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Can phantom limb pain be reduced/eliminated solely by techniques applied to peripheral nerves?

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ABSTRACT
About 0.5% of the US population (1.7 million) is living with a lost limb and this number is expected to double by 2050. This number is much higher in other parts of the world. Within days to weeks of an extremity amputation, up to 80% of these individuals develop neuropathic pain presenting as phantom limb pain (PLP). The level of PLP increases significantly by one year and remains chronic and severe for about 10% of individuals. PLP has a serious negative impact on individuals’ lives. Current pain treatment therapies, such pharmacological approaches provide limited to no pain relief, some other techniques applied to the central nervous system (CNS) and peripheral nervous system (PNS) reduce or block PLP, but none produces long-term pain suppression. Therefore, new drugs or novel analgesic methods must be developed that prevent PLP from developing, or if it develops, to reduce the level of pain. This paper examines the potential causes of PLP, and present techniques used to prevent the development of PLP, or if it develops, to reduce the level of pain. Finally it presents a novel technique being developed that eliminates/reduces chronic neuropathic pain and which may induce the long-term reduction/elimination of PLP.

1 Background
In the United States, more than 1.7 million people (0.5% of the population) are living with a lost limb, and this number is expected to double by 2050 [1]. Within days to weeks of an extremity amputation, up to 93% of individuals with an amputation experience one or more type of amputation-related pain [2]. Up to 85% develop neuropathic pain presenting as phantom limb pain (PLP) [3-8]. Although PLP may not present for months or years [9], its severity generally increases significantly over the first year following an amputation [4, 10], and has a lifetime duration [11]. For those with an amputation up to 10% suffer severe chronic PLP [4, 10, 12].

PLP has a serious negative impact on an individual’s quality of life, by being physically and mentally debilitating, negatively affects not only an individual’s potential to perform self-care, and their daily living activities essential for personal and economic independence. In addition, it may lead to depression and feelings of hopelessness. Pain is also a serious challenge for the sufferer’s caregiver support system while causing significant general societal and economic challenges. In the U.S. alone, the annual cost of dealing with neuropathic pain is estimated at more than $100 billion [13]. This amount is increased by costs associated with coping with PLP. Thus, PLP treatment remains a significant challenge and it remains essential to improve the quality of life of individuals suffering PLP.

While PLP is known to be associated with a number of cellular, neural circuit, and gene changes, few clinically applied techniques significantly alter these injury-induced changes leading to long-term blockade of the pain triggers or a reversal their
influences [14, 15]. Thus, pain relief is at best temporary. Therefore, it is critical to develop novel pharmacological or other types of treatment that prevent the development of PLP following an amputation, or eliminate PLP once it has developed.

What is PLP?

PLP is a type of neuropathic pain associated with extremity amputations. PLP presents as burning, boring, shooting, “pins and needles”, throbbing, crushing, or an electric shock. Other amputated limb-associated pains are residual limb pain, and phantom limb telescoping pain, where the level of pain increases as the apparent limb becomes shorter [16–18]. PLP must be distinguished from phantom limb sensation. Phantom limb sensations are significantly more benign than PLP, manifesting as the sensation or perception of movement coming from the missing limb or body part.

Risk factors for PLP include upper extremity amputation, bilateral amputations, the presence of pre-amputation pain, residual pain in the remaining limb, and increasing time post amputation [19]. The presence of chronic pain prior to an amputation does not appear to be associated with an increased level of late persistent PLP [8].

2 Causation of PLP

2.1 CNS changes

Cortical reorganization

The experience of neuropathic and PLP differ greatly, with neuropathic pain being associated with the injured nerve, while for patients with PLP the pain is ascribed to a specific portion of the missing appendage. This difference suggests that the development of PLP involves neurological changes associated with both the peripheral portion of the damaged nerves and their CNS connections.

Magnetoencephalography (MEG) and magnetic resonance imaging (MRI) studies on amputees indicate a positive correlation between the development of PLP and the development and extent of cortical reorganization [20]. This observation gave rise to the theory that maladaptive CNS plasticity remodeling underlies PLP [17, 21]. This theory holds that maladaptive plasticity results from the loss of afferent inputs from the amputated limb giving rise to changes in neurons and neural circuits in the brain and spinal cord [15, 19, 21, 22]. This involves afferent brain areas becoming enlarged, or that there is a shift in neuron activation into somatotopically organized deafferented brain areas, with the extent of the shift being positively associated with PLP intensity [23, 24]. According to this hypothesis eliminating neuropathic pain requires the application of techniques to the PNS, while eliminating PLP requires turning off pain triggers in both the PNS and CNS.

Although some fMRI studies support this concept [25, 26], others show no significant relationship between pain and cortical reorganization [27]. Therefore, the strength of the argument for a direct relationship between chronic pain intensity and cortical reorganization after deafferentation is weakening [19]. Considering this emerging controversy, it is not clear whether the cortical changes have a causal relationship to PLP or are merely associated with PLP. Therefore, it is possible that techniques applied only to peripheral nerves could prevent the development of, or fully eliminate, PLP once it has developed, despite the persistence of CNS reorganization [19].

2.2 PNS changes

Mechanical irritation

Following a peripheral nerve transection, the axons normally sprout and regenerate to their targets. However, they may also form a neuroma [28]. While neuroma formation is a benign process, it can induce pain if it ensheathes nerve ends in scar tissue due to excessive fibrous tissue proliferation and perineural cell overgrowth. This scar tissue can trap the ends of axons in an area of frequent contact or high pressure, such as a limb stump [28]. In addition, over time, the scar tissue can contract, placing the axons under constant pressure and causing them to become chronically inflamed, giving rise to chronic pain [29], thereby inducing mechanical activation of the nociceptive axons. Thus, symptomatic neuromas that form in the nerve stumps following an amputation are considered one of the significant triggers underlying the induction and maintenance of chronic PLP. This suggests that preventing the formation of symptomatic neuromas, or eliminating them once they have formed,
may respectively prevent or eliminate mechanical or inflammatory nociceptive neuron activation and causation of PLP.

While neuromas are associated with PLP, PLP can develop within hours of an amputation, which is before a neuroma can form. This indicates that although neuromas are associated with PLP, there are other triggers for PLP, which are discussed later, such as the up-regulation of the synthesis and insertion of voltage-gated sodium channels into nociceptive neuron causing them to exhibit spontaneous ectopic electrical activity that underlies PLP [7].

Inflammation and chronic ectopic spontaneous electrical activity

Numerous experimental studies have demonstrated that pro-inflammatory cytokines released in the region of an injury induce or facilitate neuropathic pain and hyperalgesia. Among the critical cytokines are interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [30, 31]. These cytokines act on both peripheral axons and central axons and neurons [31]. TNF-α induces pain by inducing nociceptive neuron up-regulation of genes for the transcription of voltage-gated sodium ion channels (NaV) [32]. When these channels are inserted into the neuron membrane they cause chronic spontaneous ectopic electrical activity [33, 34].

Pro-inflammatory cytokines also act centrally to induce sensitization of dorsal root ganglion (DRG) neurons [35], and pain-modulating neurons in the rostral ventromedial medulla [36]. Pro-inflammatory cytokines are also released from inflamed skin [37]. Thus, a localized inflammatory response can induce chronic pain [38]. Further, this response can be evoked by these cytokines even in the absence of nerve damage [38]. This suggests that following wound healing, inflammatory cytokines can cause spontaneous ectopic electrical activity of nociceptive neurons and the generation of chronic neuropathic pain, as well as contribute to PLP [38].

3 Reducing / eliminating PLP

3.1 Pharmacological interventions

The standard of care for treating PLP is the administration of anticonvulsants, anti-depressants, and analgesics such as gabapentin and morphine with the goal of suppressing PLP [4]. Gabapentin has variable influences on PLP [39-41], dextromethorphan may be effective [42], but memantine is not effective [43]. Antidepressants, anticonvulsants, opioids, and NMDA receptor antagonists are somewhat effective and induce more reliable analgesia [7, 44, 45]. However, not all subjects may be sensitive to the drugs, the drugs may have only a short-lived influence, or their side effects may preclude their use [46-49]. While new drugs and techniques are being developed and tested, the efficacy evidence for these treatment modalities is inconclusive.

3.2 Modifying CNS neural circuits

When pharmacological interventions are not effective, other approaches may be required to suppress PLP. The maladaptive changes that develop following an amputation are in part related to the loss of GABAergic inhibition, glutamate-mediated long-term potentiation-like changes, and changes in neuronal connectivity, including axonal sprouting. These observations gave rise to the hypothesis that behavioral interventions might suppress PLP. Effective techniques for preventing PLP from developing, or suppressing PLP once it has developed include biofeedback [50], acupuncture [51–53], with some but limited evidence for hypnosis [54–56], biofeedback [57], sensory motor training [58], psychological interventions [59, 60], and coping mechanisms [61].

Additional techniques effective against PLP include mirror box therapy, which involves visuomotor training of motor cortex activity, and results in restoring the body image in the M1 region of the motor cortex by restoring the original missing limb cortical representation, thus tricking the brain into thinking the missing limb is present [62–66], computerized visuo-motor training [63], and transcutaneous electrical nerve stimulation (TENS), which appears to interrupt pain signals before they get to the spinal cord and cortex [67–69]. Electrical stimulation of the spinal cord [70], and brain [71, 72], have the goal of suppressing PLP by altering the activity of nerve trauma-induced altered neural circuits. These studies support the hypothesis that changes in CNS neural circuits and activity underlie the etiology of PLP and that altering or reversing these maladaptive changes by inducing new
CNS inputs can reduce PLP. Although these techniques may reduce PLP, none induces optimal long-term clinical pain relief.

3.3 Neuromas

Virtually all subjects suffering PLP have a symptomatic neuroma. Removing the neuroma eliminates PLP [73]. However, 42% of the patients redevelop a symptomatic neuroma and persistent pain within 37 months [74]. Therefore, while important, neurectomy alone is not the optimal long-term PLP treatment.

The pain relief provided by a neurectomy can be increased by performing a high traction neurectomy, which involves holding the nerve under traction, cutting away the neuroma high on the nerve, and then implanting the nerve stumps into soft target tissues. Effective targets include fat [75], veins [76, 77], and muscle [78].

Relief from PLP can also be achieved by coaptating the proximal nerve stumps, which involves anastomosing two freshly transected proximal nerve stumps [79, 80]. A third approach, for reducing PLP involves, at the time of an amputation, securing the exposed nerve stump in an empty collagen nerve tube. This reduces the level of PLP that develops by 64% compared to that following traction neurectomy [79]. These results suggest that a significant component of the causation of PLP lies in the periphery, and is associated with changes nociceptive neurons changes.

3.4 Anti-inflammatory mediators

Neuropathic pain can be reduced by the application of cytokines with apparently opposite initial actions. Pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), insulin like factor-1 (ILF-1), and insulin like factor-6 (ILF-6), enhance the inflammatory state of nerve stumps. However, this pro-inflammatory action triggers a poorly understood physiological mechanism causing the site to transition from a pro- to an anti-inflammatory state in which the pain is eliminated [81, 82].

By a slower process, chronic neuropathic pain can be eliminated by the application of interleukin-10 (IL-10) and transforming growth factor-β1 (TGF-β1). They act by: (1) blocking the synthesis and release of pro-inflammatory cytokines from injury site macrophages, neutrophils and mast cells that activate those receptors [84], (3) up-regulating the release of endogenous anti-inflammatory cytokines [85-88], and (4) inducing the expression and release of the anti-inflammatory mediator IL-1 receptor agonist 6 (IL-1ra6), thus blocking IL-1β-mediated pain [89-91].

3.5 Blocking spontaneous ectopic electrical activity

As stated, chronic neuropathic pain results from nociceptive neuron spontaneous ectopic electrical activity triggered by injury/cytokine-induced release of TNF-α. TNF-α application leads to pain by inducing the up-regulation of gene transcription for voltage-gated sodium ion channels (NaV). When inserted into the membranes of nociceptive neurons, these channels cause chronic spontaneous ectopic electrical activity. The resulting pain can be blocked the application of IL-10, which down-regulates the synthesis of the NaV channels resulting in silencing the nociceptive neurons [92, 93].

3.6 Physiological source of pro- and anti-inflammatory cytokines and other mediators

All the cytokines and other mediators that induce the changes required to eliminate pain are contained in, and released by, platelets. This knowledge has led to many studies testing the efficacy of applying autologous platelet-rich plasma (PRP) to pain sites for their ability to reduce/eliminate chronic neuropathic pain. Some studies involving the systematic comparative analyses of such studies concluded that PRP is effective in reducing/eliminating pain [94–97]. However, other similar studies concluded that, although the evidence is strong, the statistical evidence is not sufficient to support the hypothesis [98–101].

The variability in analgesic effects of PRP observed in different studies is best explained by the significant differences in the studies in PRP composition and application. Thus, the PRP prepared using different PRP separation devices differs greatly in platelet concentration, the concentration and composition of platelet factors, and the bioactivity of those factors. Thus, some applied PRP may lack the capacity to reduce pain [81]. It appears that reliable and consistent
levels of PRP-induced analgesia will be achieved once PRP preparation and applications protocols are standardized.

3.7 Local and regional anesthesia

The local anesthetic lidocaine, a sodium channel blocker, blocks PLP pain [3]. However, more effective analgesia of PLP is achieved using regional anesthesia of an amputation stump, such as by brachial plexus blockade. This eliminates PLP in 50% of the patients [102]. While individuals who continue to manifest PLP following regional anesthesia show no cortical reorganization, for those who achieve pain reduction, it is mirrored by the rapid elimination of the cortical reorganization in somatosensory cortex [102,103].

Another peripheral oriented technique for reducing PLP is the use of electrical prostheses [25], and sensory stimulation [104]. Finally, pre-amputation lumbar epidural blockade with bupivacaine and morphine reduce the incidence of PLP in the first year after operation [105]. The mechanism by which pre-amputation anesthesia is effective has not been elucidated.

3.8 Novel technique for reducing/eliminating chronic neuropathic pain

PRP within a collagen tube has been used to promote the regeneration of axons across peripheral nerve gaps. After removing existing neuromas, the proximal and distal nerve stumps were secured within a collagen tube and the tube filled with PRP (Fig. 1). This induced neurological recovery in 100% of the subjects, even under conditions where standard nerve repair techniques involving bridging nerve gaps with a sensory nerve graft are not effective in inducing axon regeneration and neurological recovery [106–108].

In the study promoting nerve regeneration using PRP, prior to the nerve repair surgery, 75% of the patients were suffering chronic mild to excruciating chronic neuropathic pain. Within 3 weeks of the nerve repairs, and prior to any neurological recovery, the pain of 94% of the patients was eliminated, while for 6% it had been reduced to tolerable [109]. No pain returned more than 3 years post-surgery [108].

For technical reasons, for one patient, no attempt was made to repair the nerve gap. However, because the patient was suffering excruciating neuropathic pain, the proximal nerve stump was secured within a closed ended collagen tube filled with PRP. The pain was eliminated and did not return after more than 3 years (Fig. 2) [108].

3.9 Can PRP prevent the development of PLP?

The observed efficacy of PRP in reducing chronic neuropathic pain suggests that it might be similarly effective in preventing the development of PLP, or reducing/eliminating PLP once it has developed. This could be tested if, at the time of an amputation, the major exposed nerve stumps were secured in a close-ended collagen tube filled with PRP. The number of treated nerve stumps would depend on whether the amputation is of an upper or lower appendage, and whether high or low on the appendage. Thus, for an upper or lower arm, there would be 3 nerves (radial, median, ulnar), while for the upper and lower leg, there would be 1 and 4 nerves respectively (sciatic vs. tibial, sural, peroneal, saphenous).

3.10 Proposed mechanisms of action

A number of mechanisms can be proposed by which PRP may prevent the development of PLP. (1) Securing nerve stumps within a collagen tube filled with PRP may prevent or reduce neuroma formation, thus
keeping transected axons from becoming trapped within an inflammatory and scar tissue environment. (2) PRP released pro-inflammatory cytokines may promote the development of an enhanced inflammatory state, which, in turn, induces a rapid transition of the nerve stump environment from pro- to an anti-inflammatory. (3) PRP-released factors may block the synthesis and release of pro-inflammatory cytokines from cells residence at the injury site. (4) PRP-released factors may block gene transcription for receptors for pro-inflammatory cytokines. (5) PRP-released anti-inflammatory cytokines and other mediators may induce the release of endogenous anti-inflammatory cytokines and the expression and development of an anti-inflammatory receptor agonist. (6) PRP-released factors may eliminate nociceptive chronic neuron spontaneous ectopic electrical activity, and cortical reorganization. While the pain associated with PLP is evoked by peripheral triggers, the ability to ascribe the PLP to specific sensory modalities or specific missing tissues appears to result from the cortical reorganization caused by the loss of afferent inputs from the missing appendage. This raises the question of whether PLP results from PNS, CNS, or both PNS and CNS triggers. Similarly, there is a dispute as to whether complete and permanent PLP elimination can be achieved by applying techniques to only peripheral nerve stumps or the CNS, or must be applied to both.

This paper examines techniques tested for their ability to reduce or eliminate PLP. Clinical studies show that techniques applied to the CNS, such as mirror box therapy, pharmacological agents, electrical stimulation and hypnosis reduce PLP for a limited time. Thus, techniques applied solely to the CNS can reduce PLP.

Clinical studies have also shown that techniques applied solely to peripheral nerve stumps reduce/eliminate PLP as well as prevent PLP from developing. Thus, removing the neuroma from their proximal nerve stumps eliminates PLP [110,111]. PLP can be prevented from developing by securing nerve stumps inside an empty collagen tube can prevent the development of PLP [79, 110, 112], and implanting nerve stumps into soft tissue such as fat [113], veins [114], and muscle [115], and inside an empty collagen tube filled with PRP (black line delineates the PRP-filled collagen tube) The proximal end of the collagen tube is marked by the arrowhead and the closed distal end with a suture (arrow). The excruciating chronic neuropathic pain was eliminated within 2 months.

**Fig. 2** Photograph of the treatment of the proximal nerve stump of a radial nerve causing severe chronic neuropathic pain secured within the end of a collagen tube filled with PRP (black line delineates the PRP-filled collagen tube) The proximal end of the collagen tube is marked by the arrowhead and the closed distal end with a suture (arrow). The excruciating chronic neuropathic pain was eliminated within 2 months.

### 4 Discussion

Following an amputation, chronic PLP becomes manifest in association with the development of proximal nerve stump neuromas, chronic peripheral nerve inflammation, nociceptive neuron chronic ectopic spontaneous electrical activity, and cortical reorganization. While the pain associated with PLP is evoked by peripheral triggers, the ability to ascribe the PLP to specific sensory modalities or specific missing tissues appears to result from the cortical reorganization caused by the loss of afferent inputs from the missing appendage. This raises the question of whether PLP results from PNS, CNS, or both PNS and CNS triggers. Similarly, there is a dispute as to whether complete and permanent PLP elimination can be achieved by applying techniques to only peripheral nerve stumps or the CNS, or must be applied to both.

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Additional effective techniques for preventing PLP development include the administration of a local anesthesia [116], and regional anesthesia [102]. These results indicate that PLP can be eliminated or prevented from developing by techniques applied to peripheral nerves. However, because anesthesia only blocks PLP in about 50% of patients [102], this indicates that triggers other than nociceptive neuron spontaneous electrical activity are also responsible for PLP. But it is not clear whether these triggers lie in the CNS or PNS.

The observed efficacy of PRP in inducing the long-term elimination of chronic neuropathic pain suggests that following an amputation securing the major exposed nerve stumps in a collagen tube filled with PRP may lead to preventing the development of PLP. It also suggests that securing the nerve stumps of individuals suffering PLP in a collagen tube filled with PRP may eliminate PLP once it has developed. The paper explores mechanisms by which platelet-released cytokines and other mediators can exert these influences. In conclusion, this paper hypothesizes that application of PRP to nerve stumps prior to the development of PLP, or after PLP has developed, may respectively permanently prevent PLP from developing or permanently eliminate PLP.

Disclosure
The author declares that he has no competing interests.

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Damien P. Kuffler, Ph.D., Professor of Institute of Neurobiology, Medical Sciences Campus, University of Puerto Rico. The focus of my research is on how to restore sensory and motor function following nerve trauma. Because nerve trauma is commonly associated with chronic neuropathic pain, my clinical work is also how it might be possible to permanently reduce or eliminate chronic neuropathic pain.