuropathy in rat models [74, 75]. Importantly, this is an IL-10 dependent mechanism and also exhibits sexual dimorphic response [76]. Accordingly, sphingosine 1-phosphate receptor blockade (via an FDA-approved medication, fingolimod) can both prevent and treat established CIPN in animal models and is being tested in human clinical trials.

6.4.1.4 Endocannabinoids

A number of studies have reported the benefits of cannabinoids for CIPN-related pain syndromes in animal models, which has become more pertinent given the increased legalization of medical and recreational marijuana in many jurisdictions. Endocannabinoids have been implicated in development of CIPN-related pain [77, 78]. Activation of cannabinoid receptors has been shown to reduce CIPN pain behaviors caused by platinates [79–82] and taxanes [80, 83, 84]. The data in these studies is mixed as to whether this effect is mediated primarily by CB1 or CB2 receptors, as well as the relative importance of central versus peripheral cannabinoid receptor activation.

6.4.1.5 Miscellaneous Pathomechanisms

Several pathomechanisms have been explored as a treatment approach for established CIPN, albeit in limited studies. Metalloproteinase 2 and 9 are increased in the DRG of paclitaxel-treated rats, and a study demonstrated reversal of paclitaxel-induced allodynia with intrathecal injection of MMP9 monoclonal antibodies [85]. Histone deacetylase 6 inhibition has been shown to reverse cisplatin-induced allodynia, possibly via improved mitochondrial bioenergetics [86]. The impact of the microbiome has been studied in CIPN. Transferring gut microbiota from a mouse strain that is susceptible to CIPN (C57BL/6) into a resistant strain (129SvEV) can lead to the susceptibility in the 129SvEV strain to paclitaxel-induced neuropathic pain behaviors [87]. It has not been reported whether gut microbiome may be a target for treatment for established CIPN. Finally, an intriguing study demonstrated that voluntary wheel-running decreased paclitaxel-induced allodynia [88].

6.5 Conclusions

There has been considerable laboratory effort made at discovering therapies for established CIPN, and there are a number of promising pathomechanisms that can be further studied in the future. Some of these pathomechanisms are broad and should ameliorate CIPN from varied chemotherapeutic agents, whereas others may be more directed as specific drugs. Finally, it has become clear that in animal models of CIPN there are system level changes due to neurotoxic chemotherapy that may play synergistic or antagonistic roles and will require more sophisticated approaches to elucidate.

References

1. Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, Chauhan C, Gavin P, Lavino A, Lustberg MB, Paice J, Schneider B, Smith ML, Smith T, Terstriep S, Wagner-Johnston N, Bak K, Loprinzi CL (2014) American Society of Clinical O. prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 32(18):1941–1967. Epub 2014/04/16. https://doi.org/10.1200/JCO.2013.54.0914
2. Currie GL, Angel-Scott HN, Colvin L, Cramond F, Hair K, Khandoker L, Liao J, Macleod M, McCann SK, Morland R, Sherratt N, Stewart R, Tanriver-Ayder E, Thomas J, Wang Q, Wodarski R, Xiong R, Rice ASC, Sena ES. Animal models of chemotherapy-induced peripheral neuropathy: A machine-assisted systematic review and meta-analysis. PLoS Biol. 2019;17(5):e3000243. https://doi.org/10.1371/journal.pbio.3000243. Epub 2019/05/21. PubMed PMID: 31107871; PMCID: PMC6544332
3. Lu Y, Zhang P, Zhang Q, Yang C, Qian Y, Suo J, Tao X, Zhu J (2020) Duloxetine attenuates paclitaxel-induced peripheral nerve injury by inhibiting p53-related pathways. J Pharmacol Exp Ther 373(3):453–462. Epub 2020/04/03. https://doi.org/10.1124/jpet.120.265082
4. Mohiuddin MS, Himeno T, Inoue R, Miura-Yura E, Yamada Y, Nakai-Shimoda H, Asano S, Kato M, Motegi M, Kondo M, Seino Y, Tsunekawa S, Kato Y, Suzuki A, Naruse K, Kato K,

Nakamura J, Kamiya H. Glucagon-like peptide-1 receptor agonist protects dorsal root ganglion neurons against oxidative insult. J Diabetes Res. 2019;2019:9426014. https://doi.org/10.1155/2019/9426014. Epub 2019/03/29. PubMed PMID: 30918901; PMCID: PMC6408997

5. Klein R, Brown D, Turnley AM. Phenoxodiol protects against Cisplatin induced neurite toxicity in a PC-12 cell model. BMC Neurosci. 2007;8:61. https://doi.org/10.1186/1471-2202-8-61. Epub 2007/08/04. PubMed PMID: 17672914; PMCID: PMC1950519
6. Chambers SM, Qi Y, Mica Y, Lee G, Zhang XJ, Niu L, Bilsland J, Cao L, Stevens E, Whiting P, Shi SH, Studer L. Combined small-molecule inhibition accelerates developmental timing and converts human pluripotent stem cells into nociceptors. Nat Biotechnol. 2012;30(7):715–20. https://doi.org/10.1038/nbt.2249. Epub 2012/07/04. PubMed PMID: 22750882; PMCID: 3516136
7. Vojnits K, Mahammad S, Collins TJ, Bhatia M. Chemotherapy-induced neuropathy and drug discovery platform using human sensory neurons converted directly from adult peripheral blood. Stem Cells Transl Med. 2019;8(11):1180–91. https://doi.org/10.1002/sctm.19-0054. Epub 2019/07/28. PubMed PMID: 31347791; PMCID: PMC6811699
8. Hooijmans CR, Draper D, Ergun M, Scheffer GJ. The effect of analgesics on stimulus evoked pain-like behaviour in animal models for chemotherapy induced peripheral neuropathy- a meta-analysis. Sci Rep. 2019;9(1):17549. https://doi.org/10.1038/s41598-019-54152-8. Epub 2019/11/28. PubMed PMID: 31772391; PMCID: PMC6879539
9. Maruta T, Nemoto T, Hidaka K, Koshida T, Shirasaka T, Yanagita T, Takeya R, Tsuneyoshi I. Upregulation of ERK phosphorylation in rat dorsal root ganglion neurons contributes to oxaliplatin-induced chronic neuropathic pain. PLoS One. 2019;14(11):e0225586. https://doi.org/10.1371/journal.pone.0225586. Epub 2019/11/26. PubMed PMID: 31765435; PMCID: PMC6876879
10. Tsubota M, Fukuda R, Hayashi Y, Miyazaki T, Ueda S, Yamashita R, Koike N, Sekiguchi F, Wake H, Wakatsuki S, Ujiie Y, Araki T, Nishibori M, Kawabata A. Role of non-macrophage cell-derived HMGB1 in oxaliplatin- induced peripheral neuropathy and its prevention by the thrombin/thrombomodulin system in rodents: negative impact of anticoagulants. J Neuroinflammation. 2019;16(1):199. https://doi.org/10.1186/s12974-019-1581-6. Epub 2019/11/02. PubMed PMID: 31666085; PMCID: PMC6822350
11. Janes K, Esposito E, Doyle T, Cuzzocrea S, Tosh DK, Jacobson KA, Salvemini D. A3 adenosine receptor agonist prevents the development of paclitaxel-induced neuropathic pain by modulating spinal glial-restricted redox-dependent signaling pathways. Pain. 2014;155(12):2560–7. https://doi.org/10.1016/j.pain.2014.09.016. Epub 2014/09/23. PubMed PMID: 25242567; PMCID: PMC4529068
12. Slivicki RA, Xu Z, Mali SS, Hohmann AG. Brain permeant and impermeant inhibitors of fatty-acid amide hydrolase suppress the development and maintenance of paclitaxel-induced neuropathic pain without producing tolerance or physical dependence in vivo and synergize with paclitaxel to reduce tumor cell line viability in vitro. Pharmacol Res. 2019;142:267–82. https://doi.org/10.1016/j.phrs.2019.02.002. Epub 2019/02/11. PubMed PMID: 30739035; PMCID: PMC6878658
13. Alessandri-Haber N, Dina OA, Joseph EK, Reichling DB, Levine JD. Interaction of transient receptor potential vanilloid 4, integrin, and SRC tyrosine kinase in mechanical hyperalgesia. J Neurosci. 2008;28(5):1046–57. https://doi.org/10.1523/JNEUROSCI.4497-07.2008. Epub 2008/02/01. PubMed PMID: 18234883; PMCID: PMC6671413
14. Lin H, Heo BH, Yoon MH. A new rat model of cisplatin-induced neuropathic pain. Korean J Pain. 2015;28(4):236–43. https://doi.org/10.3344/kjp.2015.28.4.236. Epub 2015/10/27. PubMed PMID: 26495078; PMCID: PMC4610937
15. Zhang M, Du W, Acklin S, Jin S, Xia F. SIRT2 protects peripheral neurons from cisplatin-induced injury by enhancing nucleotide excision repair. J Clin Invest. 2020;130(6):2953–65. https://doi.org/10.1172/JCI123159. Epub 2020/03/07. PubMed PMID: 32134743; PMCID: PMC7260000

16. Duggett NA, Flatters SJL. Characterization of a rat model of bortezomib-induced painful neuropathy. Br J Pharmacol. 2017;174(24):4812–25. https://doi.org/10.1111/bph.14063. Epub 2017/10/04. PubMed PMID: 28972650; PMCID: PMC5727311
17. Boehmerle W, Huehnchen P, Peruzzaro S, Balkaya M, Endres M. Electrophysiological, behavioral and histological characterization of paclitaxel, cisplatin, vincristine and bortezomib-induced neuropathy in C57Bl/6 mice. Sci Rep. 2014;4:6370. https://doi.org/10.1038/srep06370. Epub 2014/09/19. PubMed PMID: 25231679; PMCID: PMC5377307
18. Huehnchen P, Muenzfeld H, Boehmerle W, Endres M. Blockade of IL-6 signaling prevents paclitaxel-induced neuropathy in C57Bl/6 mice. Cell Death Dis. 2020;11(1):45. https://doi.org/10.1038/s41419-020-2239-0. Epub 2020/01/24. PubMed PMID: 31969555; PMCID: PMC6976596
19. Miyano K, Shiraishi S, Minami K, Sudo Y, Suzuki M, Yokoyama T, Terawaki K, Nonaka M, Murata H, Higami Y, Uezono Y. Carboplatin enhances the activity of human transient receptor potential ankyrin 1 through the cyclic AMP-protein kinase A-A-Kinase Anchoring Protein (AKAP) pathways. Int J Mol Sci. 2019;20(13). https://doi.org/10.3390/ijms20133271. Epub 2019/07/07. PubMed PMID: 31277262; PMCID: PMC6651390
20. Kawashiri T, Shimizu S, Shigematsu N, Kobayashi D, Shimazoe T (2019) Donepezil ameliorates oxaliplatin-induced peripheral neuropathy via a neuroprotective effect. J Pharmacol Sci 140(3):291–294. Epub 2019/08/05. https://doi.org/10.1016/j.jphs.2019.05.009
21. Fukuda M, Yamamoto A (2004) Effect of forskolin on synaptotagmin IV protein trafficking in PC12 cells. J Biochem 136(2):245–253. Epub 2004/10/22. https://doi.org/10.1093/jb/mvh116
22. Imai S, Koyanagi M, Azimi Z, Nakazato Y, Matsumoto M, Ogihara T, Yonezawa A, Omura T, Nakagawa S, Wakatsuki S, Araki T, Kaneko S, Nakagawa T, Matsubara K. Taxanes and platinum derivatives impair Schwann cells via distinct mechanisms. Sci Rep. 2017;7(1):5947. https://doi.org/10.1038/s41598-017-05784-1. Epub 2017/07/22. PubMed PMID: 28729624; PMCID: PMC5519765
23. Blanchard JW, Eade KT, Szucs A, Lo Sardo V, Tsunemoto RK, Williams D, Sanna PP, Baldwin KK. Selective conversion of fibroblasts into peripheral sensory neurons. Nat Neurosci. 2015;18(1):25–35. https://doi.org/10.1038/nn.3887. Epub 2014/11/25. PubMed PMID: 25420069; PMCID: PMC4466122
24. Hoelting L, Klima S, Karreman C, Grinberg M, Meisig J, Henry M, Rotshteyn T, Rahnenfuhrer J, Bluthgen N, Sachinidis A, Waldmann T, Leist M. Stem cell-derived immature human dorsal root ganglia neurons to identify peripheral neurotoxicants. Stem Cells Transl Med. 2016;5(4):476–87. https://doi.org/10.5966/sctm.2015-0108. Epub 2016/03/05. PubMed PMID: 26933043; PMCID: PMC4798731
25. Rana P, Luerman G, Hess D, Rubitski E, Adkins K, Somps C (2017) Utilization of iPSC-derived human neurons for high-throughput drug- induced peripheral neuropathy screening. Toxicol In Vitro 45(Pt 1):111–118. Epub 2017/08/28. https://doi.org/10.1016/j.tiv.2017.08.014
26. Wheeler HE, Wing C, Delaney SM, Komatsu M, Dolan ME. Modeling chemotherapeutic neurotoxicity with human induced pluripotent stem cell-derived neuronal cells. PLoS One. 2015;10(2):e0118020. https://doi.org/10.1371/journal.pone.0118020. Epub 2015/02/18. PubMed PMID: 25689802; PMCID: PMC4331516
27. Wing C, Komatsu M, Delaney SM, Krause M, Wheeler HE, Dolan ME. Application of stem cell derived neuronal cells to evaluate neurotoxic chemotherapy. Stem Cell Res. 2017;22:79–88. https://doi.org/10.1016/j.scr.2017.06.006. Epub 2017/06/24. PubMed PMID: 28645005; PMCID: PMC5737666
28. Starobova H, Vetter I. Pathophysiology of chemotherapy-induced peripheral neuropathy. Front Mol Neurosci. 2017;10:174. https://doi.org/10.3389/fnmol.2017.00174. Epub 2017/06/18. PubMed PMID: 28620280; PMCID: PMC5450696
29. Hu LY, Mi WL, Wu GC, Wang YQ, Mao-Ying QL. Prevention and treatment for chemotherapy-induced peripheral neuropathy: therapies based on CIPN mechanisms. Curr Neuropharmacol. 2019;17(2):184–96. https://doi.org/10.2174/

1570159X15666170915143217. Epub 2017/09/20. PubMed PMID: 28925884; PMCID: PMC6343206
30. Wiszniak S, Schwarz Q. Notch signalling defines dorsal root ganglia neuroglial fate choice during early neural crest cell migration. BMC Neurosci. 2019;20(1):21. https://doi.org/10.1186/s12868-019-0501-0. Epub 2019/05/01. PubMed PMID: 31036074; PMCID: PMC6489353
31. Czaja K, Fornaro M, Geuna S. Neurogenesis in the adult peripheral nervous system. Neural Regen Res. 2012;7(14):1047–54. https://doi.org/10.3969/j.issn.1673-5374.2012.14.002. Epub 2012/05/15. PubMed PMID: 25722694; PMCID: PMC4340017
32. Muratori L, Ronchi G, Raimondo S, Geuna S, Giacobini-Robecchi MG, Fornaro M. Generation of new neurons in dorsal root Ganglia in adult rats after peripheral nerve crush injury. Neural Plast. 2015;2015:860546. https://doi.org/10.1155/2015/860546. Epub 2015/02/28. PubMed PMID: 25722894; PMCID: PMC4333329
33. Chen L, Gong HY, Xu L. PVT1 protects diabetic peripheral neuropathy via PI3K/AKT pathway. Eur Rev Med Pharmacol Sci. 2018;22(20):6905–11. https://doi.org/10.26355/eurrev_201810_16160. Epub 2018/11/08
34. Ceci ML, Mardones-Krsulovic C, Sanchez M, Valdivia LE, Allende ML. Axon-Schwann cell interactions during peripheral nerve regeneration in zebrafish larvae. Neural Dev. 2014;9:22. https://doi.org/10.1186/1749-8104-9-22. Epub 2014/10/19. PubMed PMID: 25326036; PMCID: PMC4214607
35. Ducommun Priest M, Navarro MF, Bremer J, Granato M. Dynein promotes sustained axonal growth and Schwann cell remodeling early during peripheral nerve regeneration. PLoS Genet. 2019;15(2):e1007982. https://doi.org/10.1371/journal.pgen.1007982. Epub 2019/02/20. PubMed PMID: 30779743; PMCID: PMC6396928
36. Hung HA, Sun G, Keles S, Svaren J. Dynamic regulation of Schwann cell enhancers after peripheral nerve injury. J Biol Chem. 2015;290(11):6937–50. https://doi.org/10.1074/jbc.M114.622878. Epub 2015/01/24. PubMed PMID: 25614629; PMCID: PMC4358118
37. Wilcox MB, Laranjeira SG, Eriksson TM, Jessen KR, Mirsky R, Quick TJ, Phillips JB. Characterising cellular and molecular features of human peripheral nerve degeneration. Acta Neuropathol Commun. 2020;8(1):51. https://doi.org/10.1186/s40478-020-00921-w. Epub 2020/04/19. PubMed PMID: 32303273; PMCID: PMC7164159
38. Mahar M, Cavalli V. Intrinsic mechanisms of neuronal axon regeneration. Nat Rev Neurosci. 2018;19(6):323–37. https://doi.org/10.1038/s41583-018-0001-8. Epub 2018/04/19. PubMed PMID: 29666508; PMCID: PMC5987780
39. Fukuda Y, Li Y, Segal RA. A mechanistic understanding of axon degeneration in chemotherapy-induced peripheral neuropathy. Front Neurosci. 2017;11:481. https://doi.org/10.3389/fnins.2017.00481. Epub 2017/09/16. PubMed PMID: 28912674; PMCID: PMC5583221
40. Hwang J, Namgung U. Cdk5 phosphorylation of STAT3 in dorsal root ganglion neurons is involved in promoting axonal regeneration after peripheral nerve injury. Int Neurourol J. 2020;24(Suppl 1):S19–27. https://doi.org/10.5213/inj.2040158.080. Epub 2020/06/03. PubMed PMID: 32482054; PMCID: PMC7285696
41. Morales M, Avila J, Gonzalez-Fernandez R, Boronat L, Soriano ML, Martin-Vasallo P. Differential transcriptome profile of peripheral white cells to identify biomarkers involved in oxaliplatin induced neuropathy. J Pers Med. 2014;4(2):282–96. https://doi.org/10.3390/jpm4020282. Epub 2015/01/08. PubMed PMID: 25563226; PMCID: PMC4263976
42. Flatters SJL, Dougherty PM, Colvin LA (2017) Clinical and preclinical perspectives on chemotherapy-induced peripheral neuropathy (CIPN): a narrative review. Br J Anaesth 119 (4):737–749. Epub 2017/11/10. https://doi.org/10.1093/bja/aex229
43. Miyagi A, Kawashiri T, Shimizu S, Shigematsu N, Kobayashi D, Shimazoe T (2019) Dimethyl fumarate attenuates Oxaliplatin-induced peripheral neuropathy without affecting the anti-tumor activity of Oxaliplatin in rodents. Biol Pharm Bull 42(4):638–644. Epub 2019/04/02. https://doi.org/10.1248/bpb.b18-00855

44. Brandolini L, Castelli V, Aramini A, Giorgio C, Bianchini G, Russo R, De Caro C, d'Angelo M, Catanesi M, Benedetti E, Giordano A, Cimini A, Allegretti M. DF2726A, a new IL-8 signalling inhibitor, is able to counteract chemotherapy-induced neuropathic pain. Sci Rep. 2019;9 (1):11729. https://doi.org/10.1038/s41598-019-48231-z. Epub 2019/08/15. PubMed PMID: 31409858; PMCID: PMC6692352
45. Galley HF, McCormick B, Wilson KL, Lowes DA, Colvin L, Torsney C. Melatonin limits paclitaxel-induced mitochondrial dysfunction in vitro and protects against paclitaxel-induced neuropathic pain in the rat. J Pineal Res. 2017;63(4):e12444. https://doi.org/10.1111/jpi.12444. Epub 2017/08/24. PubMed PMID: 28833461; PMCID: PMC5656911
46. Stage TB, Hu S, Sparreboom A, Kroetz DL (2020) Role of drug transporters in chemotherapy-induced peripheral neuropathy. Clin Transl Sci 3:1–8. https://doi.org/10.1111/cts.12915
47. Leblanc AF, Sprowl JA, Alberti P, et al. OATP1B2 deficiency protects against paclitaxel-induced neurotoxicity. J Clin Invest 2018;128(2):816–825. https://doi.org/10.1172/JCI96160
48. Geisler S, Doan RA, Strickland A, Huang X, Milbrandt J, DiAntonio A. Prevention of vincristine-induced peripheral neuropathy by genetic deletion of SARM1 in mice. Brain. 2016;139(Pt 12):3092–108. https://doi.org/10.1093/brain/aww251. Epub 2016/11/01. PubMed PMID: 27797810; PMCID: PMC5840884
49. Lazic A, Popovic J, Paunesku T, Woloschak GE, Stevanovic M. Insights into platinum-induced peripheral neuropathy-current perspective. Neural Regen Res. 2020;15(9):1623–30. https://doi.org/10.4103/1673-5374.276321. Epub 2020/03/27. PubMed PMID: 32209761; PMCID: PMC7437596
50. Tyagi S, Gupta P, Saini AS, Kaushal C, Sharma S. The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases. J Adv Pharm Technol Res. 2011;2(4):236–40. https://doi.org/10.4103/2231-4040.90879. Epub 2012/01/17. PubMed PMID: 22247890; PMCID: PMC3255347
51. Zhao X, Du W, Zhang M, Atiq ZO, Xia F. Sirt2-associated transcriptome modifications in cisplatin-induced neuronal injury. BMC Genomics. 2020;21(1):192. https://doi.org/10.1186/s12864-020-6584-2. Epub 2020/03/04. PubMed PMID: 32122297; PMCID: PMC7053098
52. Kawashiri T, Miyagi A, Shimizu S, Shigematsu N, Kobayashi D, Shimazoe T (2018) Dimethyl fumarate ameliorates chemotherapy agent-induced neurotoxicity in vitro. J Pharmacol Sci 137 (2):202–211. Epub 2018/07/26. https://doi.org/10.1016/j.jphs.2018.06.008
53. Ludman T, Melemedjian OK. Bortezomib-induced aerobic glycolysis contributes to chemotherapy-induced painful peripheral neuropathy. Mol Pain. 2019;15:1744806919837429. https://doi.org/10.1177/1744806919837429. Epub 2019/02/28. PubMed PMID: 30810076; PMCID: PMC6452581
54. Majithia N, Temkin SM, Ruddy KJ, Beutler AS, Hershman DL, Loprinzi CL. National Cancer Institute-supported chemotherapy-induced peripheral neuropathy trials: outcomes and lessons. Support Care Cancer. 2016;24(3):1439–47. https://doi.org/10.1007/s00520-015-3063-4. Epub 2015/12/22. PubMed PMID: 26686859; PMCID: PMC5078987
55. Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, Bressler LR, Fadul CE, Knox C, Le-Lindqwister N, Gilman PB, Shapiro CL, Alliance for clinical trials in O. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. Jama. 2013;309(13):1359–67. https://doi.org/10.1001/jama.2013.2813. PubMed PMID: 23549581; PMCID: PMC3912515
56. Xiao W, Naso L, Bennett GJ (2008) Experimental studies of potential analgesics for the treatment of chemotherapy-evoked painful peripheral neuropathies. Pain Med 9(5):505–517. Epub 2008/09/09. https://doi.org/10.1111/j.1526-4637.2007.00301.x
57. Zhang H, Dougherty PM. Enhanced excitability of primary sensory neurons and altered gene expression of neuronal ion channels in dorsal root ganglion in paclitaxel-induced peripheral neuropathy. Anesthesiology. 2014;120(6):1463–75. https://doi.org/10.1097/ALN.0000000000000176. Epub 2014/02/19. PubMed PMID: 24534904; PMCID: PMC4031279
58. Li Y, North RY, Rhines LD, Tatsui CE, Rao G, Edwards DD, Cassidy RM, Harrison DS, Johansson CA, Zhang H, Dougherty PM. DRG voltage- gated sodium channel 1.7 is

upregulated in paclitaxel-induced neuropathy in rats and in humans with neuropathic pain. J Neurosci. 2018;38(5):1124–36. https://doi.org/10.1523/JNEUROSCI.0899-17.2017. Epub 2017/12/20. PubMed PMID: 29255002; PMCID: PMC5792474
59. Thibault K, Calvino B, Dubacq S, Roualle-de-Rouville M, Sordoillet V, Rivals I, Pezet S (2012) Cortical effect of oxaliplatin associated with sustained neuropathic pain: exacerbation of cortical activity and down-regulation of potassium channel expression in somatosensory cortex. Pain 153(8):1636–1647. Epub 2012/06/02. https://doi.org/10.1016/j.pain.2012.04.016
60. Descoeur J, Pereira V, Pizzoccaro A, Francois A, Ling B, Maffre V, Couette B, Busserolles J, Courteix C, Noel J, Lazdunski M, Eschalier A, Authier N, Bourinet E. Oxaliplatin-induced cold hypersensitivity is due to remodelling of ion channel expression in nociceptors. EMBO Mol Med. 2011;3(5):266–78. https://doi.org/10.1002/emmm.201100134. Epub 2011/03/26. PubMed PMID: 21438154; PMCID: PMC3377073
61. Nodera H, Spieker A, Sung M, Rutkove S (2011) Neuroprotective effects of Kv7 channel agonist, retigabine, for cisplatin-induced peripheral neuropathy. Neurosci Lett 505(3):223–227. Epub 2011/09/29. https://doi.org/10.1016/j.neulet.2011.09.013
62. Li Y, Tatsui CE, Rhines LD, North RY, Harrison DS, Cassidy RM, Johansson CA, Kosturakis AK, Edwards DD, Zhang H, Dougherty PM. Dorsal root ganglion neurons become hyperexcitable and increase expression of voltage-gated T-type calcium channels (Cav3.2) in paclitaxel-induced peripheral neuropathy. Pain. 2017;158(3):417–29. https://doi.org/10.1097/j.pain.0000000000000774. Epub 2016/12/03. PubMed PMID: 27902567; PMCID: PMC5303135
63. Cai S, Tuohy P, Ma C, Kitamura N, Gomez K, Zhou Y, Ran D, Bellampalli SS, Yu J, Luo S, Dorame A, Ngan Pham NY, Molnar G, Streicher JM, Patek M, Perez-Miller S, Moutal A, Wang J, Khanna R (2020. Epub 2020/06/17) A modulator of the low-voltage activated T-type calcium channel that reverses HIV glycoprotein 120-, paclitaxel-, and spinal nerve ligation-induced peripheral neuropathies. Pain. https://doi.org/10.1097/j.pain.0000000000001955
64. Bellampalli SS, Ji Y, Moutal A, Cai S, Wijeratne EMK, Gandini MA, Yu J, Chefdeville A, Dorame A, Chew LA, Madura CL, Luo S, Molnar G, Khanna M, Streicher JM, Zamponi GW, Gunatilaka AAL, Khanna R. Betulinic acid, derived from the desert lavender *Hyptis emoryi*, attenuates paclitaxel-, HIV-, and nerve injury-associated peripheral sensory neuropathy via block of N- and T-type calcium channels. Pain. 2019;160(1):117–35. https://doi.org/10.1097/j.pain.0000000000001385. Epub 2018/09/01. PubMed PMID: 30169422; PMCID: PMC6309937
65. Makker PG, Duffy SS, Lees JG, Perera CJ, Tonkin RS, Butovsky O, Park SB, Goldstein D, Moalem-Taylor G. Characterisation of immune and Neuroinflammatory changes associated with chemotherapy-induced peripheral neuropathy. PLoS One. 2017;12(1):e0170814. https://doi.org/10.1371/journal.pone.0170814. Epub 2017/01/27. PubMed PMID: 28125674; PMCID: PMC5268425
66. Shen Y, Zhang ZJ, Zhu MD, Jiang BC, Yang T, Gao YJ (2015) Exogenous induction of HO-1 alleviates vincristine-induced neuropathic pain by reducing spinal glial activation in mice. Neurobiol Dis 79:100–110. Epub 2015/05/10. https://doi.org/10.1016/j.nbd.2015.04.012
67. Robinson CR, Zhang H, Dougherty PM. Astrocytes, but not microglia, are activated in oxaliplatin and bortezomib-induced peripheral neuropathy in the rat. Neuroscience. 2014;274:308–17. https://doi.org/10.1016/j.neuroscience.2014.05.051. Epub 2014/06/07. PubMed PMID: 24905437; PMCID: PMC4099296
68. Zhou L, Hu Y, Li C, Yan Y, Ao L, Yu B, Fang W, Liu J, Li Y (2018) Levo- corydalmine alleviates vincristine-induced neuropathic pain in mice by inhibiting an NF-kappa B-dependent CXCL1/CXCR2 signaling pathway. Neuropharmacology 135:34–47. Epub 2018/03/09. https://doi.org/10.1016/j.neuropharm.2018.03.004
69. Brandolini L, Benedetti E, Ruffini PA, Russo R, Cristiano L, Antonosante A, d'Angelo M, Castelli V, Giordano A, Allegretti M, Cimini A. CXCR1/2 pathways in paclitaxel-induced neuropathic pain. Oncotarget. 2017;8(14):23188–201. https://doi.org/10.18632/oncotarget.15533. Epub 2017/04/21. PubMed PMID: 28423567; PMCID: PMC5410296

70. Zhang H, Li Y, de Carvalho-Barbosa M, Kavelaars A, Heijnen CJ, Albrecht PJ, Dougherty PM. Dorsal root ganglion infiltration by macrophages contributes to paclitaxel chemotherapy-induced peripheral neuropathy. J Pain. 2016;17(7):775–86. https://doi.org/10.1016/j.jpain.2016.02.011. Epub 2016/03/17. PubMed PMID: 26979998; PMCID: PMC4939513
71. Luo X, Huh Y, Bang S, He Q, Zhang L, Matsuda M, Ji RR. Macrophage toll-like receptor 9 contributes to chemotherapy-induced neuropathic pain in male mice. J Neurosci. 2019;39(35):6848–64. https://doi.org/10.1523/JNEUROSCI.3257-18.2019. Epub 2019/07/05. PubMed PMID: 31270160; PMCID: PMC6733562
72. Li Y, Adamek P, Zhang H, Tatsui CE, Rhines LD, Mrozkova P, Li Q, Kosturakis AK, Cassidy RM, Harrison DS, Cata JP, Sapire K, Zhang H, Kennamer-Chapman RM, Jawad AB, Ghetti A, Yan J, Palecek J, Dougherty PM. The cancer chemotherapeutic paclitaxel increases human and rodent sensory neuron responses to TRPV1 by activation of TLR4. J Neurosci. 2015;35(39):13487–500. https://doi.org/10.1523/JNEUROSCI.1956-15.2015. Epub 2015/10/02. PubMed PMID: 26424893; PMCID: PMC4588613
73. Li Y, Zhang H, Zhang H, Kosturakis AK, Jawad AB, Dougherty PM. Toll-like receptor 4 signaling contributes to Paclitaxel-induced peripheral neuropathy. J Pain. 2014;15(7):712–25. https://doi.org/10.1016/j.jpain.2014.04.001. Epub 2014/04/24. PubMed PMID: 24755282; PMCID: PMC4083500
74. Chen Z, Doyle TM, Luongo L, Largent-Milnes TM, Giancotti LA, Kolar G, Squillace S, Boccella S, Walker JK, Pendleton A, Spiegel S, Neumann WL, Vanderah TW, Salvemini D. Sphingosine-1-phosphate receptor 1 activation in astrocytes contributes to neuropathic pain. Proc Natl Acad Sci U S A. 2019;116(21):10557–62. https://doi.org/10.1073/pnas.1820466116. Epub 2019/05/10. PubMed PMID: 31068460; PMCID: PMC6534990
75. Janes K, Little JW, Li C, Bryant L, Chen C, Chen Z, Kamocki K, Doyle T, Snider A, Esposito E, Cuzzocrea S, Bieberich E, Obeid L, Petrache I, Nicol G, Neumann WL, Salvemini D. The development and maintenance of paclitaxel-induced neuropathic pain require activation of the sphingosine 1-phosphate receptor subtype 1. J Biol Chem. 2014;289(30):21082–97. https://doi.org/10.1074/jbc.M114.569574. Epub 2014/05/31. PubMed PMID: 24876379; PMCID: PMC4110312
76. Stockstill K, Wahlman C, Braden K, Chen Z, Yosten GL, Tosh DK, Jacobson KA, Doyle TM, Samson WK, Salvemini D. Sexually dimorphic therapeutic response in bortezomib-induced neuropathic pain reveals altered pain physiology in female rodents. Pain. 2020;161(1):177–84. https://doi.org/10.1097/j.pain.0000000000001697. Epub 2019/09/07. PubMed PMID: 31490328; PMCID: PMC6923586
77. Deng L, Cornett BL, Mackie K, Hohmann AG. CB1 knockout mice unveil sustained CB2-mediated antiallodynic effects of the Mixed CB1/CB2 agonist CP55,940 in a mouse model of paclitaxel-induced neuropathic pain. Mol Pharmacol. 2015;88(1):64–74. https://doi.org/10.1124/mol.115.098483. Epub 2015/04/24. PubMed PMID: 25904556; PMCID: PMC4468646
78. Uhelski ML, Khasabova IA, Simone DA. Inhibition of anandamide hydrolysis attenuates nociceptor sensitization in a murine model of chemotherapy-induced peripheral neuropathy. J Neurophysiol. 2015;113(5):1501–10. https://doi.org/10.1152/jn.00692.2014. Epub 2014/12/17. PubMed PMID: 25505113; PMCID: PMC4346731
79. Mulpuri Y, Marty VN, Munier JJ, Mackie K, Schmidt BL, Seltzman HH, Spigelman I. Synthetic peripherally-restricted cannabinoid suppresses chemotherapy-induced peripheral neuropathy pain symptoms by CB1 receptor activation. Neuropharmacology. 2018;139:85–97. https://doi.org/10.1016/j.neuropharm.2018.07.002. Epub 2018/07/08. PubMed PMID: 29981335; PMCID: PMC6883926
80. King KM, Myers AM, Soroka-Monzo AJ, Tuma RF, Tallarida RJ, Walker EA, Ward SJ. Single and combined effects of Delta(9) – tetrahydrocannabinol and cannabidiol in a mouse model of chemotherapy- induced neuropathic pain. Br J Pharmacol. 2017;174(17):2832–41. https://doi.org/10.1111/bph.13887. Epub 2017/05/27. PubMed PMID: 28548225; PMCID: PMC5554313

81. Vera G, Cabezos PA, Martin MI, Abalo R (2013) Characterization of cannabinoid-induced relief of neuropathic pain in a rat model of cisplatin- induced neuropathy. Pharmacol Biochem Behav 105:205–212. Epub 2013/03/05. https://doi.org/10.1016/j.pbb.2013.02.008
82. Khasabova IA, Khasabov S, Paz J, Harding-Rose C, Simone DA, Seybold VS. Cannabinoid type-1 receptor reduces pain and neurotoxicity produced by chemotherapy. J Neurosci. 2012;32 (20):7091–101. https://doi.org/10.1523/JNEUROSCI.0403-12.2012. Epub 2012/05/18. PubMed PMID: 22593077; PMCID: PMC3366638
83. Segat GC, Manjavachi MN, Matias DO, Passos GF, Freitas CS, Costa R, Calixto JB (2017) Antiallodynic effect of beta-caryophyllene on paclitaxel- induced peripheral neuropathy in mice. Neuropharmacology 125:207–219. Epub 2017/07/22. https://doi.org/10.1016/j.neuropharm.2017.07.015
84. Deng L, Guindon J, Cornett BL, Makriyannis A, Mackie K, Hohmann AG. Chronic cannabinoid receptor 2 activation reverses paclitaxel neuropathy without tolerance or cannabinoid receptor 1-dependent withdrawal. Biol Psychiatry. 2015;77(5):475–87. https://doi.org/10.1016/j.biopsych.2014.04.009. Epub 2014/05/24. PubMed PMID: 24853387; PMCID: PMC4209205
85. Tonello R, Lee SH, Berta T (2019) Monoclonal antibody targeting the matrix metalloproteinase 9 prevents and reverses paclitaxel-induced peripheral neuropathy in Mice. J Pain 20 (5):515–527. https://doi.org/10.1016/j.jpain.2018.11.003. Epub 2018/11/25. PubMed PMID: 30471427; PMCID: PMC6511475
86. Krukowski K, Ma J, Golonzhka O, Laumet GO, Gutti T, van Duzer JH, Mazitschek R, Jarpe MB, Heijnen CJ, Kavelaars A (2017) HDAC6 inhibition effectively reverses chemotherapy-induced peripheral neuropathy. Pain 158(6):1126–1137. https://doi.org/10.1097/j.pain.0000000000000893. Epub 2017/03/08. PubMed PMID: 28267067; PMCID: PMC5435512
87. Ramakrishna C, Corleto J, Ruegger PM, Logan GD, Peacock BB, Mendonca S, Yamaki S, Adamson T, Ermel R, McKemy D, Borneman J, Cantin EM (2019) Dominant role of the gut microbiota in chemotherapy induced neuropathic pain. Sci Rep. 9(1):20324. https://doi.org/10.1038/s41598-019-56832-x. Epub 2020/01/01. PubMed PMID: 31889131; PMCID: PMC6937259
88. Slivicki RA, Mali SS, Hohmann AG (2019) Voluntary exercise reduces both chemotherapy-induced neuropathic nociception and deficits in hippocampal cellular proliferation in a mouse model of paclitaxel-induced peripheral neuropathy. Neurobiol Pain 6:100035. https://doi.org/10.1016/j.ynpai.2019.100035. Epub 2019/09/19. PubMed PMID: 31528755; PMCID: PMC6739464