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Chemotherapy-induced peripheral neuropathy (CIPN): disease mechanisms, experimental models and emerging prevention strategies

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a common, dose-limiting side effect of several classes of anticancer agents, with complex pathophysiology that is distinct from other neuropathies, such as diabetic neuropathy. Here, we provide a comprehensive review of CIPN, linking clinical presentations and implicated anticancer therapeutics to their underlying molecular mechanisms. We discuss both conventional chemotherapy agents and emerging modalities, including antibody-drug conjugates. We also critically evaluate experimental models of CIPN, spanning *in vivo*, *ex vivo*, and both classical and emerging advanced *in vitro* human-derived models, alongside methodological advances capable of providing deeper mechanistic insight into CIPN. Importantly, we examine current and emerging strategies for CIPN prevention, emphasising the need to prioritise prevention over symptomatic management. By integrating clinical insights, established and emerging mechanistic understanding, and a comprehensive overview of experimental models and methodological advances alongside emerging preventive interventions, this review uniquely serves as both a clinical and biological guide to CIPN. It aims to bridge the gap between bench and bedside, supporting both researchers and clinicians in advancing effective prevention strategies to combat CIPN, a significant unmet need affecting patients during treatment and throughout cancer survivorship.

Keywords

Chemotherapy-induced peripheral neuropathy, neurotoxicity mechanisms, cell models, oxidative stress, limb cryotherapy, prevention, patient-reported outcomes, translational models.

Introduction to CIPN

Chemotherapy-induced peripheral neuropathy (CIPN) is a multifaceted, often chronic, and dose-limiting severe side effect of chemotherapy treatment estimated to affect up to 19-85% of cancer patients.¹ Whilst the definition of CIPN varies due to the complexity of clinical presentation, CIPN is regarded as a common adverse effect of several antineoplastic drugs of multiple classes, and its severity often leads to dose reduction or treatment cessation, thus affecting prognosis and survival.

Clinical Presentation and Assessment

Typically, CIPN presents in a 'glove and stocking' distribution most commonly manifesting as sensory neuropathy, including both mechanical and thermal allodynia, numbness and paraesthesia. There is considerable symptom variation, including intense pain, burning, electric shock-like pain and impaired or loss of sensory perception and numbness.² Patients have also reported altered motor function, including gait and balance disturbances, and distal weakness. Albeit less common, reports have included changes to autonomic function, such as altered urinary and sexual function.³

CIPN can present months (or even years) after completion of chemotherapy treatment, a phenomenon referred to as 'coasting'. This delayed onset is particularly associated with platinum-based therapies and presents a significant clinical challenge, as it limits the ability to reassess and modify treatment protocols in a timely manner to mitigate neuropathy severity.⁴ The long-term burden of CIPN is substantial. Studies in childhood cancer survivors have reported symptoms of peripheral neuropathy in 53% of patients assessed up to 29 years post-treatment.⁵ Furthermore, a recent clinical study in patients receiving taxane or platinum therapy, reported that the odds of patients preferring to discontinue treatment due to CIPN increased 30-fold when informed that symptoms could be permanent.⁶ The impact of CIPN on both patient quality-of-life and survivorship represents one of the greatest challenges in cancer care.

A recent publication has identified several CIPN assessment tools including 3 clinician-based grading scales, 20 patient-reported outcome measures (PROMs) and 8 objective measurements.⁷ Clinician-based grading tools include the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), the most commonly used tool, which assesses sensory, motor, and autonomic symptoms alongside physical function. Other grading tools include the World Health Organization Chemotherapy-Induced Peripheral Neuropathy Criterion (WHO CIPN) and the Ajani Scale, which focuses on sensory and motor neuropathy, particularly walking ability. These tools employ direct clinical observations and interviews, including patient and family interviews.⁷ Despite their clinical utility,

clinician-based grading tools may underestimate symptom severity compared with patient reports. Combining these assessments with patient-reported outcome measures (PROMs), such as the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-CIPN20 (EORTC QLQ-CIPN20), can therefore provide additional assessment of symptom presentation and burden, as well as the impact of CIPN on quality of life.⁸ A study comparing NCI-CTCAE and EORTC QLQ-CIPN20 assessments reported poor correlation between the two methods at the individual-patient level. Importantly, PROM assessment identified symptoms at lower cumulative chemotherapy doses than NCI-CTCAE assessment.⁹ Given the subjective nature of pain, the use of quantitative tools to assess characteristics of CIPN including sensation, strength, pain, vibration, temperature and electrical activity are also being actively explored.⁷

Antineoplastic Therapeutic Agents Associated with CIPN

Chemotherapy drugs

CIPN is associated with several classes of systemically administered anticancer agents, including platinum, taxanes, vinca alkaloids, anti-metabolites, and proteasome inhibitors.¹⁰ Figure 1 provides a schematic summary of the clinical presentation and hypothesised pathophysiology for the major chemotherapy drug classes discussed in this review.

Among these, platinum-based agents (such as cisplatin, oxaliplatin, carboplatin) are consistently reported as being amongst the most prevalent agents in CIPN development.¹¹ Platinum agents target the genome in cancer cells by forming DNA-platinum adducts resulting in cell cycle arrest and apoptosis. In neuronal cells, altered nucleoli and decreased production of ribosomal RNA has been reported upon platinum exposure. Despite their post-mitotic state, neurons are highly metabolically active, rendering them particularly vulnerable to platinum-induced DNA damage. This results in multiple forms of cellular injury, including mitochondrial dysfunction, oxidative stress, and lipid peroxidation.¹²

Taxane chemotherapy drugs typically bind β -tubulin subunits promoting microtubule polymerisation and stabilisation by preventing depolymerisation and disrupting normal microtubule dynamics, thus resulting in inhibition of cell division and induction of apoptosis. In neuronal cells, taxane-induced neurotoxicity has been associated with disruption of microtubule-dependent axonal transport.^{13, 14} By contrast, vinca alkaloids, such as vincristine, inhibit microtubule assembly and promote microtubule destabilisation. Despite these opposing effects on microtubule dynamics, both drug classes can disrupt anterograde (soma to distal axon) and retrograde (distal axon to soma) axonal transport, contributing to axonal degeneration.¹⁴

Recent *in vitro* studies investigating the effects of taxanes (paclitaxel) and vinca alkaloids (vincristine) have lent support to these hypotheses. It was shown that exposure to paclitaxel induced morphological axon abnormalities, including axon retraction / thickening and formation of microtubule fragments. Moreover, alterations in drug efflux capacity were reported, with inhibition of efflux transporters associated with increased neurotoxicity following lengthy exposure to vincristine and paclitaxel.¹⁵

Anti-metabolite drugs such as cytarabine (Ara-C) exhibit toxicity by interfering with DNA synthesis; neurotoxicity is primarily associated with the central nervous system (CNS) due to the permeability of the blood-brain barrier (BBB) to these agents.¹⁶ Despite such drug classes being associated with CIPN, the incidence of neurotoxicity triggered by anti-metabolites varies and is considered to be rare.¹⁷ This variation may be due to the combination of chemotherapy agents administered, making it challenging to discern if the neurotoxic effect is attributed exclusively to the effect of the anti-metabolite drug, or it is the result of combinatorial administration with established CIPN-associated chemotherapy regimens.

¹⁸

Unlike the ability of some anti-metabolite drugs to permeate the BBB, proteasome inhibitors are documented to accumulate in the peripheral nervous system (PNS) due to their inability to permeate the BBB. Treatment with the first-generation proteasome inhibitor bortezomib has been associated with several effects on the PNS, including morphological abnormalities of cells in the dorsal root ganglion (DRG) excluding the soma of sensory neurons and axonal degeneration. It has been hypothesised that bortezomib causes increased tubulin polymerisation, accounting for similarities in the observed pathophysiology reported for tubulin targeting drugs taxanes and vinca alkaloids.^{19, 20}

Antibody-Drug Conjugates (ADCs)

Antibody-drug conjugates represent a novel class of anti-neoplastic biologics that have been developed to create a targeted, cancer cell-specific therapeutic approach, which aims to reduce off-target toxicity by combining the target specificity of monoclonal antibodies with the strong cytotoxicity of small chemotherapeutic agents.²¹ The ADC structure consists of a monoclonal antibody designed to recognise a tumour-specific target antigen conjugated to a cytotoxic drug (payload) by a chemical linker. Upon binding to the target antigen, the ADC is internalised and the payload released. Despite the specificity of ADCs, neurotoxicity is increasingly reported as a common side effect of treatment. Proposed mechanisms of ADC-induced neurotoxicity include non-target uptake of the ADCs, premature release of their highly potent payloads into circulation and the extended half-life of ADCs in comparison to small molecule drugs. The high proportion of clinically used ADCs containing tubulin-

inhibiting payloads is of concern in the context of neurotoxicity due to the tubulin-rich structure of neuronal cells.²² Whilst traditional chemotherapy is primarily associated with sensory neuropathy, reports of neuropathy associated with ADC treatment also extend to peripheral motor neuropathy, demyelinating disorders and neuromuscular disorders.^{23, 24} Despite the innovative development of targeted ADCs, neuropathy remains a prevalent side effect of treatment and, similarly to traditional chemotherapy, dose adjustment remains the main strategy in reducing ADC-mediated neurotoxicity.²⁵

Collectively, these observations suggest that, despite the well-defined targets for these antineoplastic agent classes, subsequent neurotoxicity is a universal off-target side effect (Figure 1). Therefore, rather than causing CIPN via a common target mechanism, it is more likely that these different (based on target specificity) neurotoxic ‘insults’ mechanistically merge downstream of the initial target and thus utilise a common (universal) downstream effector(s) to drive the pathophysiology of CIPN. Table 1 provides a summary of the different classes of drugs used as cancer therapeutics in the clinic and their association with the pathophysiology of CIPN.

Current Biological Understanding of CIPN

Barriers of the Nervous System

The nervous system is histologically unique in that there are no clearly defined anatomical boundaries between the CNS and PNS systems. However, there are differences in their cell populations, allowing functionally distinct roles in the nervous system and a particular predisposition for damage in the peripheral system.²⁶ The increased off-target neurotoxicity observed in the PNS during chemotherapy treatment, in comparison to the CNS, may be attributed to the differences between the barriers of the nervous system, the blood-brain barrier (BBB) and blood-nerve barrier (BNB). The BBB is composed of multiple cell types including microvascular endothelial cells, astrocytes and mature pericytes forming the basement membrane and tight junctions.²⁷ The BBB is selectively permeable to some water-soluble small molecules and low molecular weight lipophilic chemotherapy drugs due to the presence of strong tight junctions inhibiting transcellular and paracellular transport; by contrast, larger molecules require transport to enter the CNS.²⁸ In comparison, the BNB is more permeable to chemotherapy drugs due to its weaker tight junctions, increased permeability and limited efflux capacity thus resulting in increased entry and subsequent accumulation of chemotherapy drugs.^{1, 29} The capacity of the BBB and BNB to repair is also different; the presence of astrocytes in the BBB allows proximal repair and maintenance, whilst the BNB relies on immune cell activation³⁰ which is suppressed during chemotherapy treatment.

Research on the involvement of the BNB in this context has identified the contributing role of the BNB in CIPN pathogenesis³¹, accounting for the PNS-specific symptoms mostly associated with CIPN.

Homeostatic Blood-Nerve Barrier Responses to Nerve Injury

The permeability of the BNB is dynamic, facilitating injury responses and nerve repair. It has been shown to increase during acute neuroinflammation, allowing immune cell infiltration, and tissue recovery.³² Studies using rodents to investigate the effect of local nerve injury on BNB permeability and neuropathy symptoms reported that injection of healthy mice with serum from mice with nerve injuries induced mechanical allodynia and increased BNB permeability.³⁰ However, more recent research has indicated that changes to the BNB following Schwann cell activation are due to alterations in transport across the barrier, with enhanced transcytosis raising permeability. Despite the increased susceptibility to damage in BNB in comparison to the BBB, the presence of macrophages engulfing material entering the BNB affords an additional protective mechanism.²⁹ These hypotheses imply that both structural and functional changes may occur to the BNB during nerve injury, resulting in increased chemotherapy neurotoxicity.

The homeostatic response to nerve injury may therefore present a paradox during chemotherapy treatment and CIPN development, whereby mechanisms that normally facilitate tissue repair may inadvertently increase susceptibility to further neurotoxicity. Studies investigating the role of BNB in post-surgical pain reported that homeostatic disruption of the BNB may last up to 7 days until normal tissue function is restored.³³ This prolonged increased susceptibility of the BNB may be particularly problematic considering the cyclic and repetitive delivery of chemotherapy agents. Chemotherapy is administered in cycles with infusion times lasting 1-3 hours and may be repeated over consecutive days, often with multiple chemotherapy agents administered throughout treatment.³⁴ The combined prolonged vulnerability of the BNB during repair and extended exposure to cytotoxic agents may further contribute to the pathogenesis of CIPN, due to increased transport and permeability of the BNB facilitating accumulation and cytotoxicity of these drugs. This is supported by studies reporting accumulation of oxaliplatin in the DRG of mice models after treatment, implicating drug accumulation as a contributing pathological mechanism.³⁵ Consideration of the biology of the PNS and the capacity of chemotherapy drugs to induce multiple cytotoxic effects may explain the pathogenesis of CIPN. Cancer chemotherapy treatment often involves intense treatment regimens resulting in repeated exposure to multiple drug classes and thus intense neurotoxicity, preventing effective neuroprotective responses and/or nerve regeneration.

Proposed Molecular Pathophysiology of CIPN

Axon Degradation

Whilst cells of the PNS are broadly considered to be non-proliferative targets of chemotherapy drugs, early research described some limited regenerative properties of Schwann cells to repair the PNS after nerve injury, which may be considered as a degree of proliferative activity.³⁶ However, the off-target toxicity caused by multiple chemotherapy agents may be attributed to the structural vulnerability of neuronal cells. This is particularly apparent during treatment with mitotic inhibitors (including vinca alkaloids and taxanes), whereby drugs exhibit anticancer effects by depolymerisation of microtubules³⁷ and stabilisation of microtubules resulting in cell cycle arrest.³⁸

In neuronal cells, microtubules form important structural and dynamic cytoskeletal units maintaining morphology, transportation and signalling. Microtubule defects and axonopathies have been identified as a common pathology across multiple neurodegenerative diseases due to neurotoxin exposure.³⁹ The ‘dying-back’ response, whereby distal axonal degradation occurs towards the cell body, resulting in dysfunction and cell death, has been shown to affect transport between the soma and synapse resulting in impaired signal transduction, accumulation of cellular by-products and reduced axonal regeneration capacity.⁴⁰ Research on paclitaxel treatment of post-mitotic neurons supports the hypothesis that neuronal structure vulnerability contributes to the observed cytotoxicity in peripheral nerves. It has been shown that paclitaxel induces persistent alterations in microtubule dynamics, and taxane-induced neuropathy is widely attributed to its microtubule-stabilising effects, which disrupt axonal transport and lead to axonopathy and myelin degeneration.⁴¹ Investigations on both the surrounding environment and the cellular biology of neuronal cells identified several related hypotheses of CIPN pathogenesis, which ultimately converge on distal axonal degeneration.⁴²

Axonal Transport

Maintenance of intracellular transport is essential for neuronal function, enabling the movement of cargo across the morphologically complex neuronal architecture required for axonal growth, plasticity and neurotransmission.⁴³ Transport is facilitated by microtubule networks and ATPase motor proteins (dynein and kinesin) to allow efficient cargo transfer via anterograde (soma to axon) and retrograde (terminal ends to soma) transport, respectively.⁴³ Of particular importance is mitochondrial cycling, with impaired mitochondrial trafficking associated with peripheral nerve degeneration and cell death.⁴⁴

Whilst it is anticipated that microtubule targeting drugs directly affect axonal trafficking, work comparing paclitaxel and oxaliplatin (a DNA targeting agent with mitochondrial toxicity) demonstrated comparative axon length degradation (67.85% and 65.97%, respectively) despite their distinct mechanisms of action.⁴⁵ Beyond its direct microtubule effects, research has demonstrated paclitaxel-induced transcriptomic and proteomic changes associated with degradation of essential axonal proteins and scaffold proteins associated with impaired axonal transport.⁴⁴ These findings not only support the role of disrupted axonal transport as a contributing mechanisms in CIPN, but also suggest that transport dysfunction may extend beyond the direct structural effects of microtubule-targeting chemotherapies.

Oxidative Stress

The specific structural and functional properties of the PNS render it particularly susceptible to mitochondrial dysfunction and oxidative stress-mediated damage. These include high membrane phospholipid content, presence of mitochondrial axoplasm, limited antioxidant capabilities and ineffective mitochondrial DNA repair systems.^{42, 46} The mitochondria have many essential roles in all cell types including formation of Adenosine Triphosphate (ATP), Tricarboxylic acid cycle (TCA), reactive oxygen species (ROS) formation and cell death (apoptosis) regulation.⁴⁷ Several characteristics of CIPN can be attributed to neuronal mitochondrial dysfunction including abnormal mitochondrial morphology, impairment of ATP production and oxidative stress induction.⁴⁸ Abnormal mitochondrial morphology and function have been reported following vinca alkaloid, taxane, and platinum treatments. Mitochondrial swelling, loss of critical structural components including crista, calcium homeostasis disruption and reduced antioxidant capacity have been documented following chemotherapy drug treatment.⁴⁹ Downstream consequences of mitochondrial damage include overproduction of ROS, changes in membrane excitability, protein and lipid peroxidation, demyelination and disruption of microtubule transport and ultimately axon degeneration.^{42, 50}

Interestingly, *in vitro* investigations indicate that oxidative stress precedes overt axonal damage in vincristine-induced neurotoxicity, challenging the prevailing view that microtubule disruption is the primary initiating event. It was shown that low-dose vincristine treatment induces mitochondrial dysfunction by reducing basal respiration rates for up to 24 hours, reflecting both immediate and prolonged effects of vincristine on mitochondrial function, ultimately contributing to downstream axon damage.⁵¹ These findings suggest that oxidative stress may have a primary role in the neurotoxicity of agents which are traditionally considered to mediate structural damage.

Whilst several characteristics of CIPN have been attributed to generic oxidative stress induction, emerging evidence highlights drug-specific and nervous system site-specific effects of ROS, resulting in sustained oxidative stress within the nervous system. *In vivo* studies reported PNS-specific oxidative stress induction by cisplatin that could not be attenuated by ROS scavengers, in comparison to the primarily CNS-specific paclitaxel-induced oxidative stress which was responsive to ROS blockade. Furthermore, ROS generated by different agents differentially activated CNS- and PNS-resident cell populations, thereby shaping distinct inflammatory responses. Together, these findings underscore not only the heterogeneity of chemotherapy-induced oxidative stress, but also the specificity of downstream molecular responses, supporting the need for drug- and ROS species-specific neuroprotective strategies.⁵² The substantial molecular and structural consequences of ROS induction across multiple classes of chemotherapeutic agents further support oxidative stress as a central driver of CIPN pathogenesis, with the capacity to induce both acute neurotoxicity and persistent neuronal dysfunction and/or apoptosis. Importantly, oxidative stress may also propagate neuronal injury through downstream processes including lipid peroxidation, providing an additional mechanistic link to emerging pathways implicated in CIPN.

Lipid Peroxidation

Lipids are essential structural cellular components, required for energy storage, and function as signalling molecules. The high lipid content of neuronal cells membranes enriched with polyunsaturated fatty acid-containing lipids (PUFA), combined with prolonged exposure to reactive oxygen species results in formation of lipid hydroperoxides. These lipid hydroperoxides react with iron to form highly reactive lipid radicals, contributing to cellular damage including increased membrane tension, altered ion channel activity, loss of ionic homeostasis, the execution of ferroptosis, and membrane rupture.⁵³
⁵⁴ Whilst the pathological link between chemotherapy-induced oxidative stress and CIPN development has been well established, the role of lipid peroxidation and ferroptosis is an emerging area of interest. A recent clinical study investigating lipid peroxidation in paclitaxel-induced CIPN reported decreased antioxidant capacity, characterised by reduced glutathione (GSH), alongside increased circulating lipid oxidation products in patients with breast cancer. Importantly the study reported that detection of these changes preceded symptom development, highlighting their potential as early biomarkers.⁵⁵ Whilst *in vitro* studies investigating lipid peroxidation in CIPN are limited, evidence from other neurodegenerative conditions provides mechanistic support for further investigation. Studies in Parkinson's disease have reported increased intracellular lipid peroxidation products malondialdehyde⁵⁶, iron accumulation, decreased GSH, and downregulation of glutathione peroxidase 4 (GPX4) in mouse models⁵⁷.

Collectively, these emerging findings support further investigation of lipid peroxidation and ferroptosis as potential contributors to CIPN pathophysiology and as possible biomarkers for early neurotoxicity.

Ferroptosis Induction

Ferroptosis is a distinct form of regulated cell death, characterised by iron-dependent accumulation of lipid peroxides, resulting in extensive membrane lipid peroxidation and ultimately membrane rupture.⁵⁸ Iron is essential for numerous metabolic processes and, consequently, its cellular uptake, storage and transport are tightly regulated.⁵⁹ Cellular defence against ferroptosis involves several antioxidant systems, including GSH, GPX4, and nicotinamide adenine dinucleotide phosphate (NADPH)-ferroptosis suppressor protein 1 (FSP1) function. Together these systems limit lipid membrane peroxidation, inhibit ferroptosis, downstream altered ion flux, and biophysical membrane effects resulting in membrane rupture and cell death.⁵³ Cisplatin has been associated with disruption of iron homeostasis through induction of ferritinophagy which degrades the iron storage protein ferritin, increasing intracellular free iron, intracellular ROS via the Fenton reaction, and decreasing cellular antioxidant capacity by depleting GSH and reducing GPX4 expression.⁶⁰ Although the contribution of ferroptosis to CIPN is an emerging hypothesis, research investigating the role of ferroptosis in chemotherapy-treated neuronal models of peripheral neuropathy remains limited. However, in mouse models of cisplatin-induced sensorineural hearing loss, treatment of spiral ganglion neurons (SGNs) was associated with increased expression of nuclear receptor coactivator 4 (NCOA4), promoting ferritinophagy and intracellular iron accumulation. This was accompanied by reduced GPX4 protein levels, providing evidence of increased iron availability and impaired antioxidant defence consistent with ferroptosis.⁶¹ Therefore, further investigation of ferroptosis in CIPN may provide both mechanistic insight into chemotherapy-induced neurotoxicity and potential therapeutic opportunities. Emerging studies of GPX4-targeted approaches for pain modulation outside the context of CIPN further support the exploration of ferroptosis-associated pathways as potential targets for neuroprotection.⁶²

Role of Accessory Cells

Recent research is extending beyond the predominantly neuronal focus of CIPN to consider interactions between neurons and accessory cells as potential contributors to CIPN development and recovery. Existing evidence suggests that satellite glial cells (SGCs) in the dorsal root ganglia (DRG) sense and respond to peripheral nerve injury through intercellular signalling that can promote neuronal regeneration. Recent single-cell RNA-seq studies have further demonstrated injury-induced changes in

SGCs associated with regenerative growth in sensory neurons.⁶³ Beyond intercellular signalling, accumulating evidence highlights the importance of peripheral glial cells in providing metabolic support to neuronal cells. In mouse models, paclitaxel increased intercellular gaps and reduced the formation of tunnelling nanotubes (TNTs), which facilitate mitochondrial transfer between SGCs and neurons. These findings suggest that disruption of mitochondrial transfer, and consequently glial cell-mediated metabolic support, may contribute to CIPN pathophysiology.⁶⁴ Similarly, Schwann cells⁶⁵ may also protect injured axons through metabolic adaptation. Following axonal injury, SCs undergo a metabolic shift towards glycolysis that coincides with the axonal energy deficit preceding degeneration. SCs can also provide pyruvate and lactate to metabolically stressed axons, potentially mitigating the bioenergetic failure associated with axonal degeneration.⁶⁶ Collectively, these emerging observations support a view of CIPN pathophysiology that extends beyond direct neuronal cell injury and highlight the importance of considering neurons and peripheral glial cells as functional units. Greater understanding of these intercellular interactions may reveal previously unrecognised mechanisms of chemotherapy-induced neurotoxicity and identify novel opportunities for neuroprotective strategies.

Ion Channel Dysfunction

Chemotherapy can disrupt neuronal functionality by altering membrane excitability, resulting in aberrant action potential generation and spontaneous neuronal firing. Studies using rodent DRGs reported paclitaxel-induced elevation of sodium channels activity (NaV1.7 and NaV1.8) at distal nerve endings in a dose-dependent manner, resulting in increased neuronal activity and spontaneous firing.⁶⁷ In addition to voltage-gated sodium channels, chemotherapy dysregulates the transient receptor potential (TRP) family of ion channels, which are a specialised group of cation channels that are considered sensory detectors of chemical, thermal, and mechanical stimuli⁶⁸. Of particular relevance to CIPN is transient receptor potential vanilloid 1 (TRPV1), due to its role in the detection of noxious stimuli. Using healthy donor-derived iPSC sensory neurons, paclitaxel and vincristine treatment has been shown to increase TRPV1 mRNA expression, associated with enhanced sensitivity to noxious stimuli.¹⁵ These findings are consistent with the clinical (sensory) manifestations of CIPN observed in patients treated with these chemotherapy agents.⁶⁹ More recently, prolonged exposure to bortezomib has been shown to induce long-lasting TRPV1 sensitisation in primary sensory neurons. TRPV1 knockout mice were protected from bortezomib-induced epidermal nerve fibre loss and loss of sensory discrimination, further supporting TRPV1 sensitisation as a contributor to bortezomib-induced neuropathy.⁷⁰ Ion channel specific sensitivities have also been implicated in drug-specific clinical presentations. For example, acute (24-hour) *in vitro* oxaliplatin treatment resulted in functional

upregulation of the heat sensitive transient receptor potential cation channel subfamily M member 3 (TRPM3), while genetic deletion or pharmacological inhibition of TRPM3 reduced oxaliplatin-induced cold and mechanical hypersensitivity *in vivo*.⁷¹ In addition to the direct sensitising effects of chemotherapy on ion channels, cellular byproducts of chemotherapy toxicity impact ion channel activity. Transient receptor potential ankyrin 1 (TRPA1) demonstrates particular sensitivity to reactive products of oxidative stress, with TRPA1 dysfunction also considered a main contributing mechanism in symptom progression from acute to chronic mechanical and cold hypersensitivity; evidence supporting its involvement in oxaliplatin-induced peripheral neuropathy has been reported in both *in vivo* and clinical studies.^{72, 73} Collectively, these findings highlight ion channel dysfunction as an important mechanistic link between chemotherapy-induced neuronal toxicity, altered excitability and the sensory manifestations of CIPN.

Experimental Models for the Study of CIPN

Despite the identification of physical (structural) targets for the major drug classes associated with CIPN, and growing evidence of their downstream physiological effects (particularly the induction of ROS and oxidative stress), the precise molecular mechanisms of CIPN remain incompletely defined. To address this, a range of experimental models has been developed to study disease pathophysiology. The following sections critically evaluate these models, highlighting their respective strengths and limitations.

In Vivo (Animal) Models

Early CIPN research relied heavily on rodent models incorporating relatively simple behavioural assays to investigate disease pathophysiology. Protocols for pre-clinical assessments of CIPN using rodents include treatment of animals with relevant chemotherapy drugs administered using intravenous, intraperitoneal or subcutaneous injection and behavioural investigations of the effect of these drugs¹. To unravel the effects of chemotherapy drugs, animal studies aim to observe and characterise nociception, commonly defined as the response of the PNS to stimuli which may be mechanical, chemical, thermal or electrical.⁷⁴ Quantitative assessment of the effects of these drugs often relies on the observation of 'pain-like behaviours' in response to stimuli, and include shaking, licking the affected area and paw withdrawal.

To address the limitations of pain behaviour assessment, quantitative assessments including the Von Frey test have been developed to quantify mechanical thresholds⁷⁵ and hot-and-cold plate testing to record thermal threshold testing⁷⁴. More recently, approaches such as the Mouse Grimace Scale (MGS) have been introduced to provide additional assessment of spontaneous pain-related behaviour. The MGS employs periodic surveillance to generate images and videos for manual scoring to quantify changes across five facial action units – orbital tightening, nose bulge, cheek bulge, ear position, and whisker movement in response to stimuli.⁷⁶ To reduce reliance on manual scoring, semi-automated approaches such as PainFace have been developed. PainFace uses machine-learning algorithms to analyse video recordings and detect facial action units, generating an overall grimace score.⁷⁷ Despite reduction in manual scoring bias, cage-side assessment is also believed to affect rodent behaviour due to the innate prey animal response to hide pain behaviour. More recently, GrimACE has combined automated image acquisition with automated MGS analysis in a multimodal cage-side pain-assessment system. Although automated MGS approaches still require initial training against manually scored data, GrimACE enables image and video acquisition within a more naturalistic environment, reducing observer interference while permitting automated analysis. The system demonstrated improved automated detection and assessment of postoperative pain compared with conventional cage-side assessment.⁷⁸ Whilst the principles underlying these assays have informed the development of nerve conduction studies for CIPN assessment, their clinical utility remains limited⁷⁹ due to underlying reliance on investigator experience and subjective behavioural assessment, innate (e.g. grooming and exploration) and learned (e.g. avoidance) behavioural interference during testing and the requirement of acclimation to test equipment.⁷⁴ Furthermore, the lack of standardisation in chemotherapy dosing and routes of administration across CIPN studies limits comparability and clinical translatability.^{80,81,82} Additionally, *in vivo* studies are typically limited to monotherapies⁸³, with cisplatin, paclitaxel, and oxaliplatin among the most frequently studied agents despite the use of combination therapies since 1958 to combat drug resistance⁸⁴. Whilst more recent studies have incorporated tumour bearing models⁸⁵, earlier work largely excluded malignant model incorporation which is problematic as altered baseline nociceptive thresholds have been reported in tumour bearing mice⁸⁶. Critically, regardless of the method used to identify and quantify behaviours, a sustained criticism of these models is the reliance on immediate, short-term pain responses to model a pathology which is characteristically defined by long-term neuropathic pain.⁸⁷

Ex Vivo Models and Examination of Skin Biopsies

Whilst *in vivo* models can recapitulate some aspects of the clinical presentation associated with chemotherapy treatment, they do not permit identification of the detailed biological mechanisms of disease development. To address this limitation, *in vivo* studies can be complemented by *ex vivo* examination of tissues obtained from experimental animals, providing an important link between behavioural phenotypes and underlying pathology.⁸⁵ These approaches involve analysis of tissues extracted from model organisms under conditions designed to preserve, as far as possible, their biological state at the point of collection. In-depth dissection of the brain, spinal cord and paw skin of chemotherapy-treated and euthanized mice allows a more comprehensive analysis of disease pathology *in vivo* for the comparison between disease presentation in the CNS and PNS.⁸⁸ This combinatorial *in vivo* and *ex vivo* approach allows the findings of mouse behavioural studies to be associated with potential biological mechanisms of CIPN development. Yet, the translatability of such findings from animal models to human disease clearly poses its own caveats.

Skin biopsies have been used in monitoring diabetic neuropathy, with reduced intraepidermal nerve fibre density (IENFD) before symptom onset, representing a potential biomarker for subclinical diabetic neuropathy. However, when this was explored in the context of oxaliplatin-induced peripheral neuropathy no significant reduction in IENFD was reported until 6 months post treatment.⁸⁹ Whilst this delayed loss of IENFD may reflect the ‘coasting’ phenomenon associated with platinum agents, these findings suggest limitations in the use of IENFD as an early diagnostic biomarker of CIPN.

***In Vitro* Cell Models**

Whilst *in vivo* and *ex vivo* models have advanced our understanding of chemotherapy-associated symptoms, they provide limited resolution for dissecting the underlying molecular mechanisms of CIPN. By contrast, *in vitro* cell models offer a complementary and more controllable platform, enabling high-throughput investigation of neuronal cytotoxicity and the precise cellular pathways involved, although their suitability for CIPN research ultimately depends on the specific biological question being addressed. These models are discussed below and summarised in Table 2, which provides a comparative overview of such models used to study CIPN pathophysiology, alongside their respective advantages and limitations.

PC12

Isolated from a rat adrenal tumour in 1976, the PC12 pheochromocytoma is one of the most frequently used cell lines in neurological research.⁹⁰ A review addressing the strengths and limitations of *in vitro*

models of CIPN reported that 25% of the studies analysed utilised PC12 as a cell model.⁹¹ PC12 cells are often selected for their ability to differentiate into sympathetic ganglion neurons when treated in culture with nerve growth factor (NGF) with extended processes reported in 80% of cells after 2 weeks of NGF treatment.⁹⁰ Differentiated cells are reported to secrete and respond to neurotransmitters, form functional synapses and can be co-cultured with other neuronal cells including microglia and astrocytes.⁹²

The methods employed for the differentiation of PC12 cells vary within the literature, with differentiation period durations ranging from 3 days to 14+ days.⁹³ Notably, literature characterising cells from multiple laboratories reported large experimental variability between PC12 variants, including loss of responsiveness to NGF to induce differentiation. Comparison of PC12 cell lines across 4 independent laboratories identified morphological, functional and molecular differences.⁹⁰ Furthermore, differentiation efficiency is reliant on vessel coating, as PC12 cells are cultured as non-adherent cell aggregates but require adherence to substrate to initiate differentiation. To address this, the adherent PC12 (PC12 Adh) sub-line is often used; however, differentiation efficiency in this variant is markedly reduced (<2%), limiting its utility in studies requiring mature neuronal phenotypes.⁹² Collectively, despite the practical advantages conferred by their immortalised nature, these limitations – together with their non-human origin and tumour-derived phenotype – restrict the physiological relevance and applicability of PC12 cells as models of CIPN.

SH-SY5Y

The SH-SY5Y line, derived from a human metastatic neuroblastoma, exhibits genetic alterations due to its malignant nature⁹⁴ and demonstrates inherent genomic instability.⁹⁵ It is widely used in neurodegenerative research and is often considered comparable to embryonic stem cell-derived neural progenitors⁹⁶, with applications spanning disorders such as Parkinson's and Alzheimer's disease in both undifferentiated and differentiated states⁹⁷. SH-SY5Y cells can undergo differentiation into a neuron-like phenotype upon exposure to retinoic acid, resulting in neurite outgrowth, increased electrical excitability, synapse formation, and neurotransmitter activity.⁹⁸ However, several factors should be considered when using this model, including variability between adherent and suspension sublines, the presence of morphologically distinct neuroblast-like and epithelial-like populations, and the implications of its tumour-derived origin.⁹⁹ Notably also, tumour-derived cells have adapted to promote cell survival affecting cell signalling responses, immune escape mechanism and altered response to drugs.¹⁰⁰ Although SH-SY5Y cells overcome species-related limitations associated with PC12, their malignant origin presents a challenge when modelling non-cancerous disease processes. In addition,

transcriptomic comparisons between SH-SY5Y cells and murine DRG neurons have revealed reduced expression of key receptors involved in neuroinflammation and neuropathic pain, including transient receptor potential vanilloid 1 (TRPV1), which is associated with nociceptive hypersensitivity¹⁰¹, suggesting SHSY-5Y may not be an adequately suitable or representative model for the study of CIPN.

NTERA-2 (NT2)

Human pluripotent embryonal NTERA-2 cells (referred to as NT2) represent an experimentally valuable cell line to bridge the gap between *in vivo* and tumour cell-derived neuronal *in vitro* models, whilst addressing inherent limitations of pluripotent stem cells. Despite their original derivation from a primary testicular embryonal carcinoma, NT2 cells are committed neural progenitors with strikingly strong capacity to differentiate into a heterogeneous population of neurons (NT2-N) and glial cells, thus providing an unlimited and scalable source of differentiation material.¹⁰²

Cancer-derived cell lines such as rat PC12 and human SH-SY5Y are widely used due to their relative homogeneity, low cost, and ease of maintenance. However, these models are limited by inherent genomic alterations, progressive instability ('drift') with passage, and phenotypic characteristics that more closely reflect their tumour origin than the biological processes under investigation.¹⁰³ By contrast, despite possessing an abnormal karyotype, NT2 cells possess properties which allow them to be considered in the same class as human pluripotent stem cells. In fact, early characterisation of cells derived from the rare human teratocarcinoma origin of NT2 cells, identified the presence of embryonic stem cell-like populations.¹⁰⁴ Upon treatment with retinoic acid (RA), NT2 cells undergo stable and irreversible differentiation into neuronal and glial lineages, expressing cytoskeletal proteins, surface markers, and synaptic/secretory components characteristic of mature neuronal cells.^{102, 105}

Comparative studies have demonstrated that NT2-derived neurons (NT2-N) closely resemble human foetal neurons (HFNs) in both molecular marker expression and functional properties, including neurotransmitter activity and the generation of action potentials.¹⁰² The physiological relevance of NT2-derived neuronal cells is supported by their use as *in vitro* system for developmental neurotoxicity testing.¹⁰⁶ Importantly also, the normality of NT2-N neurons has been demonstrated by FDA approved trials using NT2-N grafts as cell transplants for stroke patients, reporting feasibility, safety and tolerability in patients.¹⁰⁷ Moreover, it has been shown that such early grafts implanted into nude mice did not revert to undifferentiated neoplastic states^{108, 109}, further attesting to the stability of NT2 cells.

Collectively, the ability of NT2 cells to undergo stable differentiation into terminal neuronal populations exhibiting molecular, structural, and functional characteristics comparable to HFNs positions this

model as a robust and physiologically relevant platform for *in vitro* studies. These biological attributes, combined with their scalability and capacity to generate heterogeneous neural populations, render NT2 cells particularly well suited for high-throughput and mechanistic investigations of CIPN. Consequently, NT2-N cells may provide a physiologically relevant platform for modelling of disease pathophysiology.

Human Embryonic Stem Cells (hESCs)

Originating from the inner mass of the blastocyst during mammalian embryonic development, human embryonic stem cells (hESCs) have been widely utilised as human disease models, notably mostly for neurological diseases due to their pluripotency to differentiate into numerous relevant cell types. Whilst hESCs have therapeutic applications such as spinal cord transplants, their use in neurodegenerative research has been relatively limited¹¹⁰ and has progressively declined in favour of induced pluripotent stem cells (iPSCs), a shift largely driven by ethical considerations associated with their embryonic origin.¹¹¹

Induced Pluripotent Stem Cells (iPSCs)

Research using induced pluripotent stem cells (iPSCs) aims to address the limitations of existing *in vivo* and *in vitro* cellular models of neuropathy by enabling the development of tissue-relevant human systems. The establishment of iPSCs provides an alternative to hESCs by addressing the ethical and safety concerns associated with hESC-based research.¹¹² iPSCs are generated through the reprogramming of somatic cells into pluripotent lines capable of differentiating into a wide range of cell types, including both monocultures and complex three-dimensional cultures that can be transplanted *in vivo*.¹¹³ The use of iPSCs has enabled development of multicellular neural organoids, providing valuable insights into neurodegenerative disorders such as Parkinson's and Alzheimer's disease.¹¹⁴ They can be commercially available or derived from donor patients, each presenting distinct experimental considerations.

Whilst iPSCs are often considered as the most representative model of human disease, studies comparing the use of donor-derived iPSCs identified considerable donor-to-donor variability of iPSCs used in CIPN in response to chemotherapy drug treatment, with reported differences in half-maximal inhibitory concentrations for the same drug.^{115, 116} Whilst donor-specific iPSC derivatives may be advantageous in exploring personalised susceptibility to CIPN, caution should be exercised upon generalising interpretation of experimental findings. As a result, many studies utilise commercially

available iPSC-derived neuronal models (e.g. iCell and Peri.4U neurons) to improve experimental consistency.

Yet, a key limitation of both donor-derived and commercially available iPSCs is the immature phenotype of iPSC-derived cells. This immaturity restricts formation of structural neuronal networks required to recapitulate a more representative neuronal environment, thus limiting the applicability of using iPSCs as a cellular model for investigating unique disease characteristics, in particular chronic chemotherapy exposure and ‘coasting’ effects.¹¹³ Finally, additional significant practical constraints include the high cost and the technical demands associated with maintaining iPSC cultures, including challenges in cell viability and scalability.¹¹⁷ Consequently, many investigators opt to using established, immortalised cell lines as more accessible and reliable alternatives.

Organoid Cultures

Organoid culture systems are increasingly utilised to overcome limitations of traditional 2D models by incorporating 3D cellular structures enabling interactions between multiple cellular populations, creating a more physiologically relevant representation.¹¹⁸ Recently, human iPSC-derived DRG-organoids (iDRGOs), incorporating sensory neurons, satellite glial, and Schwann cells have been generated to compare the response of 3D and 2D systems to evaluate neurotoxicity of bortezomib, vincristine and paclitaxel. Exposure of iDRGOs to these agents induced characteristic features associated with CIPN, including impaired neurite outgrowth, supporting their potential utility for modelling chemotherapy-induced neurotoxicity within a multicellular, physiologically relevant system. However, despite the increased cellular complexity of the 3D model, impairment of neurite outgrowth was less pronounced in iDRGOs than in 2D cultures. This highlights an important consideration: increased physiological complexity does not necessarily enhance the sensitivity of individual quantitative toxicity readouts, hence conventional 2D systems may remain advantageous for measuring specific endpoints such as neurite outgrowth.¹¹⁹ Nevertheless, organoid models offer advantages for investigating multicellular interactions that cannot readily be recapitulated in simpler, more reductive, systems, providing opportunities to explore the contribution of neuronal-glial interactions and other multicellular processes to CIPN pathophysiology.

Lab-on-a-Chip and Microfluidics Platforms

To address limitations of conventional cellular models for investigating CIPN, lab-on-a-chip (LoC) systems represent an emerging class of miniaturised technologies that integrate microfluidic platforms

to model biological processes within defined and controlled microenvironments. These technologies have facilitated the development of micro-physiological and nerve-on-a-chip models with improved physiological relevance.¹²⁰ Their application to CIPN research has demonstrated the capacity to reproduce multiple features of chemotherapy-induced neurotoxicity. A rat nerve-on-a-chip (RNoaC) model enabled assessment of CIPN-relevant functional and structural endpoints, including alterations in mitochondrial membrane potential and histopathological measurements such as nerve diameter, respectively.¹²¹ More recently, this technology has been applied to assess and distinguish somatic and axonal toxicity induced by oxaliplatin, paclitaxel and vincristine. Primary rat DRG neurons were cultured within spatially separated compartments, enabling regional assessment of chemotherapy-induced toxicity. Distinct patterns of toxicity were observed, with somatic toxicity associated with paclitaxel and oxaliplatin, and axonal toxicity associated with vincristine and paclitaxel. Automated AI-assisted image analysis was additionally applied to individual cellular compartments, enabling high-throughput morphological assessment and demonstrating the potential for scalable analysis of chemotherapy-induced toxicity.¹²² Collectively, LoC and microfluidic platforms represent an important methodological advance in CIPN modelling, providing greater spatial control and enabling compartment-specific assessment of neurotoxicity within physiologically relevant experimental systems.

Methodological Advances – Individual, Integrative and Spatial ‘Omics’ Approaches

The use of omics approaches has facilitated the comprehensive characterisation of biological systems and their interactions in disease through the analysis of multiple classes of biomolecules, including transcriptomics, proteomics, lipidomics and metabolomics.¹⁰⁵ Transcriptomic approaches have been used to characterise chemotherapy-induced toxicity, with bulk RNA expression analysis of the DRG identifying drug-specific transcriptional signatures, including vincristine-induced upregulation of genes associated with neuroinflammation.¹²³ Methodological advances in single-cell RNA sequencing (scRNAseq) or single-nuclei RNA sequencing (snRNAseq) enable transcriptional changes to be resolved across individual cell populations, providing insights into cell-type-specific responses. For example, investigation of sensory neuron–glia interactions identified oxaliplatin-induced modulation of inflammatory processes across neuronal and glial cell populations, highlighting cellular heterogeneity within complex tissues and experimental systems.¹²³

Beyond transcriptomics, proteomic approaches assess changes in protein expression, providing insight into the downstream cellular consequences of chemotherapy-induced toxicity. Proteomic analysis of blood samples from patients with breast cancer receiving paclitaxel-based chemotherapy identified upregulation of ADH4, associated with oxidative stress, and downregulation of VOPP1, associated with

mitochondrial dysfunction.¹²⁴ Such findings demonstrate the potential of proteomic profiling to identify patient-associated molecular processes underlying CIPN and pathways of potential therapeutic relevance.

Lipidomics provides complementary insight into alterations in cellular lipid composition and metabolism, which are increasingly implicated in CIPN pathophysiology.⁴⁴ Studies using human iPSC-derived sensory neurons have demonstrated that paclitaxel exposure is associated with downregulation of lipid metabolism and alterations in membrane lipid composition.⁴⁴ The potential clinical utility of lipidomics has also been demonstrated through analysis of plasma samples from patients receiving paclitaxel therapy. Using mass spectrometry-based lipidomic profiling, increased sphinganine-1-phosphate (SA1P), associated with TRPV1 and SA1P receptor signalling, was detected in patients reporting neuropathy, identifying a potential mechanistic pathway and therapeutic target identified via lipidomics.¹²⁵

Metabolomics enables comprehensive analysis of metabolites within biological systems and has been applied both to investigate mechanisms underlying CIPN and to explore potential diagnostic and prognostic biomarkers. Metabolomic profiling of patients with breast cancer has identified significant differences associated with CIPN, including alterations in metabolites linked to opioid and CREB signalling. Differences in metabolomic profiles between patients with and without CIPN were detectable within one month, with differences persisting at the 12-month timepoint.¹²⁶ Therefore, in addition to providing biological insight into metabolic changes associated with CIPN, metabolomic approaches may facilitate identification of potential clinical biomarkers of CIPN.¹²⁷

Beyond individual omics approaches, integration of multiple datasets can provide a more holistic understanding of CIPN pathophysiology by linking molecular changes across different biological levels. Using human iPSC-derived sensory neurons as a model of paclitaxel-induced CIPN, integration of transcriptomic, proteomic and lipidomic analyses demonstrated concordance between transcriptomic changes and downstream alterations identified through proteomic and lipidomic profiling.⁴⁴ Such approaches can therefore connect changes in gene expression with downstream molecular and functional consequences, providing greater mechanistic resolution than individual datasets alone.

More recently, spatial omics approaches have provided an additional dimension by preserving information on the spatial organisation of molecular changes within tissues and cellular systems. These approaches have considerable potential to resolve cell-type-specific responses, intercellular interactions and spatial patterns of toxicity. However, despite their increasing application in areas such as cancer biology, direct application of spatial omics to CIPN remains limited.¹²⁸ Collectively, the integration of single-cell, multi-omics and spatial approaches may therefore provide opportunities to

define the cellular and molecular heterogeneity of CIPN and inform the development of increasingly physiologically relevant experimental models.

Current and Emerging Strategies for CIPN Prevention

Due to the severity and often chronic nature of CIPN, there is a rapidly increasing interest in identifying prevention approaches to combat CIPN. As discussed in the previous sections, irreversible chemotherapy-induced neuronal injury, including mitochondrial dysfunction, oxidative stress, axonal degeneration, and neuroinflammation can precede and underpin clinical symptom presentation. This temporal relationship between subclinical neuronal damage and subsequent symptom onset has important implications for intervention strategy. By the time CIPN symptoms manifest, substantial and often permanent neuronal injury will have already occurred, limiting the potential for therapeutic reversal. Accordingly, this review prioritises prevention over symptomatic management as the most impactful clinical strategy.

A range of candidate interventions has been explored as prevention or treatment strategies for CIPN, including ion channel-targeted therapies, anti-inflammatory drugs, antioxidants, cannabinoids, antidepressants and antiseizure medication.^{129, 130} However, consistent with the evidence discussed below, current international clinical guidelines conclude that no pharmacological agents can be recommended for routine prevention of CIPN. The American Society of Clinical Oncology Clinical Practice guideline update highlights the modest benefit of Duloxetine for symptomatic management, but not prevention, and emphasises dose reduction or discontinuation of chemotherapy as the most effective strategy to avoid development of severe neuropathy¹³¹. Similarly, guidance from the European Society for Medical Oncology and position statements from the Multinational Association of Supportive Care in Cancer emphasise supportive care, early detection, and enrolment in clinical trials for prevention strategies.¹³² These conclusions reflect the heterogeneity of trial designs, the diversity of agent- and regimen-specific mechanisms of neurotoxicity, and the limited availability of high-quality phase III evidence, underscoring a significant unmet need for mechanism-based prevention strategies.

In parallel with pharmacological approaches, there has been increasing interest in non-pharmacological strategies for CIPN prevention, particularly those that aim to modulate the biological response of peripheral nerves to neurotoxic agents. Interventions such as limb cryotherapy, cryocompression, compression therapy, structured exercise programmes, and neuromodulatory techniques have emerged as promising candidates, supported by favourable safety profiles, biological plausibility, and growing clinical evidence, particularly in taxane-associated CIPN.^{131, 132} These approaches are likely to

act through a combination of mechanisms, including modulation of local tissue physiology, metabolic activity, and cellular stress responses. In addition, reduced drug delivery (hence drug exposure) may contribute to their protective effects, as suggested by cooling-related studies in other tissue systems.

¹³³ Importantly, these modalities represent a shift toward interventions that can complement systemic chemotherapy while minimising risks of tumour protection or pharmacokinetic interference.

Collectively, this evolving landscape reframes CIPN prevention from a predominantly pharmacological challenge to a broader, multidisciplinary paradigm integrating physical modulation, rehabilitation science, and supportive care innovation. Given the scale of the unmet need, both pharmacological and non-pharmacological approaches remain under active investigation. Below, we highlight the most promising strategies, summarise the current evidence, and identify key gaps and research priorities.

Pharmacological strategies

Antidepressants

Antidepressants modulate central pain processing through serotonergic and noradrenergic pathways and are effective in several neuropathic pain syndromes, providing a theoretical basis for CIPN symptom control. ^{134, 135} Such agents, including duloxetine, venlafaxine and tricyclic antidepressants, have been extensively evaluated in the context of CIPN, primarily for the management of established neuropathic pain rather than prevention. ^{136, 137} Across clinical guidelines, these agents are not recommended for preventive use, as randomised trials have failed to demonstrate consistent reductions in the incidence or severity of CIPN when administered prophylactically. ^{131, 132} Duloxetine, in particular, previously held a unique position in guideline recommendations as the only agent endorsed for treatment of painful CIPN. However, a recent randomized phase II trial demonstrated that prophylactic duloxetine did not reduce the incidence or severity of oxaliplatin-induced peripheral neuropathy compared with placebo. ¹³⁸ Thus, despite the potential role of Duloxetine in managing established painful CIPN, the current evidence does not support the use of antidepressants as a preventive strategy. ^{137, 139}

Anticonvulsants

Anticonvulsants such as gabapentin and pregabalin have also been investigated as preventive strategies based on their efficacy in other neuropathic pain syndromes. ¹³⁴ These agents reduce neuronal excitability by modulating calcium channel activity and synaptic neurotransmitter release, supporting their use in neuropathic pain conditions. ¹⁴⁰ However, randomized studies have not demonstrated

consistent and clinically meaningful evidence supporting the use of anticonvulsants in CIPN.^{141, 142, 143} A small randomized, placebo-controlled trial evaluating gabapentin for the prevention of paclitaxel-induced peripheral neuropathy reported a statistically significant reduction in neuropathy incidence or severity in the gabapentin arm; however, the small sample size limits the generalizability of these findings.¹⁴¹ Another pilot trial of pregabalin for prevention of paclitaxel-associated neuropathy failed to demonstrate a protective effect, with sensory neuropathy scores not differing significantly between groups.¹⁴³ Consequently, clinical guidelines uniformly advise against the routine prophylactic use of anticonvulsants for CIPN prevention.¹³¹

Antioxidants and putative neuroprotective agents

Antioxidants and putative neuroprotective agents, including glutathione, vitamin E, alpha-lipoic acid, acetyl-L-carnitine and manganese-based compounds (such as calmagrofodipir) have been among the most intensively studied pharmacological approaches for CIPN prevention.^{144, 145} These agents aim to mitigate oxidative stress, mitochondrial dysfunction and inflammatory signalling implicated in chemotherapy-induced neuronal injury, particularly in platinum-based regimens.^{46, 146} While early-phase and small randomised trials suggested potential benefit for some agents (vitamin E in cisplatin-treated patients reported reduced neurotoxicity incidence)¹⁴⁵, subsequent larger and more rigorous studies have yielded inconsistent or negative results, and in some cases evidence of harm, most notably with acetyl-L-carnitine.¹⁴⁷ Most notably, a randomised, placebo-controlled trial for the prevention of taxane-induced neuropathy reported that acetyl-L-carnitine not only failed to prevent CIPN but was associated with worse functional outcomes, with significantly increased CIPN symptoms at 24 weeks compared to placebo, providing direct evidence of harm.¹⁴⁸ Similarly, trials of glutathione, alpha-lipoic acid, and calmagrofodipir have not demonstrated consistent protective effects in large studies.¹³¹ As a result, clinical guidelines do not recommend antioxidant or neuroprotective agents for routine prevention, highlighting the need for greater mechanistic understanding and caution regarding drug–drug interactions with chemotherapy.

Calcium and magnesium infusions

Calcium and magnesium were hypothesised to stabilise neuronal membranes and reduce oxaliplatin-induced hyperexcitability and acute neurotoxicity.¹⁴⁹ Calcium and magnesium infusions were widely explored for the prevention of oxaliplatin-induced peripheral neuropathy following early observational reports of benefit. However, subsequent randomised controlled trials failed to confirm a consistent

protective effect, and concerns were raised regarding potential interference with antitumor efficacy, although these remain controversial.^{150, 151} In light of the lack of reproducible benefit and unresolved safety considerations, guidelines advise against the routine use of calcium and magnesium infusions for CIPN prevention.

Non-pharmacological approaches

Compression therapy (tight gloves/surgical-glove technique)

Compression therapy alone, often implemented pragmatically using tight or undersized gloves, has been proposed as a method to reduce distal limb perfusion during chemotherapy administration¹⁵². Small studies, including self-controlled trials and observational reports, suggest potential benefit in reducing sensory symptoms.¹⁵³ In clinical practice, compression protocols typically involve wearing gloves one size smaller than usual before, during, and after chemotherapy infusion; however, these approaches remain largely empirical and are not underpinned by robust biological evidence. Importantly, it remains unclear whether compression meaningfully alters drug delivery or availability in peripheral tissues, or how the timing and duration of compression influence potential protective effects. Consistent with this uncertainty, the literature reports mixed findings, with some studies demonstrating no statistically significant reduction in CIPN incidence between experimental and control groups.¹⁵⁴ Furthermore, although compression is generally well tolerated and not associated with significant adverse effects, there remains a lack of definitive evidence supporting its efficacy as a standalone preventive strategy.¹⁵⁵ Overall, clinical evidence remains limited, with substantial variability in applied pressure, duration, and safety monitoring.¹⁵⁶ The absence of standardised protocols and objective pharmacokinetic data has hindered broader adoption. Future studies should prioritise well-powered randomised controlled trials to define optimal pressure thresholds, assess vascular safety, and quantify local chemotherapy exposure under compression conditions. In particular, dose-response relationships for applied pressure and pharmacokinetic measurements under compression are required to clarify underlying mechanisms and improve translational relevance.

Structured exercise and physiotherapy (multimodal rehabilitation)

Structured exercise and physiotherapy programmes have gained increasing attention as preventive and mitigating strategies for CIPN, based on their systemic effects (improved microvascular perfusion, anti-inflammatory signalling, mitochondrial function and preservation of neuromuscular integrity).¹⁵⁷ Randomised trials and meta-analyses indicate that peri-chemotherapy structured exercise

programmes (aerobic, resistance, and sensorimotor training) improve CIPN symptom scores, balance and quality of life.^{158, 159} A landmark randomised clinical trial demonstrated that a structured sensorimotor and resistance training programme initiated during chemotherapy significantly reduced the incidence and severity of CIPN compared to usual care, with clinically meaningful improvements in EORTC QLQ-CIPN20 sensory scores.¹⁵⁸ Furthermore, a randomised controlled trial comparing sensorimotor exercise and resistance training to usual care in patients receiving neurotoxic chemotherapy reported significantly reduced CIPN symptom burden in the exercise groups, with the sensorimotor exercise arm also demonstrating improvements in postural stability and balance.¹⁶⁰ While exercise is unlikely to prevent neuronal drug exposure directly, it may enhance neural resilience and provide functional compensation.¹⁶¹ Evidence for true prevention remains evolving, and heterogeneity in exercise prescription and outcome measures limits cross-study comparisons; nevertheless, the favourable safety profile and broad survivorship benefits support continued investigation in adequately powered, standardised prevention trials.¹⁶⁰ Large randomized trials with standardised exercise protocols and objective functional endpoints are warranted, whilst identification of biological mediators (inflammatory cytokines, mitochondrial markers) will support causality in CIPN prevention.

Acupuncture / electroacupuncture and neuromodulatory therapies

Acupuncture and neuromodulatory interventions, including electroacupuncture and transcutaneous electrical nerve stimulation (TENS), represent additional non-pharmacological approaches with growing interest. These modalities are thought to modulate nociceptive processing, local blood flow and neuroimmune signalling, providing analgesic and possibly neuroprotective effects.¹⁶² Several small studies and systematic reviews suggest improvements in sensory symptoms and patient-reported outcomes. However, most studies have focused on treatment rather than prevention of established CIPN, and methodological challenges such as blinding and use of sham controls remain significant.^{163, 164} Larger, rigorously designed trials incorporating objective neurophysiological endpoints and long-term follow-up are required before these approaches can be considered for preventive use. In parallel, mechanistic studies (particularly those assessing neuroimmune biomarkers and local perfusion) will be important to enhance biological interpretability.

Limb Cryotherapy

Limb cryotherapy, with or without compression, has emerged as one of the most extensively studied non-pharmacological strategy for CIPN prevention, particularly in patients receiving taxane-based

chemotherapy.^{139, 165} By reducing peripheral blood flow and tissue metabolism during infusion, cooling is hypothesized to limit local drug delivery to distal nerves, thereby attenuating neurotoxicity. Cryotherapy delivery methods have evolved considerably, from frozen gloves and socks to advanced continuous-flow cryotherapy systems, with earlier approaches yielding variable outcomes and limited effects on standard neuropathy scales despite modest improvements in patient-reported symptoms.^{166, 167} Continuous-flow systems have demonstrated superior tolerability and consistent cooling over extended durations, with clinical studies confirming reduced paclitaxel-induced neurotoxicity. Further refinement through cryocompression, which combines controlled cooling with dynamic pressure, has enabled delivery of lower temperatures while maintaining tolerability¹⁶⁸⁻¹⁷⁰ notably, one study reported CIPN prevention in 65% of patients, with no cases of severe neuropathy observed.¹⁷¹ In a subsequent feasibility study of concomitant scalp cooling and limb cryocompression, the approach demonstrated an acceptable safety profile with no treatment discontinuations due to cryocompression-related adverse events.¹⁶⁸ The strongest clinical evidence supports prevention of taxane-associated CIPN, while findings for oxaliplatin remain less consistent yet emerging.^{172, 173, 153} A multicentre randomized controlled trial reported modest improvements in patient-reported sensory symptoms in the intervention arm compared with the control, although differences in EORTC QLQ-CIPN20 scores did not reach statistical significance.¹⁷² Ongoing investigation includes the Phase III randomised trial of the Paxman Limb Cryocompression System (NCT05642611), which is expected to provide important insights into optimal cooling and compression parameters.

Despite these encouraging advances, several challenges constrain definitive conclusions, including heterogeneity in device type, temperature, duration, and timing, as well as tolerability concerns such as cold intolerance and limited follow-up durations.¹³¹ Mechanistic studies directly linking cooling to reduced nerve drug exposure also remain limited.^{162, 174} Limb cryotherapy closely mirrors the established paradigm of scalp cooling for chemotherapy-induced alopecia¹⁷⁵, and whilst cytoprotective mechanisms, including attenuation of drug uptake, suppression of oxidative stress, and modulation of cellular metabolism, have been well characterised in non-neuronal systems such as keratinocytes and hair follicle models^{133, 176, 177} equivalent evidence in neuronal systems is currently lacking. Rather than representing a fundamental limitation, this gap identifies a critical and tractable opportunity for translational research. Appropriately designed *in vitro* and human-relevant neuronal model systems could define the mechanistic basis of cooling-mediated neuroprotection, while future progress will require standardisation of treatment protocols and large multi-centre Phase III trials with extended follow-up to assess persistent neuropathy and confirm clinical efficacy (NCT05642611, NCT07064798).

Translational Bridging in CIPN Prevention: Aligning Mechanisms, Models and Clinical Strategy

A central challenge in CIPN research lies in bridging mechanistic insights with clinically effective prevention strategies. While increasingly complex *in vivo*, *ex vivo*, and *in vitro* models have advanced understanding of disease pathology, their translational value is often constrained by variability, limited mechanistic resolution, and difficulty in isolating specific biological processes. Conversely, more reductive experimental systems, although arguably lacking full physiological complexity, offer the ability to interrogate discrete cellular and molecular mechanisms with high precision.

Importantly, these approaches should be viewed as complementary rather than competing. The selection of an appropriate model should be guided by the biological question under investigation. In this context, simplified human-relevant systems can provide critical mechanistic insights that are not readily accessible in more complex models. For example, in human *in vitro* keratinocyte and hair follicle models, cooling has been shown to attenuate chemotherapy-induced cytotoxicity through modulation of drug uptake, oxidative stress, and cellular metabolism.¹⁷⁷ These findings highlight that protective effects may arise not solely from reduced tissue exposure, but also from intracellular and stress-response mechanisms that influence cellular susceptibility to chemotherapy drug-induced injury. This paradigm is highly relevant to CIPN, where convergent molecular mechanisms (including mitochondrial dysfunction, oxidative stress, and axonal degeneration) are shared across multiple chemotherapeutic agents. The ability to isolate and interrogate these processes in controlled systems provides a powerful framework for identifying and optimising protective strategies.

Bridging clinical practice with effective CIPN prevention therefore requires experimental models that capture key features of chemotherapy-induced nerve injury, including mechanistic diversity and temporal progression. To date, many pharmacological strategies have focused on downstream symptom modulation or broad neuroprotection, while preclinical models have often relied on systems that do not fully reflect the complexity of human disease.¹⁷⁸ However, rather than prioritising increasing model complexity alone, progress will depend on aligning model selection with the mechanisms under investigation. This may include the use of more representative *in vivo* systems, alongside human-relevant, robust and high-throughput *in vitro* approaches such as multicellular neuronal co-cultures and micro-physiological platforms⁸⁵, as well as emerging neuronal models, including stem cell- and cell line-based systems and advanced microfluidic platforms¹⁷⁹. Such approaches could enable targeted investigation of processes including axonal integrity, mitochondrial function, neuroinflammation, and barrier dynamics, thereby improving translational relevance while maintaining experimental tractability.

Within this context, non-pharmacological interventions, such as limb cooling, can be understood not simply as empirical approaches, but as biologically informed strategies that modulate key determinants of neurotoxicity. By influencing local tissue physiology, metabolic demand, and cellular stress responses (and potentially altering drug delivery or uptake), controlled cryotherapy represents a multifaceted intervention aligned with the underlying mechanisms of CIPN. Accordingly, among other emerging strategies, limb cooling currently represents the most clinically advanced approach for CIPN prevention, providing a strong foundation for the further development of biology-guided interventions.

Collectively, advancing CIPN prevention will require the integration of mechanistic understanding with appropriately selected experimental models. A translationally effective strategy depends on the deliberate alignment of biological insight, experimental design, and subsequent clinical application.

Conclusions and future perspectives

CIPN remains a significant unmet clinical challenge with a huge impact on cancer patient survivorship, with limited effective strategies for prevention despite substantial advances in understanding its underlying biology. In light of the limited success of existing pharmacological interventions in alleviating established CIPN symptoms, with duloxetine representing the only agent with modest guideline-level support for symptomatic management, and given that irreversible molecular neuronal injury precedes clinical presentation¹⁸⁰, it is increasingly evident that prevention (rather than symptom management) represents the most effective strategy for combating CIPN.

Despite these advances, a disconnect remains between mechanistic understanding, experimental model systems and clinical translation. The increasingly recognised complexity of CIPN, encompassing oxidative stress, mitochondrial dysfunction, lipid peroxidation, ion-channel dysfunction, impaired axonal transport and degeneration, together with interactions between neuronal and non-neuronal cells, reinforces the need for preventive strategies aligned with the biological processes driving chemotherapy-induced neurotoxicity.

Emerging experimental and methodological approaches provide important opportunities to address this translational gap. Human-derived neuronal models, multicellular organoid and micro-physiological systems, together with single-cell, integrative and spatial omics approaches, offer increasing capacity to resolve cell-specific mechanisms, intercellular interactions and spatial patterns of toxicity. Integration of these approaches with clinically relevant biomarkers may enable earlier identification of neuronal injury and provide a stronger biological basis for the development and evaluation of targeted preventive interventions.

In this context, non-pharmacological approaches such as limb cryotherapy represent a promising direction, offering the potential to modulate key determinants of neuronal susceptibility without interfering with systemic anticancer regimen efficacy. Among emerging strategies, limb cooling is supported by an expanding body of clinical evidence demonstrating favourable tolerability and efficacy. While mechanistic understanding in neuronal systems remains to be fully established, insights from biologically relevant models in other tissues provide a strong foundation for its translational potential.

Future progress will depend on the integration of mechanistic insights with appropriately selected experimental models and well-designed clinical studies. This includes the development of standardised protocols, incorporation of objective biomarkers, and generation of high-quality clinical evidence through adequately powered trials with long-term follow-up. In parallel, advancing our mechanistic understanding, particularly through human-relevant *in vitro* and translational model systems, will be essential to optimise intervention strategies and define their biological basis.

Collectively, these considerations support a shift toward biology-guided, mechanism-driven prevention strategies for CIPN, reinforcing the view that, when aligned with underlying disease mechanisms, CIPN should not be regarded as an inevitable consequence of chemotherapy treatment, but rather as a clinically actionable target for prevention.

Declarations

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Consent for publication

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Author contributions

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Figure captions

Figure 1. Mechanisms and Clinical Presentation of Chemotherapy-Induced Peripheral Neuropathy (CIPN) by Drug Class

Schematic illustration of the clinical features and currently hypothesised pathophysiological mechanisms underlying CIPN emergence across all major treatment regimens. Drug categories include taxanes, platinum compounds, vinca alkaloids, antibody-drug conjugates, and immunomodulatory agents. Common clinical manifestations (such as paraesthesia, dysesthesia and motor impairment) are mapped to distinct neuronal cell alterations, including microtubule disruption, oxidative stress induction, axonal transport defects and sensory fibre degeneration to contextualize site-specific drug effects. Central and peripheral nervous system structures are depicted appropriately. Created using BioRender (<https://BioRender.com>).

Tables

Table 1. Chemotherapy drug classes and their association with CIPN pathophysiology

Table 2. Experimental models for the study of CIPN and its mechanisms

Table 1. Chemotherapy drug classes and their association with CIPN pathophysiology

Chemotherapy Class	Drug	CIPN Presentation	Hypothesised Pathophysiology	Duration	References
Platinum	Cisplatin, Oxaliplatin, Carboplatin	Sensory: Paraesthesia in extremities including cold sensitive paraesthesia (particularly oxaliplatin), allodynia, sensory ataxia Motor: Lower limb movement disorders, fasciculation and cramps	Nerve excitability due to altered ion channel activity Adducts in nuclear and mitochondrial DNA Oxaliplatin chelating calcium triggering axonal hyperexcitability.	Transient, acute, coasting, chronic	181, 182, 183, 16, 180, 184-188
Taxanes	Paclitaxel, Docetaxel	Sensory: Paraesthesia in the extremities, hypoesthesia, dysesthesia, hyperalgesia Motor: Deficits in fine motor skills and walking; reductions in/absence of ankle reflexes; motor deficits primarily associated with lower extremities	Retrograde axonopathy Axonal transport disruption	Transient, acute and coasting	180, 181, 183, 185, 189

Vinca Alkaloids	Vincristine Sulphate Salt, Vinblastine, Vindesine	Sensory: paraesthesia in extremities, allodynia, hyperalgesia; length dependent neuropathy Motor: Walking impairment, fine motor impairment; paediatric-specific motor presentations; distal weakness and functional mobility	Axonal transport disruption Impaired mitochondrial function	Acute, transient, coasting, chronic	180, 181, 186, 16, 183, 185, 187
Anti-metabolites	Cytarabine, Fluorouracil (%-FU), Cytosine arabinoside Methotrexate* *CIPN is infrequent	Sensory: allodynia, paraesthesia. Motor: weakness	Genetic predisposition Interference with DNA synthesis	Transient	17, 190-192
Proteasome Inhibitors	Bortezomib	Sensory: paraesthesia, vibration sensitivity, hyperalgesia, proprioception changes	Endoplasmic reticulum stress in peripheral nerve fibres	Acute, reversible, chronic	181-183, 185, 11, 16, 180, 20, 70, 186-188

		Motor: Ankle hyporeflexia, distal impairment, muscle weakness, atrophy, impaired reflexes	Deterioration of sensory nerve fibres (A β , A δ & C) Increased tubulin polymerisation, microtubule stability Altered axonal transport TRPV1 sensitisation		
Alkylating Agents * * Generally, not associated with CIPN, exclusively Ifosfamide	Ifosfamide	Sensory: Paraesthesia in the lower extremities	Activation of proinflammatory cytokines and neuroinflammation Oxidative stress	Transient	181
Immunomodulatory	Thalidomide, lenalidomide, pomalidomide	Sensory: Paraesthesia and allodynia of lower extremities Motor: Less common	Deterioration of sensory nerve fibres (A β , A δ , C) Anti-angiogenic effects affecting nerve vasculature	Acute, transient and irreversible (Thalidomide)	183, 185
Antibody-drug conjugates (ADCs)	Brentuximab vendotin (BV), T-DM1, Polatuzumab vedotin, Enfortumab vedotin, Trastuzumab emtansine, Gemtuzumab	Sensory: Paraesthesia, hyperesthesia Motor: Mild distal weakness, walking deficits	Inhibition of microtubule dependent axon transport Length-dependent axonopathy fitting 'dying back' Sensory large nerve fibre neuropathy	Acute, transient and long term	25, 182, 185, 187, 193, 194

	ozogamicin, Ado- trastuzumab Emtansine, Famtrastuzumab deruxtecan Sacituzumab govitecan				
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Table 2. Experimental models for the study of CIPN and its mechanisms

Cell Line	Origin	Advantages	Disadvantages	Application in CIPN-related studies	References
PC12	Clonal cell line from an induced, transplantable rat pheochromocytoma	Differentiate into sympathetic ganglion neurons Adherent variant available Immortalised - unlimited differentiation material Can be co-cultured with other neuronal cells	Rodent origin Malignant properties NGF required - expensive inducer Varied in NGF responsiveness Significant clonal variation Low differentiation response in adherent clone Differentiation dependent on vessel (substratum) coating	Rodent origin, less representative of human disease	90, 92, 93
SHSY-5Y	Human metastatic neuroblastoma	Human origin Comparable to embryonic stem cell derived neurons	Existence of both neuroblast-like and epithelial-like cells Malignant origin	Limited application in diseases other than Parkinson's Limited characterisation of differentiation processes	96, 97, 195, 196, 94, 101, 197

		Differentiate into neurons dopaminergic neurons, adrenergic or cholinergic neurons depending on differentiation protocol used Immortalised - unlimited differentiation material Responsive to multiple differentiation inducers (RA, phenol esters, neurotrophins, BDNF)	Genetic instability and drift	Variation in differentiation inducer combinations, protocol, and differentiation times	
LUHMES	Human adapted mesencephalic cell line, neuronal precursor cells	Human origin Immortalised - unlimited differentiation material Tetracycline-controlled model without oncogene expression Differentiate into dopaminergic neurons Differentiable with tetracycline, cAMP, and GDNF exposure	Generates only dopaminergic neuron accounting for less than 1% of brain neuronal population	Generates only dopaminergic neuron of the CNS, limited in study CIPN due to heterogeneity of the PNS	95, 198-201

		Compatible with 3D cell models			
hESC-derived neurons	Pluripotent cells derived from inner cell mass of the blastocyst	Human origin Karyotypically normal Multilineage potential Unlimited proliferation potential Generate neural stem cells and functional neurons	Ethical and regulatory considerations, legislation limiting use of hESC research in many countries Costly cell culture reagents Co-culture with mouse embryonic fibroblast cells (concerns of transmission or animal-derived pathogens) Human feeder layers introduce variation Limited success in high-throughput assays	Dissection to isolate cells has poor success rate	202-206
Ex-vivo culture of rodent DRG	Rodent derived DRGs containing sensory neuron cell bodies	Heterogenous cell population Cultures of adult DRGs do not require the addition of neurotrophic factors	Requires use of animals Rodent origin Post-mitotic, cannot be passaged or expanded Embryonic and neonatal cultures still require NGF	Limitations of animal chemotherapy treatment prior to dissection Not suitable for high-throughput screening	207, 208, 209

Human Donor iPSCs	Pluripotent stem cells derived from human patients	Human origin Replicates disease pathology Overcome ethical limitations of hECS Can be co-cultured to study cell interactions Capacity to self-organise and form 3D organoids Contain disease-relevant genetic information Allow patient-specific treatments / studies	Genetic instability Extensive culture times requiring induction iPSC-derived cell immaturity High associated costs Donors' genetic information - donor variation	Donor specificity limits generalisation of findings	113, 210-213
Commercially available iPSCs (iCell, Peri4U)	Pluripotent stem cells	Rapid cell recovery and establishment of neuronal cultures Negate lengthy culture of neural progenitors and additional differentiation of human donor iPSCs	Costly to culture, requiring expertise Finite growth Variation between commercially available iPSCs	Chemotherapy drug response variation observed between commercially available lines Require co-culture to reflect heterogeneity and complexity of disease	214, 215, 216-218

		Maintain neuronal populations for longer timescales than hECS/donor-derived (>28 days) High degree of purity in neuronal culture	Genotypic variation between iPSCs caused by differentiation process Homogeneity less informative in disease modelling, require co-culture		
NT2	Human embryonal carcinoma	Human origin and pluripotent properties Differentiate along neuroectodermal lineages (precursors) and subsequently into neurons Terminal differentiation, characteristically like human foetal neurons Respond to both RA and alternatively AraC Heterogenous neuronal population (neurons, astrocytes, radial glial)	Differentiation process 4-6 weeks when using RA with low rate of differentiation RA differentiation variability: exposure time, concentration, addition of mitotic inhibitors, media change frequency Unstable RA cultures: instability in aqueous solution, unstable in cell culture media, unstable when exposed to air, light and temperature. Adsorption of RA by glass and plasticware in culture. Mitotic, derived from a metastasis of primary	Used to assess sodium azide and amifostine mitigation of cisplatin induced oxidative stress of NT2N cells differentiated by RA Limited reports on application as a model for CIPN	15, 102, 105, 219-222

		Further differentiate into motor neurons Express neurotransmitters and high voltage activated calcium channels Express receptors associated with neuroinflammation and neuropathic pain (such as TRPV1)	testicular embryonal carcinoma Karyotypically abnormal		
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References

1. Chen X, Gan Y, Au NPB, et al. Current understanding of the molecular mechanisms of chemotherapy-induced peripheral neuropathy. *Front Mol Neurosci* 2024; 17: 1345811. 20240410. DOI: 10.3389/fnmol.2024.1345811.
2. Zajackowska R, Kocot-Kepska M, Leppert W, et al. Mechanisms of Chemotherapy-Induced Peripheral Neuropathy. *Int J Mol Sci* 2019; 20 20190322. DOI: 10.3390/ijms20061451.
3. D'Souza RS, Alvarez GAM, Dombrov-Johnson M, et al. Evidence-Based Treatment of Pain in Chemotherapy-Induced Peripheral Neuropathy. *Curr Pain Headache Rep* 2023; 27: 99-116. 20230414. DOI: 10.1007/s11916-023-01107-4.
4. Colvin LA. Chemotherapy-induced peripheral neuropathy: where are we now? *Pain* 2019; 160 Suppl 1: S1-S10. DOI: 10.1097/j.pain.0000000000001540.
5. Kandula T, Farrar MA, Cohn RJ, et al. Chemotherapy-Induced Peripheral Neuropathy in Long-term Survivors of Childhood Cancer: Clinical, Neurophysiological, Functional, and Patient-Reported Outcomes. *JAMA Neurol* 2018; 75: 980-988. DOI: 10.1001/jamaneurol.2018.0963.
6. Jun Y, Tao X, Choi J, et al. Mixed-methods Study of the Effect of Chemotherapy-induced Peripheral Neuropathy Symptom Permanence on Patient's Willingness to Alter Neurotoxic Chemotherapy Treatment. *Res Sq* 2025 20250513. DOI: 10.21203/rs.3.rs-6304310/v1.
7. Chen K, Antonen E, Nadler MB, et al. Assessment tools for chemotherapy-induced peripheral neuropathy: a narrative review of clinician, patient-reported, and objective measures. *JNCI Cancer Spectr* 2026; 10. DOI: 10.1093/jncics/pkaf119.
8. Li T, Park SB, Battaglini E, et al. Assessing chemotherapy-induced peripheral neuropathy with patient reported outcome measures: a systematic review of measurement properties and considerations for future use. *Qual Life Res* 2022; 31: 3091-3107. 20220521. DOI: 10.1007/s11136-022-03154-7.
9. Tan AC, McCrary JM, Park SB, et al. Chemotherapy-induced peripheral neuropathy-patient-reported outcomes compared with NCI-CTCAE grade. *Support Care Cancer* 2019; 27: 4771-4777. 20190410. DOI: 10.1007/s00520-019-04781-6.
10. Inoue M, Matsumoto K, Tanaka M, et al. Analysis of chemotherapy-induced peripheral neuropathy using the Japanese Adverse Drug Event Report database. *Sci Rep* 2021; 11: 11324. 20210531. DOI: 10.1038/s41598-021-90848-6.
11. Lee KT, Bulls HW, Hoogland AI, et al. Chemotherapy-Induced Peripheral Neuropathy (CIPN): A Narrative Review and Proposed Theoretical Model. *Cancers (Basel)* 2024; 16 20240718. DOI: 10.3390/cancers16142571.
12. Lazic A, Popovic J, Paunesku T, et al. Insights into platinum-induced peripheral neuropathy-current perspective. *Neural Regen Res* 2020; 15: 1623-1630. DOI: 10.4103/1673-5374.276321.
13. da Costa R, Passos GF, Quintao NLM, et al. Taxane-induced neurotoxicity: Pathophysiology and therapeutic perspectives. *Br J Pharmacol* 2020; 177: 3127-3146. 20200603. DOI: 10.1111/bph.15086.
14. Gupta R and Bhaskar A. Chemotherapy-induced peripheral neuropathic pain. *BJA Education* 2015; 16: 115-119. DOI: 10.1093/bjaed/mkv044.
15. Mortensen C, Thomsen MT, Chua KC, et al. Modeling mechanisms of chemotherapy-induced peripheral neuropathy and chemotherapy transport using

- induced pluripotent stem cell-derived sensory neurons. *Neuropharmacology* 2024; 258: 110062. 20240705. DOI: 10.1016/j.neuropharm.2024.110062.
16. Was H, Borkowska A, Bagues A, et al. Mechanisms of Chemotherapy-Induced Neurotoxicity. *Front Pharmacol* 2022; 13: 750507. 20220328. DOI: 10.3389/fphar.2022.750507.
17. Jules R, Thaper A, Foster R, et al. 5-Fluorouracil Neurotoxicity in the Absence of Dihydropyrimidine Dehydrogenase Deficiency Case Report. *Neurohospitalist* 2022; 12: 366-370. 20220103. DOI: 10.1177/19418744211068913.
18. Apiraksattayakul N, Jitprapaikulsan J, Sanpakit K, et al. Potential neurotoxicity associated with methotrexate. *Sci Rep* 2024; 14: 18548. 20240809. DOI: 10.1038/s41598-024-69263-0.
19. Yokoyama C, Sueyoshi Y, Ema M, et al. Induction of oxidative stress by anticancer drugs in the presence and absence of cells. *Oncol Lett* 2017; 14: 6066-6070. 20170914. DOI: 10.3892/ol.2017.6931.
20. Staff NP, Podratz JL, Grassner L, et al. Bortezomib alters microtubule polymerization and axonal transport in rat dorsal root ganglion neurons. *Neurotoxicology* 2013; 39: 124-131. 20130912. DOI: 10.1016/j.neuro.2013.09.001.
21. Chen B, Zheng X, Wu J, et al. Antibody-drug conjugates in cancer therapy: current landscape, challenges, and future directions. *Mol Cancer* 2025; 24: 279. 20251103. DOI: 10.1186/s12943-025-02489-2.
22. von Itzstein MS, Rashdan S, Dahlberg SE, et al. Incidence and correlates of high-grade chemotherapy-induced peripheral neuropathy in patients with lung cancer. *Oncologist* 2025; 30. DOI: 10.1093/oncolo/oyaf036.
23. Molassiotis A, Cheng HL, Lopez V, et al. Are we mis-estimating chemotherapy-induced peripheral neuropathy? Analysis of assessment methodologies from a prospective, multinational, longitudinal cohort study of patients receiving neurotoxic chemotherapy. *BMC Cancer* 2019; 19: 132. 20190208. DOI: 10.1186/s12885-019-5302-4.
24. Tang L, Sun C, Liu W, et al. A pharmacovigilance study on antibody-drug conjugate (ADC)-related neurotoxicity based on the FDA adverse event reporting system (FAERS). *Front Pharmacol* 2024; 15: 1362484. 20240207. DOI: 10.3389/fphar.2024.1362484.
25. Zhang J, Yang H and Lu Y. Management of neurotoxic reactions induced by antibody-drug conjugates. *Asia Pac J Oncol Nurs* 2024; 11: 100595. 20240914. DOI: 10.1016/j.apjon.2024.100595.
26. Lanigan LG, Russell DS, Woolard KD, et al. Comparative Pathology of the Peripheral Nervous System. *Vet Pathol* 2021; 58: 10-33. 20201005. DOI: 10.1177/0300985820959231.
27. Wu D, Chen Q, Chen X, et al. The blood-brain barrier: structure, regulation, and drug delivery. *Signal Transduct Target Ther* 2023; 8: 217. 20230525. DOI: 10.1038/s41392-023-01481-w.
28. Doolittle ND, Muldoon LL, Culp AY, et al. Delivery of chemotherapeutics across the blood-brain barrier: challenges and advances. *Adv Pharmacol* 2014; 71: 203-243. 20140822. DOI: 10.1016/bs.apha.2014.06.002.
29. Malong L, Napoli I, Casal G, et al. Characterization of the structure and control of the blood-nerve barrier identifies avenues for therapeutic delivery. *Dev Cell* 2023; 58: 174-191 e178. 20230126. DOI: 10.1016/j.devcel.2023.01.002.

30. Richner M, Ferreira N, Dudele A, et al. Functional and Structural Changes of the Blood-Nerve-Barrier in Diabetic Neuropathy. *Front Neurosci* 2018; 12: 1038. 20190114. DOI: 10.3389/fnins.2018.01038.
31. Hu Y, Girdenyte M, Roest L, et al. Analysis of the contributing role of drug transport across biological barriers in the development and treatment of chemotherapy-induced peripheral neuropathy. *Fluids Barriers CNS* 2024; 21: 13. 20240208. DOI: 10.1186/s12987-024-00519-7.
32. Kaur C, Villarreal E, Cabe MH, et al. Blood nerve barrier permeability enables nerve targeting of circulating nanoparticles in experimental autoimmune neuritis. *Sci Rep* 2025; 15: 11763. 20250406. DOI: 10.1038/s41598-025-96231-z.
33. Wu PZ, Yao J, Meng B, et al. Blood-nerve barrier enhances chronic postsurgical pain via the HIF-1alpha/ aquaporin-1 signaling axis. *BMC Anesthesiol* 2023; 23: 381. 20231121. DOI: 10.1186/s12871-023-02306-7.
34. Lan MJ, Yao DF, Zhu LL, et al. The Rate of Infusion Represents an Important Aspect of Administering Anticancer Agents. *Risk Manag Healthc Policy* 2023; 16: 2531-2541. 20231122. DOI: 10.2147/RMHP.S442692.
35. Park JH, Chae J, Roh K, et al. Oxaliplatin-Induced Peripheral Neuropathy via TRPA1 Stimulation in Mice Dorsal Root Ganglion Is Correlated with Aluminum Accumulation. *PLoS One* 2015; 10: e0124875. 20150430. DOI: 10.1371/journal.pone.0124875.
36. Kim HA, Mindos T and Parkinson DB. Plastic fantastic: Schwann cells and repair of the peripheral nervous system. *Stem Cells Transl Med* 2013; 2: 553-557. 20130701. DOI: 10.5966/sctm.2013-0011.
37. Zhang Y, Yang SH and Guo XL. New insights into Vinca alkaloids resistance mechanism and circumvention in lung cancer. *Biomed Pharmacother* 2017; 96: 659-666. 20171106. DOI: 10.1016/j.biopha.2017.10.041.
38. Mollaei M, Hassan ZM, Khorshidi F, et al. Chemotherapeutic drugs: Cell death- and resistance-related signaling pathways. Are they really as smart as the tumor cells? *Transl Oncol* 2021; 14: 101056. 20210306. DOI: 10.1016/j.tranon.2021.101056.
39. Yaron A and Schuldiner O. Common and Divergent Mechanisms in Developmental Neuronal Remodeling and Dying Back Neurodegeneration. *Curr Biol* 2016; 26: R628-R639. DOI: 10.1016/j.cub.2016.05.025.
40. Prior R, Van Helleputte L, Benoy V, et al. Defective axonal transport: A common pathological mechanism in inherited and acquired peripheral neuropathies. *Neurobiol Dis* 2017; 105: 300-320. 20170224. DOI: 10.1016/j.nbd.2017.02.009.
41. Landowski LM, Dyck PJ, Engelstad J, et al. Axonopathy in peripheral neuropathies: Mechanisms and therapeutic approaches for regeneration. *J Chem Neuroanat* 2016; 76: 19-27. 20160502. DOI: 10.1016/j.jchemneu.2016.04.006.
42. Park SB, Cetinkaya-Fisgin A, Argyriou AA, et al. Axonal degeneration in chemotherapy-induced peripheral neurotoxicity: clinical and experimental evidence. *J Neurol Neurosurg Psychiatry* 2023; 94: 962-972. 20230404. DOI: 10.1136/jnnp-2021-328323.
43. Doerksen AH, Herath NN and Sanders SS. Fat traffic control: S-acylation in axonal transport. *Mol Pharmacol* 2025; 107: 100039. 20250416. DOI: 10.1016/j.molpha.2025.100039.
44. Schinke C, Maierhof SK, Hew L, et al. Time-resolved multi-omic analysis of paclitaxel exposure in human iPSC-derived sensory neurons unveils mechanisms of

- chemotherapy-induced peripheral neuropathy. *Cell Death Dis* 2026; 17: 211. 20260210. DOI: 10.1038/s41419-026-08445-2.
45. Albin B, Adhikari P, Tiwari AP, et al. Electrical stimulation enhances mitochondrial trafficking as a neuroprotective mechanism against chemotherapy-induced peripheral neuropathy. *iScience* 2024; 27: 109052. 20240130. DOI: 10.1016/j.isci.2024.109052.
46. Areti A, Yerra VG, Naidu V, et al. Oxidative stress and nerve damage: role in chemotherapy induced peripheral neuropathy. *Redox Biol* 2014; 2: 289-295. 20140118. DOI: 10.1016/j.redox.2014.01.006.
47. Mukherjee S, Bhatti GK, Chhabra R, et al. Targeting mitochondria as a potential therapeutic strategy against chemoresistance in cancer. *Biomed Pharmacother* 2023; 160: 114398. 20230209. DOI: 10.1016/j.biopha.2023.114398.
48. Doyle TM and Salvemini D. Mini-Review: Mitochondrial dysfunction and chemotherapy-induced neuropathic pain. *Neurosci Lett* 2021; 760: 136087. 20210626. DOI: 10.1016/j.neulet.2021.136087.
49. Canta A, Pozzi E and Carozzi VA. Mitochondrial Dysfunction in Chemotherapy-Induced Peripheral Neuropathy (CIPN). *Toxics* 2015; 3: 198-223. 20150605. DOI: 10.3390/toxics3020198.
50. Carrasco C, Naziroglu M, Rodriguez AB, et al. Neuropathic Pain: Delving into the Oxidative Origin and the Possible Implication of Transient Receptor Potential Channels. *Front Physiol* 2018; 9: 95. 20180214. DOI: 10.3389/fphys.2018.00095.
51. Gomez-Deza J, Slavutsky AL, Nebiyu M, et al. Local production of reactive oxygen species drives vincristine-induced axon degeneration. *Cell Death Dis* 2023; 14: 807. 20231208. DOI: 10.1038/s41419-023-06227-8.
52. Shim HS, Bae C, Wang J, et al. Peripheral and central oxidative stress in chemotherapy-induced neuropathic pain. *Mol Pain* 2019; 15: 1744806919840098. DOI: 10.1177/1744806919840098.
53. Dixon SJ and Olzmann JA. The cell biology of ferroptosis. *Nat Rev Mol Cell Biol* 2024; 25: 424-442. 20240216. DOI: 10.1038/s41580-024-00703-5.
54. Liu C, Liu Z, Dong Z, et al. Multifaceted interplays between the essential players and lipid peroxidation in ferroptosis. *J Genet Genomics* 2025; 52: 1071-1081. 20250123. DOI: 10.1016/j.jgg.2025.01.009.
55. Maity A, Metz N, Fleck K, et al. Can chemotherapy-induced peripheral neuropathy be predicted? Implications for future prevention and treatment of this side-effect. In: *CANCER RESEARCH 2024, AMER ASSOC CANCER RESEARCH* 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA
56. Brunsvig PF, Andersen A, Aamdal S, et al. Pharmacokinetic analysis of two different docetaxel dose levels in patients with non-small cell lung cancer treated with docetaxel as monotherapy or with concurrent radiotherapy. *BMC Cancer* 2007; 7: 197. 20071023. DOI: 10.1186/1471-2407-7-197.
57. Zheng Y, Huang H, Wang S, et al. Metabolic stress exacerbates Parkinson's disease pathology through mitochondrial dysfunction and ferroptosis. *NPJ Parkinsons Dis* 2026 20260516. DOI: 10.1038/s41531-026-01389-6.
58. Ruan J, He XK, Zhang SO, et al. Progress in Research on the Mechanisms and Therapeutic Targets of Ferroptosis in Peripheral Nerve Injury and Repair. *ASN Neuro* 2026; 18: 2678168. 20260527. DOI: 10.1080/17590914.2026.2678168.

-
59. Jiang T, Ma W, Dong W, et al. Ferroptosis-associated transcriptional factors in neurological diseases: molecular mechanisms and therapeutic prospects. *Exp Mol Med* 2025; 57: 2763-2781. 20251229. DOI: 10.1038/s12276-025-01611-0.
 60. Lin J, Zhang Y, Guan H, et al. Myricitrin inhibited ferritinophagy-mediated ferroptosis in cisplatin-induced human renal tubular epithelial cell injury. *Front Pharmacol* 2024; 15: 1372094. 20240607. DOI: 10.3389/fphar.2024.1372094.
 61. Wang X, Xu L, Meng Y, et al. FOXO1-NCOA4 Axis Contributes to Cisplatin-Induced Cochlea Spiral Ganglion Neuron Ferroptosis via Ferritinophagy. *Adv Sci (Weinh)* 2024; 11: e2402671. 20240829. DOI: 10.1002/advs.202402671.
 62. Fan S, Wang K, Zhang T, et al. Mechanisms and Therapeutic Potential of GPX4 in Pain Modulation. *Pain Ther* 2025; 14: 21-45. 20241106. DOI: 10.1007/s40122-024-00673-8.
 63. Avraham O, Deng PY, Jones S, et al. Satellite glial cells promote regenerative growth in sensory neurons. *Nat Commun* 2020; 11: 4891. 20200929. DOI: 10.1038/s41467-020-18642-y.
 64. Xu J, Li Y, Novak C, et al. Mitochondrial transfer from glia to neurons protects against peripheral neuropathy. *Nature* 2026; 650: 951-960. 20260107. DOI: 10.1038/s41586-025-09896-x.
 65. Canon E, Cosgaya JM, Scsucova S, et al. Rapid effects of retinoic acid on CREB and ERK phosphorylation in neuronal cells. *Mol Biol Cell* 2004; 15: 5583-5592. 20040915. DOI: 10.1091/mbc.e04-05-0439.
 66. Babetto E, Wong KM and Beirowski B. A glycolytic shift in Schwann cells supports injured axons. *Nat Neurosci* 2020; 23: 1215-1228. 20200817. DOI: 10.1038/s41593-020-0689-4.
 67. Baker CA, Tyagi S, Higerd-Rusli GP, et al. Paclitaxel effects on axonal localization and vesicular trafficking of Na(V)1.8. *Front Mol Neurosci* 2023; 16: 1130123. 20230213. DOI: 10.3389/fnmol.2023.1130123.
 68. Pozzi E, Terribile G, Cherchi L, et al. Ion Channel and Transporter Involvement in Chemotherapy-Induced Peripheral Neurotoxicity. *Int J Mol Sci* 2024; 25 20240614. DOI: 10.3390/ijms25126552.
 69. Boyette-Davis JA, Cata JP, Driver LC, et al. Persistent chemoneuropathy in patients receiving the plant alkaloids paclitaxel and vincristine. *Cancer Chemother Pharmacol* 2013; 71: 619-626. 20121211. DOI: 10.1007/s00280-012-2047-z.
 70. Sprague JM, Yekkiralala AS, Singh B, et al. Bortezomib-induced neuropathy is in part mediated by the sensitization of TRPV1 channels. *Commun Biol* 2023; 6: 1228. 20231205. DOI: 10.1038/s42003-023-05624-1.
 71. Aloï VD, Pinto S, Van Bree R, et al. TRPM3 as a novel target to alleviate acute oxaliplatin-induced peripheral neuropathic pain. *Pain* 2023; 164: 2060-2069. 20230419. DOI: 10.1097/j.pain.0000000000002906.
 72. Nassini R, Materazzi S, Benemei S, et al. The TRPA1 Channel in Inflammatory and Neuropathic Pain and Migraine. In: Nilius B, Gudermann T, Jahn R, et al. (eds) *Reviews of Physiology, Biochemistry and Pharmacology, Vol 167*. Cham: Springer International Publishing, 2014, pp.1-43.
 73. Marynissen H, Pinto S, Van Ranst N, et al. Increased TRPA1 functionality in the skin of rats and cancer patients following oxaliplatin treatment. *The Journal of Pain* 2025; 28. DOI: 10.1016/j.jpain.2025.104794.

-
74. Deuis JR, Dvorakova LS and Vetter I. Methods Used to Evaluate Pain Behaviors in Rodents. *Front Mol Neurosci* 2017; 10: 284. 20170906. DOI: 10.3389/fnmol.2017.00284.
75. Godinho PAR, Silva PGB, Lisboa MRP, et al. Electronic von Frey as an objective assessment tool for oxaliplatin-induced peripheral neuropathy: A prospective longitudinal study. *Eur J Cancer Care (Engl)* 2021; 30: e13360. 20201120. DOI: 10.1111/ecc.13360.
76. Whittaker AL, Liu Y and Barker TH. Methods Used and Application of the Mouse Grimace Scale in Biomedical Research 10 Years on: A Scoping Review. *Animals (Basel)* 2021; 11 20210303. DOI: 10.3390/ani11030673.
77. McCoy ES, Park SK, Patel RP, et al. Development of PainFace software to simplify, standardize, and scale up mouse grimace analyses. *Pain* 2024; 165: 1793-1805. 20240213. DOI: 10.1097/j.pain.0000000000003187.
78. Sturman O, Schmutz M, Lorimer T, et al. GrimACE: automated, multimodal cage-side assessment of pain and well-being in mice. *Lab Anim (NY)* 2026; 55: 137-146. 20260305. DOI: 10.1038/s41684-026-01695-9.
79. Tay N, Laakso EL, Schweitzer D, et al. Chemotherapy-induced peripheral neuropathy in children and adolescent cancer patients. *Front Mol Biosci* 2022; 9: 1015746. 20221014. DOI: 10.3389/fmolb.2022.1015746.
80. Perse M. Cisplatin Mouse Models: Treatment, Toxicity and Translatability. *Biomedicines* 2021; 9 20211007. DOI: 10.3390/biomedicines9101406.
81. Alaei M, Moetamani-Ahmadi M, Mahaki H, et al. Nanoliposomal oxaliplatin ameliorates chemotherapy-induced neuropathy. *Neurosci Lett* 2023; 812: 137367. 20230705. DOI: 10.1016/j.neulet.2023.137367.
82. Geisler S, Doan RA, Strickland A, et al. Prevention of vincristine-induced peripheral neuropathy by genetic deletion of SARM1 in mice. *Brain* 2016; 139: 3092-3108. 20161025. DOI: 10.1093/brain/aww251.
83. Balayssac D, Durif J, Lambert C, et al. Exploring Serum Biomarkers for Neuropathic Pain in Rat Models of Chemotherapy-Induced Peripheral Neuropathy: A Comparative Pilot Study with Oxaliplatin, Paclitaxel, Bortezomib, and Vincristine. *Toxics* 2023; 11 20231208. DOI: 10.3390/toxics11121004.
84. Jin H, Wang L and Bernards R. Rational combinations of targeted cancer therapies: background, advances and challenges. *Nat Rev Drug Discov* 2023; 22: 213-234. 20221212. DOI: 10.1038/s41573-022-00615-z.
85. White D, Abdulla M, Park SB, et al. Targeting translation: A review of preclinical animal models in the development of treatments for chemotherapy-induced peripheral neuropathy. *J Peripher Nerv Syst* 2023; 28: 179-190. 20230412. DOI: 10.1111/jns.12544.
86. Agnes JP, Santos VWD, das Neves RN, et al. Antioxidants Improve Oxaliplatin-Induced Peripheral Neuropathy in Tumor-Bearing Mice Model: Role of Spinal Cord Oxidative Stress and Inflammation. *J Pain* 2021; 22: 996-1013. 20210324. DOI: 10.1016/j.jpain.2021.03.142.
87. Sewell RDE. Neuropathic pain models and outcome measures: a dual translational challenge. *Ann Transl Med* 2018; 6: S42. DOI: 10.21037/atm.2018.09.58.
88. Thomas A, Okine BN, Finn DP, et al. Peripheral deficiency and antiallodynic effects of 2-arachidonoyl glycerol in a mouse model of paclitaxel-induced neuropathic pain. *Biomed Pharmacother* 2020; 129: 110456. 20200627. DOI: 10.1016/j.biopha.2020.110456.

-
89. Kroigard T, Schroder HD, Qvortrup C, et al. Characterization and diagnostic evaluation of chronic polyneuropathies induced by oxaliplatin and docetaxel comparing skin biopsy to quantitative sensory testing and nerve conduction studies. *Eur J Neurol* 2014; 21: 623-629. 20140125. DOI: 10.1111/ene.12353.
 90. Chua P and Lim WK. Optimisation of a PC12 cell-based in vitro stroke model for screening neuroprotective agents. *Sci Rep* 2021; 11: 8096. 20210414. DOI: 10.1038/s41598-021-87431-4.
 91. Lehmann HC, Staff NP and Hoke A. Modeling chemotherapy induced peripheral neuropathy (CIPN) in vitro: Prospects and limitations. *Exp Neurol* 2020; 326: 113140. 20191205. DOI: 10.1016/j.expneurol.2019.113140.
 92. Wiatrak B, Kubis-Kubiak A, Piwowar A, et al. PC12 Cell Line: Cell Types, Coating of Culture Vessels, Differentiation and Other Culture Conditions. *Cells* 2020; 9: 20200414. DOI: 10.3390/cells9040958.
 93. Sierra-Fonseca JA, Najera O, Martinez-Jurado J, et al. Nerve growth factor induces neurite outgrowth of PC12 cells by promoting Gbetagamma-microtubule interaction. *BMC Neurosci* 2014; 15: 132. 20141231. DOI: 10.1186/s12868-014-0132-4.
 94. Xicoy H, Wieringa B and Martens GJ. The SH-SY5Y cell line in Parkinson's disease research: a systematic review. *Mol Neurodegener* 2017; 12: 10. 20170124. DOI: 10.1186/s13024-017-0149-0.
 95. Smirnova L, Harris G, Delp J, et al. A LUHMES 3D dopaminergic neuronal model for neurotoxicity testing allowing long-term exposure and cellular resilience analysis. *Arch Toxicol* 2016; 90: 2725-2743. 20151208. DOI: 10.1007/s00204-015-1637-z.
 96. Hoffmann LF, Martins A, Majolo F, et al. Neural regeneration research model to be explored: SH-SY5Y human neuroblastoma cells. *Neural Regen Res* 2023; 18: 1265-1266. DOI: 10.4103/1673-5374.358621.
 97. Lopez-Suarez L, Awabdh SA, Coumoul X, et al. The SH-SY5Y human neuroblastoma cell line, a relevant in vitro cell model for investigating neurotoxicology in human: Focus on organic pollutants. *Neurotoxicology* 2022; 92: 131-155. 20220729. DOI: 10.1016/j.neuro.2022.07.008.
 98. Targett IL, Crompton LA, Conway ME, et al. Differentiation of SH-SY5Y neuroblastoma cells using retinoic acid and BDNF: a model for neuronal and synaptic differentiation in neurodegeneration. *In Vitro Cell Dev Biol Anim* 2024; 60: 1058-1067. 20240717. DOI: 10.1007/s11626-024-00948-6.
 99. Kaya ZB, Santiago-Padilla V, Lim M, et al. Optimizing SH-SY5Y cell culture: exploring the beneficial effects of an alternative media supplement on cell proliferation and viability. *Sci Rep* 2024; 14: 4775. 20240227. DOI: 10.1038/s41598-024-55516-5.
 100. Burai S, Kovacs R, Molnar T, et al. Comprehensive analysis of different tumor cell-line produced soluble mediators on the differentiation and functional properties of monocyte-derived dendritic cells. *PLoS One* 2022; 17: e0274056. 20221004. DOI: 10.1371/journal.pone.0274056.
 101. Yin K, Baillie GJ and Vetter I. Neuronal cell lines as model dorsal root ganglion neurons: A transcriptomic comparison. *Mol Pain* 2016; 12: 20160429. DOI: 10.1177/1744806916646111.
 102. Haile Y, Fu W, Shi B, et al. Characterization of the NT2-derived neuronal and astrocytic cell lines as alternative in vitro models for primary human neurons and astrocytes. *J Neurosci Res* 2014; 92: 1187-1198. 20140507. DOI: 10.1002/jnr.23399.

-
103. Richter M, Piwocka O, Musielak M, et al. From Donor to the Lab: A Fascinating Journey of Primary Cell Lines. *Front Cell Dev Biol* 2021; 9: 711381. 20210722. DOI: 10.3389/fcell.2021.711381.
 104. Andrews PW. Germ cell tumors, cell surface markers, and the early search for human pluripotent stem cells. *Bioessays* 2024; 46: e2400094. 20240808. DOI: 10.1002/bies.202400094.
 105. Abolpour Mofrad S, Kuenzel K, Friedrich O, et al. Optimizing neuronal differentiation of human pluripotent NT2 stem cells in monolayer cultures. *Dev Growth Differ* 2016; 58: 664-676. 20160926. DOI: 10.1111/dgd.12323.
 106. Stern M, Gierse A, Tan S, et al. Human Ntera2 cells as a predictive in vitro test system for developmental neurotoxicity. *Arch Toxicol* 2014; 88: 127-136. 20130807. DOI: 10.1007/s00204-013-1098-1.
 107. Hara K, Yasuhara T, Maki M, et al. Neural progenitor NT2N cell lines from teratocarcinoma for transplantation therapy in stroke. *Prog Neurobiol* 2008; 85: 318-334. 20080426. DOI: 10.1016/j.pneurobio.2008.04.005.
 108. Kleppner SR, Robinson KA, Trojanowski JQ, et al. Transplanted human neurons derived from a teratocarcinoma cell line (NTera-2) mature, integrate, and survive for over 1 year in the nude mouse brain. *J Comp Neurol* 1995; 357: 618-632. DOI: 10.1002/cne.903570410.
 109. Watson DJ, Longhi L, Lee EB, et al. Genetically modified NT2N human neuronal cells mediate long-term gene expression as CNS grafts in vivo and improve functional cognitive outcome following experimental traumatic brain injury. *J Neuropathol Exp Neurol* 2003; 62: 368-380. DOI: 10.1093/jnen/62.4.368.
 110. Avila-Gonzalez D, Gidi-Grenat MA, Garcia-Lopez G, et al. Pluripotent Stem Cells as a Model for Human Embryogenesis. *Cells* 2023; 12 20230420. DOI: 10.3390/cells12081192.
 111. Kim HJ and Park JS. Usage of Human Mesenchymal Stem Cells in Cell-based Therapy: Advantages and Disadvantages. *Dev Reprod* 2017; 21: 1-10. 20170331. DOI: 10.12717/DR.2017.21.1.001.
 112. Volarevic V, Markovic BS, Gazdic M, et al. Ethical and Safety Issues of Stem Cell-Based Therapy. *Int J Med Sci* 2018; 15: 36-45. 20180101. DOI: 10.7150/ijms.21666.
 113. Cerneckis J, Cai H and Shi Y. Induced pluripotent stem cells (iPSCs): molecular mechanisms of induction and applications. *Signal Transduction and Targeted Therapy* 2024; 9: 112. DOI: 10.1038/s41392-024-01809-0.
 114. Costamagna G, Comi GP and Corti S. Advancing Drug Discovery for Neurological Disorders Using iPSC-Derived Neural Organoids. *Int J Mol Sci* 2021; 22 20210306. DOI: 10.3390/ijms22052659.
 115. Mortensen C, Andersen NE and Stage TB. Bridging the Translational Gap in Chemotherapy-Induced Peripheral Neuropathy with iPSC-Based Modeling. *Cancers (Basel)* 2022; 14 20220815. DOI: 10.3390/cancers14163939.
 116. Schinke C, Fernandez Vallone V, Ivanov A, et al. Modeling chemotherapy induced neurotoxicity with human induced pluripotent stem cell (iPSC) -derived sensory neurons. *Neurobiol Dis* 2021; 155: 105391. 20210511. DOI: 10.1016/j.nbd.2021.105391.
 117. Kim JH, Kawase E, Bharti K, et al. Perspectives on the cost of goods for hPSC banks for manufacture of cell therapies. *NPJ Regen Med* 2022; 7: 54. 20220929. DOI: 10.1038/s41536-022-00242-7.

-
118. Struzyna LA and Watt ML. The Emerging Role of Neuronal Organoid Models in Drug Discovery: Potential Applications and Hurdles to Implementation. *Mol Pharmacol* 2021; 99: 256-265. 20210205. DOI: 10.1124/molpharm.120.000142.
 119. Hrstka SCL, Jahnke M, Meng-Lin K, et al. Human iPSC-Derived Dorsal Root Ganglion Organoid Modeling of Chemotherapy-Induced Peripheral Neuropathy. *Cells* 2026; 15 20260419. DOI: 10.3390/cells15080724.
 120. Borenstein JT, Cummins G, Dutta A, et al. Bionanotechnology and bioMEMS (BNM): state-of-the-art applications, opportunities, and challenges. *Lab Chip* 2023; 23: 4928-4949. 20231121. DOI: 10.1039/d3lc00296a.
 121. Kramer L, Nguyen HT, Jacobs E, et al. Modeling chemotherapy-induced peripheral neuropathy using a Nerve-on-a-chip microphysiological system. *ALTEX* 2020; 37: 350-364. 20200507. DOI: 10.14573/altex.2001181.
 122. Matsuda K, Han X, Matsuda N, et al. Development of an In Vitro Assessment Method for Chemotherapy-Induced Peripheral Neuropathy (CIPN) by Integrating a Microphysiological System (MPS) with Morphological Deep Learning of Soma and Axonal Images. *Toxics* 2023; 11 20231010. DOI: 10.3390/toxics11100848.
 123. Piga I, Bonomo R, Chinello C, et al. Using an integrated omics approach to uncover the mechanisms underlying chemotherapy-induced peripheral neuropathy (CIPN). *Commun Med (Lond)* 2026; 6 20260506. DOI: 10.1038/s43856-026-01622-6.
 124. Kittaka N, Tahara H, Akazawa T, et al. Exploratory identification of candidate biomarkers and molecular contributors to paclitaxel-induced peripheral neuropathy in patients with breast cancer through proteomic analysis. *Front Pain Res (Lausanne)* 2026; 7: 1813700. 20260616. DOI: 10.3389/fpain.2026.1813700.
 125. Lotsch J, Gasimli K, Malkusch S, et al. Machine learning and biological validation identify sphingolipids as potential mediators of paclitaxel-induced neuropathy in cancer patients. *Elife* 2024; 13 20240930. DOI: 10.7554/eLife.91941.
 126. Sharma A, Johnson KB, Sen A, et al. Longitudinal multi-omics analyses of chemotherapy-induced peripheral neuropathy in response to taxanes. *BMC Cancer* 2025; 25: 1591. 20251015. DOI: 10.1186/s12885-025-14901-7.
 127. Verma P, Devaraj J, Skiles JL, et al. A Metabolomics Approach for Early Prediction of Vincristine-Induced Peripheral Neuropathy. *Sci Rep* 2020; 10: 9659. 20200615. DOI: 10.1038/s41598-020-66815-y.
 128. McKenzie M, Irac SE, Chen Z, et al. Integrative spatial omics and artificial intelligence: transforming cancer research with omics data and AI. *Semin Cancer Biol* 2026; 119: 65-82. 20260109. DOI: 10.1016/j.semcancer.2026.01.002.
 129. Majithia N, Temkin SM, Ruddy KJ, et al. National Cancer Institute-supported chemotherapy-induced peripheral neuropathy trials: outcomes and lessons. *Support Care Cancer* 2016; 24: 1439-1447. 20151219. DOI: 10.1007/s00520-015-3063-4.
 130. Desforges AD, Hebert CM, Spence AL, et al. Treatment and diagnosis of chemotherapy-induced peripheral neuropathy: An update. *Biomed Pharmacother* 2022; 147: 112671. 20220129. DOI: 10.1016/j.biopha.2022.112671.
 131. Loprinzi CL, Lacchetti C, Bleeker J, et al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update. *J Clin Oncol* 2020; 38: 3325-3348. 20200714. DOI: 10.1200/JCO.20.01399.
 132. Jordan B, Margulies A, Cardoso F, et al. Systemic anticancer therapy-induced peripheral and central neurotoxicity: ESMO-EONS-EANO Clinical Practice Guidelines

- for diagnosis, prevention, treatment and follow-up. *Ann Oncol* 2020; 31: 1306-1319. 20200730. DOI: 10.1016/j.annonc.2020.07.003.
133. Dunnill C, Ibraheem K, Peake M, et al. Cooling-mediated protection from chemotherapy drug-induced cytotoxicity in human keratinocytes by inhibition of cellular drug uptake. *PLoS One* 2020; 15: e0240454. 20201015. DOI: 10.1371/journal.pone.0240454.
134. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 2007; 132: 237-251. 20071024. DOI: 10.1016/j.pain.2007.08.033.
135. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* 2015; 14: 162-173. 20150107. DOI: 10.1016/S1474-4422(14)70251-0.
136. Durand JP, Deplanque G, Montheil V, et al. Efficacy of venlafaxine for the prevention and relief of oxaliplatin-induced acute neurotoxicity: results of EFOF, a randomized, double-blind, placebo-controlled phase III trial. *Ann Oncol* 2012; 23: 200-205. 20110322. DOI: 10.1093/annonc/mdr045.
137. Smith EM, Pang H, Cirrincione C, et al. 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: 1359-1367. DOI: 10.1001/jama.2013.2813.
138. Smith EML, Lee M, Scott MR, et al. Alliance A221805: Duloxetine to Prevent Oxaliplatin-Induced Chemotherapy-Induced Peripheral Neuropathy: A Randomized, Double-Blind, Placebo-Controlled Phase II Study. *JCO Oncology Advances* 2026; 3: e2500107. DOI: 10.1200/oa-25-00107.
139. Loprinzi CL, Lustberg MB, Hershman DL, et al. Chemotherapy-induced peripheral neuropathy: ice, compression, both, or neither? *Ann Oncol* 2020; 31: 5-6. DOI: 10.1016/j.annonc.2019.10.009.
140. Gee NS, Brown JP, Dissanayake VU, et al. The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2delta subunit of a calcium channel. *J Biol Chem* 1996; 271: 5768-5776. DOI: 10.1074/jbc.271.10.5768.
141. Aghili M, Zare M, Mousavi N, et al. Efficacy of gabapentin for the prevention of paclitaxel induced peripheral neuropathy: A randomized placebo controlled clinical trial. *Breast J* 2019; 25: 226-231. 20190217. DOI: 10.1111/tbj.13196.
142. Rao RD, Michalak JC, Sloan JA, et al. Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). *Cancer* 2007; 110: 2110-2118. DOI: 10.1002/cncr.23008.
143. Shinde SS, Seisler D, Soori G, et al. Can pregabalin prevent paclitaxel-associated neuropathy?--An ACCRU pilot trial. *Support Care Cancer* 2016; 24: 547-553. 20150709. DOI: 10.1007/s00520-015-2807-5.
144. Brami C, Bao T and Deng G. Natural products and complementary therapies for chemotherapy-induced peripheral neuropathy: A systematic review. *Crit Rev Oncol Hematol* 2016; 98: 325-334. 20151123. DOI: 10.1016/j.critrevonc.2015.11.014.
145. Schloss JM, Colosimo M, Airey C, et al. Nutraceuticals and chemotherapy induced peripheral neuropathy (CIPN): a systematic review. *Clin Nutr* 2013; 32: 888-893. 20130413. DOI: 10.1016/j.clnu.2013.04.007.

-
146. Starobova H and Vetter I. Pathophysiology of Chemotherapy-Induced Peripheral Neuropathy. *Front Mol Neurosci* 2017; 10: 174. 20170531. DOI: 10.3389/fnmol.2017.00174.
147. Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2014; 32: 1941-1967. 20140414. DOI: 10.1200/JCO.2013.54.0914.
148. Hershman DL, Unger JM, Crew KD, et al. Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for the prevention of taxane-induced neuropathy in women undergoing adjuvant breast cancer therapy. *J Clin Oncol* 2013; 31: 2627-2633. 20130603. DOI: 10.1200/JCO.2012.44.8738.
149. Blackwell KL, Dewhirst MW, Liotcheva V, et al. HER-2 gene amplification correlates with higher levels of angiogenesis and lower levels of hypoxia in primary breast tumors. *Clin Cancer Res* 2004; 10: 4083-4088. DOI: 10.1158/1078-0432.CCR-03-0695.
150. Jordan B, Jahn F, Beckmann J, et al. Calcium and Magnesium Infusions for the Prevention of Oxaliplatin-Induced Peripheral Neurotoxicity: A Systematic Review. *Oncology* 2016; 90: 299-306. 20160512. DOI: 10.1159/000445977.
151. Wen F, Zhou Y, Wang W, et al. Ca/Mg infusions for the prevention of oxaliplatin-related neurotoxicity in patients with colorectal cancer: a meta-analysis. *Ann Oncol* 2013; 24: 171-178. 20120816. DOI: 10.1093/annonc/mds211.
152. Tsuyuki S, Senda N, Kanng Y, et al. Evaluation of the effect of compression therapy using surgical gloves on nanoparticle albumin-bound paclitaxel-induced peripheral neuropathy: a phase II multicenter study by the Kamigata Breast Cancer Study Group. *Breast Cancer Res Treat* 2016; 160: 61-67. 20160912. DOI: 10.1007/s10549-016-3977-7.
153. Wan Z, Huang J, Wang X, et al. Compression Therapy for Prevention of Chemotherapy-Induced Peripheral Neuropathy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Pain Res* 2024; 17: 4509-4519. 20241224. DOI: 10.2147/JPR.S488470.
154. Maihofner C, Diel I, Tesch H, et al. Chemotherapy-induced peripheral neuropathy (CIPN): current therapies and topical treatment option with high-concentration capsaicin. *Support Care Cancer* 2021; 29: 4223-4238. 20210223. DOI: 10.1007/s00520-021-06042-x.
155. Okazaki M, Bando H, Terasaki A, et al. Safety and Efficacy of Compression Therapy to Prevent Chemotherapy-Induced Peripheral Neuropathy in Lower Extremities of Breast Cancer Patients: A Pilot Study. *Cureus* 2024; 16: e60998. 20240524. DOI: 10.7759/cureus.60998.
156. Kotani H, Terada M, Mori M, et al. Compression therapy using surgical gloves does not prevent paclitaxel-induced peripheral neuropathy: results from a double-blind phase 2 trial. *BMC Cancer* 2021; 21: 548. 20210513. DOI: 10.1186/s12885-021-08240-6.
157. Chung KH, Park SB, Streckmann F, et al. Mechanisms, Mediators, and Moderators of the Effects of Exercise on Chemotherapy-Induced Peripheral Neuropathy. *Cancers (Basel)* 2022; 14 20220226. DOI: 10.3390/cancers14051224.

-
158. Streckmann F, Elter T, Lehmann HC, et al. Preventive Effect of Neuromuscular Training on Chemotherapy-Induced Neuropathy: A Randomized Clinical Trial. *JAMA Intern Med* 2024; 184: 1046-1053. DOI: 10.1001/jamainternmed.2024.2354.
159. Tanay MAL, Armes J, Moss-Morris R, et al. A systematic review of behavioural and exercise interventions for the prevention and management of chemotherapy-induced peripheral neuropathy symptoms. *J Cancer Surviv* 2023; 17: 254-277. 20210312. DOI: 10.1007/s11764-021-00997-w.
160. Muller J, Weiler M, Schneeweiss A, et al. Preventive effect of sensorimotor exercise and resistance training on chemotherapy-induced peripheral neuropathy: a randomised-controlled trial. *Br J Cancer* 2021; 125: 955-965. 20210705. DOI: 10.1038/s41416-021-01471-1.
161. Tamburin S, Park SB, Schenone A, et al. Rehabilitation, exercise, and related non-pharmacological interventions for chemotherapy-induced peripheral neurotoxicity: Systematic review and evidence-based recommendations. *Crit Rev Oncol Hematol* 2022; 171: 103575. 20211228. DOI: 10.1016/j.critrevonc.2021.103575.
162. Yeh ML, Liao RW, Yeh PH, et al. Acupuncture-related interventions improve chemotherapy-induced peripheral neuropathy: A systematic review and network meta-analysis. *BMC Complement Med Ther* 2024; 24: 310. 20240819. DOI: 10.1186/s12906-024-04603-1.
163. Hwang MS, Lee HY, Choi TY, et al. A systematic review and meta-analysis of the efficacy of acupuncture and electroacupuncture against chemotherapy-induced peripheral neuropathy. *Medicine (Baltimore)* 2020; 99: e19837. DOI: 10.1097/MD.00000000000019837.
164. Jin Y, Wang Y, Zhang J, et al. Efficacy and Safety of Acupuncture against Chemotherapy-Induced Peripheral Neuropathy: A Systematic Review and Meta-Analysis. *Evid Based Complement Alternat Med* 2020; 2020: 8875433. 20201109. DOI: 10.1155/2020/8875433.
165. Chan A, Elsayed A, Ng DQ, et al. A global survey on the utilization of cryotherapy and compression therapy for the prevention of chemotherapy-induced peripheral neuropathy. *Support Care Cancer* 2022; 30: 10001-10007. 20221010. DOI: 10.1007/s00520-022-07383-x.
166. Sundar R, Bandla A, Tan SS, et al. Limb Hypothermia for Preventing Paclitaxel-Induced Peripheral Neuropathy in Breast Cancer Patients: A Pilot Study. *Front Oncol* 2016; 6: 274. 20170110. DOI: 10.3389/fonc.2016.00274.
167. Oneda E, Meriggi F, Zanotti L, et al. Innovative Approach for the Prevention of Chemotherapy-Induced Peripheral Neuropathy in Cancer Patients: A Pilot Study With the Hilotherm Device, the Poliambulanza Hospital Experience. *Integr Cancer Ther* 2020; 19: 1534735420943287. DOI: 10.1177/1534735420943287.
168. Bandla A, Wong R, Santhanakrishnan P, et al. Safety and feasibility of concomitant scalp cooling and limb cryocompression to prevent paclitaxel-induced alopecia and neuropathy. *Support Care Cancer* 2025; 33: 180. 20250212. DOI: 10.1007/s00520-024-08982-6.
169. Bandla A, Tan S, Kumarakulasinghe NB, et al. Safety and tolerability of cryocompression as a method of enhanced limb hypothermia to reduce taxane-induced peripheral neuropathy. *Support Care Cancer* 2020; 28: 3691-3699. 20191206. DOI: 10.1007/s00520-019-05177-2.

-
170. Binder J, Unver E, Clayton J, et al. A Limb Hypothermia Wearable for Chemotherapy-Induced Peripheral Neuropathy: A Mixed-Methods Approach in Medical Product Development. *Front Digit Health* 2020; 2: 573234. 20201215. DOI: 10.3389/fdgth.2020.573234.
171. Wong HCY, Wallen MP, Chan AW, et al. Multinational Association of Supportive Care in Cancer (MASCC) clinical practice guidance for the prevention of breast cancer-related arm lymphoedema (BCRAL): international Delphi consensus-based recommendations. *EClinicalMedicine* 2024; 68: 102441. 20240202. DOI: 10.1016/j.eclinm.2024.102441.
172. Beijers AJM, Bonhof CS, Mols F, et al. Multicenter randomized controlled trial to evaluate the efficacy and tolerability of frozen gloves for the prevention of chemotherapy-induced peripheral neuropathy. *Ann Oncol* 2020; 31: 131-136. DOI: 10.1016/j.annonc.2019.09.006.
173. Coolbrandt A, Tobback H, Govaerts R, et al. A randomized controlled trial of hand/foot-cooling by hilotherapy to prevent oxaliplatin-related peripheral neuropathy in patients with malignancies of the digestive system. *ESMO Open* 2023; 8: 101205. 20230403. DOI: 10.1016/j.esmoop.2023.101205.
174. Sphar BG, Bowe C and Dains JE. The Impact of Peripheral Cooling on Chemotherapy-Induced Peripheral Neuropathy: An Integrative Review. *J Adv Pract Oncol* 2020; 11: 845-857. 20201101. DOI: 10.6004/jadpro.2020.11.8.5.
175. Dunnill CJ, Al-Tameemi W, Collett A, et al. A Clinical and Biological Guide for Understanding Chemotherapy-Induced Alopecia and Its Prevention. *The Oncologist* 2018; 23: 84-96. DOI: 10.1634/theoncologist.2017-0263.
176. Al-Tameemi W, Dunnill C, Hussain O, et al. Use of in vitro human keratinocyte models to study the effect of cooling on chemotherapy drug-induced cytotoxicity. *Toxicol In Vitro* 2014; 28: 1366-1376. 20140801. DOI: 10.1016/j.tiv.2014.07.011.
177. Ibraheem K, Smith A, Collett A, et al. Prevention of chemotherapy drug-mediated human hair follicle damage: combined use of cooling with antioxidant suppresses oxidative stress and prevents matrix keratinocyte cytotoxicity. *Front Pharmacol* 2025; 16: 1558593. 20250708. DOI: 10.3389/fphar.2025.1558593.
178. Flatters SJL, Dougherty PM and Colvin LA. Clinical and preclinical perspectives on Chemotherapy-Induced Peripheral Neuropathy (CIPN): a narrative review. *Br J Anaesth* 2017; 119: 737-749. DOI: 10.1093/bja/aex229.
179. Amartumur S, Nguyen H, Huynh T, et al. Neuropathogenesis-on-chips for neurodegenerative diseases. *Nat Commun* 2024; 15: 2219. 20240312. DOI: 10.1038/s41467-024-46554-8.
180. Staff NP, Grisold A, Grisold W, et al. Chemotherapy-induced peripheral neuropathy: A current review. *Ann Neurol* 2017; 81: 772-781. 20170605. DOI: 10.1002/ana.24951.
181. Grisold W, Cavaletti G and Windebank AJ. Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention. *Neuro Oncol* 2012; 14 Suppl 4: iv45-54. DOI: 10.1093/neuonc/nos203.
182. Gupta P, Makkar TK, Goel L, et al. Role of inflammation and oxidative stress in chemotherapy-induced neurotoxicity. *Immunol Res* 2022; 70: 725-741. 20220720. DOI: 10.1007/s12026-022-09307-7.

-
183. Molinares D, Kurtevski S and Zhu Y. Chemotherapy-Induced Peripheral Neuropathy: Diagnosis, Agents, General Clinical Presentation, and Treatments. *Curr Oncol Rep* 2023; 25: 1227-1235. 20230913. DOI: 10.1007/s11912-023-01449-7.
184. Imai S, Koyanagi M, Azimi Z, et al. Taxanes and platinum derivatives impair Schwann cells via distinct mechanisms. *Sci Rep* 2017; 7: 5947. 20170720. DOI: 10.1038/s41598-017-05784-1.
185. Li T, Mizrahi D, Goldstein D, et al. Chemotherapy and peripheral neuropathy. *Neurol Sci* 2021; 42: 4109-4121. 20210826. DOI: 10.1007/s10072-021-05576-6.
186. Stage TB, Hu S, Sparreboom A, et al. Role for Drug Transporters in Chemotherapy-Induced Peripheral Neuropathy. *Clin Transl Sci* 2021; 14: 460-467. 20201109. DOI: 10.1111/cts.12915.
187. Yang Y, Zhao B, Lan H, et al. Bortezomib-induced peripheral neuropathy: Clinical features, molecular basis, and therapeutic approach. *Crit Rev Oncol Hematol* 2024; 197: 104353. 20240413. DOI: 10.1016/j.critrevonc.2024.104353.
188. Lamberti A, Villalba-Riquelme E, Fernandez-Carvajal A, et al. Decoding chemotherapy-induced peripheral neuropathy: ion channels, disease models, and future directions. *Front Pharmacol* 2026; 17: 1762734. 20260623. DOI: 10.3389/fphar.2026.1762734.
189. Hammond EA, Pitz M, Lambert P, et al. Quantitative sensory profiles of upper extremity chemotherapy induced peripheral neuropathy: Are there differences in sensory profiles for neuropathic versus nociceptive pain? *Can J Pain* 2019; 3: 169-177. 20191003. DOI: 10.1080/24740527.2019.1665992.
190. Bhojwani D, Sabin ND, Pei D, et al. Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia. *J Clin Oncol* 2014; 32: 949-959. 20140218. DOI: 10.1200/JCO.2013.53.0808.
191. Gonzalez-Burguera I, Ricobaraza A, Aretxabala X, et al. Highly efficient generation of glutamatergic/cholinergic NT2-derived postmitotic human neurons by short-term treatment with the nucleoside analogue cytosine beta-D-arabinofuranoside. *Stem Cell Res* 2016; 16: 541-551. 20160303. DOI: 10.1016/j.scr.2016.02.038.
192. Karki K, Adhikari S, Shrestha S, et al. Cytarabine-induced peripheral neuropathy in a young patient with acute myeloid leukemia: a case report. *Ann Med Surg (Lond)* 2024; 86: 3082-3085. 20240312. DOI: 10.1097/MS9.0000000000001937.
193. Theocharopoulos C, Lialios PP, Samarkos M, et al. Antibody-Drug Conjugates: Functional Principles and Applications in Oncology and Beyond. *Vaccines (Basel)* 2021; 9 20210929. DOI: 10.3390/vaccines9101111.
194. Fu Z, Gao C, Wu T, et al. Peripheral neuropathy associated with monomethyl auristatin E-based antibody-drug conjugates. *iScience* 2023; 26: 107778. 20230829. DOI: 10.1016/j.isci.2023.107778.
195. D'Aloia A, Pastori V, Blasa S, et al. A new advanced cellular model of functional cholinergic-like neurons developed by reprogramming the human SH-SY5Y neuroblastoma cell line. *Cell Death Discov* 2024; 10: 24. 20240112. DOI: 10.1038/s41420-023-01790-7.
196. Shipley MM, Mangold CA and Szpara ML. Differentiation of the SH-SY5Y Human Neuroblastoma Cell Line. *J Vis Exp* 2016: 53193. 20160217. DOI: 10.3791/53193.
197. Simoes RF, Ferrao R, Silva MR, et al. Refinement of a differentiation protocol using neuroblastoma SH-SY5Y cells for use in neurotoxicology research. *Food Chem Toxicol* 2021; 149: 111967. 20210106. DOI: 10.1016/j.fct.2021.111967.

-
198. Tushaus J, Kataka ES, Zaucha J, et al. Neuronal Differentiation of LUHMES Cells Induces Substantial Changes of the Proteome. *Proteomics* 2021; 21: e2000174. 20201008. DOI: 10.1002/pmic.202000174.
199. Harischandra DS, Rokad D, Ghaisas S, et al. Enhanced differentiation of human dopaminergic neuronal cell model for preclinical translational research in Parkinson's disease. *Biochim Biophys Acta Mol Basis Dis* 2020; 1866: 165533. 20190820. DOI: 10.1016/j.bbadis.2019.165533.
200. Hollerhage M, Stepath M, Kohl M, et al. Transcriptome and Proteome Analysis in LUHMES Cells Overexpressing Alpha-Synuclein. *Front Neurol* 2022; 13: 787059. 20220411. DOI: 10.3389/fneur.2022.787059.
201. Zhang XM, Yin M and Zhang MH. Cell-based assays for Parkinson's disease using differentiated human LUHMES cells. *Acta Pharmacol Sin* 2014; 35: 945-956. DOI: 10.1038/aps.2014.36.
202. Desbordes SC, Placantonakis DG, Ciro A, et al. High-throughput screening assay for the identification of compounds regulating self-renewal and differentiation in human embryonic stem cells. *Cell Stem Cell* 2008; 2: 602-612. DOI: 10.1016/j.stem.2008.05.010.
203. Hardingham GE, Patani R, Baxter P, et al. Human embryonic stem cell-derived neurons as a tool for studying neuroprotection and neurodegeneration. *Mol Neurobiol* 2010; 42: 97-102. 20100430. DOI: 10.1007/s12035-010-8136-2.
204. Hengstschrager M and Rosner M. Embryoid research calls for reassessment of legal regulations. *Stem Cell Res Ther* 2021; 12: 356. 20210619. DOI: 10.1186/s13287-021-02442-2.
205. Khan M, Yusuf M, Al Robaian M, et al. Isolation and characterization of four novel beta-Sitosterol esters from *Salvadora persica* Linn. *Nat Prod Res* 2018; 32: 1639-1647. 20171102. DOI: 10.1080/14786419.2017.1395426.
206. Shi J, Wu M, Fang S, et al. Saponins enhance the stability and cost-efficiency of human embryonic stem cell culture. *Cell Regen* 2025; 14: 3. 20250121. DOI: 10.1186/s13619-024-00220-y.
207. Jung M, Dourado M, Maksymetz J, et al. Cross-species transcriptomic atlas of dorsal root ganglia reveals species-specific programs for sensory function. *Nat Commun* 2023; 14: 366. 20230123. DOI: 10.1038/s41467-023-36014-0.
208. Lin YT and Chen JC. Dorsal Root Ganglia Isolation and Primary Culture to Study Neurotransmitter Release. *J Vis Exp* 2018 20181006. DOI: 10.3791/57569.
209. Smith PR, Meyer A, Loerch S, et al. Protocol for the isolation and culture of mouse dorsal root ganglion neurons for imaging applications. *STAR Protoc* 2023; 4: 102717. 20231117. DOI: 10.1016/j.xpro.2023.102717.
210. Moy AB, Kamath A, Ternes S, et al. The Challenges to Advancing Induced Pluripotent Stem Cell-Dependent Cell Replacement Therapy. *Med Res Arch* 2023; 11 20231129. DOI: 10.18103/mra.v11i11.4784.
211. Park S, Gwon Y, Khan SA, et al. Engineering considerations of iPSC-based personalized medicine. *Biomater Res* 2023; 27: 67. 20230707. DOI: 10.1186/s40824-023-00382-x.
212. Supakul S, Murakami R, Oyama C, et al. Mutual interaction of neurons and astrocytes derived from iPSCs with APP V717L mutation developed the astrocytic phenotypes of Alzheimer's disease. *Inflammation and Regeneration* 2024; 44: 8. DOI: 10.1186/s41232-023-00310-5.

-
213. Xu Z, Yang J, Xin X, et al. Merits and challenges of iPSC-derived organoids for clinical applications. *Frontiers in Cell and Developmental Biology* 2023; 11. Review. DOI: 10.3389/fcell.2023.1188905.
214. Berry BJ, Akanda N, Smith AS, et al. Morphological and functional characterization of human induced pluripotent stem cell-derived neurons (iCell Neurons) in defined culture systems. *Biotechnol Prog* 2015; 31: 1613-1622. 20150911. DOI: 10.1002/btpr.2160.
215. Schwartzentruber J, Foskolou S, Kilpinen H, et al. Molecular and functional variation in iPSC-derived sensory neurons. *Nat Genet* 2018; 50: 54-61. 20171211. DOI: 10.1038/s41588-017-0005-8.
216. Tukker AM, Wijnolts FMJ, de Groot A, et al. Human iPSC-derived neuronal models for in vitro neurotoxicity assessment. *Neurotoxicology* 2018; 67: 215-225. 20180619. DOI: 10.1016/j.neuro.2018.06.007.
217. Wing C, Komatsu M, Delaney SM, et al. Application of stem cell derived neuronal cells to evaluate neurotoxic chemotherapy. *Stem Cell Res* 2017; 22: 79-88. 20170615. DOI: 10.1016/j.scr.2017.06.006.
218. Xiong C, Chua KC, Stage TB, et al. Human Induced Pluripotent Stem Cell Derived Sensory Neurons are Sensitive to the Neurotoxic Effects of Paclitaxel. *Clin Transl Sci* 2021; 14: 568-581. 20201219. DOI: 10.1111/cts.12912.
219. Coyle DE, Li J and Baccei M. Regional differentiation of retinoic acid-induced human pluripotent embryonic carcinoma stem cell neurons. *PLoS One* 2011; 6: e16174. 20110120. DOI: 10.1371/journal.pone.0016174.
220. Ghiasvand K, Amirfazli M, Moghimi P, et al. The role of neuron-like cell lines and primary neuron cell models in unraveling the complexity of neurodegenerative diseases: a comprehensive review. *Mol Biol Rep* 2024; 51: 1024. 20240928. DOI: 10.1007/s11033-024-09964-x.
221. Popovic J, Klajn A, Paunesku T, et al. Neuroprotective Role of Selected Antioxidant Agents in Preventing Cisplatin-Induced Damage of Human Neurons In Vitro. *Cell Mol Neurobiol* 2019; 39: 619-636. 20190314. DOI: 10.1007/s10571-019-00667-7.
222. Sharow KA, Temkin B and Asson-Batres MA. Retinoic acid stability in stem cell cultures. *Int J Dev Biol* 2012; 56: 273-278. DOI: 10.1387/ijdb.113378ks.