A Biomaterial Cap for Prevention of Symptomatic Neuroma

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Executive Summary

SYMPTOMATIC END NEUROMA is an impairing sequela of nerve amputation and transection injuries. The authors propose a medical device to prevent painful neuroma by "capping" terminal nerve ends.

Neuromas form after peripheral nerve injury followed by improper intrinsic repair. The resultant tumor is a bulb of entangled axon fibers and non-neural tissue growth [1]. While this condition can emerge in the middle of nerve; *i.e.*, neuroma-in-continuity, this proposal will focus on treating neuromas at nerve ends. It is estimated as many as 61% – 74% of end neuromas cause residual limb pain, which is resistant to most pharmacologic analgesic methods [2]. There is no consensus on how to best treat an already formed neuroma; surgical management most usually involves tumor excision followed by transposition into bone or muscle, or traction neurectomy. Bone or muscle transposition is not always anatomically possible and success rates are variable [3]. Neurectomy is favored for its simplicity but is associated with unacceptable rates of neuroma recurrence and pain [4].

The proposed solution is a nerve cap device intended to protect terminal or transected nerve ends *at the time of injury* where repair is unattainable or undesired. The cap is a surgical implant that is a tubular device with one open end and one sealed end (cap). The device secures over the nerve end and separates it from the surrounding soft tissue bed, isolating it from external neurotrophic factors and mechanical stimuli. The cap is a bovine pericardial-derived matrix that remodels during the healing process, enveloping the regenerating axon fibers to prevent tumor formation. With respect to this device, a formal design process was undertaken beginning with background research of the problem and user needs development. Theoretical verification, validation, and risk assessment was completed for the final design, following applicable standards and U.S. FDA regulations. Past research and currently marketed devices support the feasibility and success of the nerve cap approach [2].

The anticipated FDA regulatory pathway is a Premarket Notification. The (Axogen) Axoguard Nerve Cap and Polyganics Nerve Capping Device precede the proposed design as legally marketed Class II medical devices [5], [6]. The authors' solution is comparatively simpler in design and differentiated in material.

User population essentially comprises all persons with a nerve amputation or transection injury. Approximately 185,000 limb amputations are performed annually with post-amputation symptomatic neuroma occuring at a 15% rate [7], [8]. Federal (U.S.) law should restrict this device to sale by or on the order of a physician. The planned sale price is $2500.

I. Description of the Problem to be Solved

Neuroma is defined as a benign proliferation of neural tissue. It is widely accepted that injury of the perineurium permits neuroma to form, as with in an intact perineurium, the axon fibers cannot escape. As axons regenerate into the extra perineurial space where tissue damage is present, compounds released during inflammation can aid neuroma formation. Transected nerve ends are especially susceptible to

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neuroma, with internal nerve structures exposed and lacking a distal target to grow to [1].

Etiology (summary):

1. Nerve lesion, Wallerian degeneration.
2. Formation of axonal sprouts.
3. Growth into unorganized bundles of axon fibers.
4. Bulbous growth of neural and non-neural tissue.

Neuroma is associated with allodyna and hyperalgesia, which can cause significant disability. Neuroma pain is amplified by mechanical stimuli such as from scar tissue, and is resistant to a variety of pharmacological therapies including non-steroidal anti-inflammatory drugs (NSAIDs) and local anesthetic injections [1]. Surgical management is elected when symptoms affect quality of life; for example, precluding the proper fitting and successful use of a prosthetic. Traction neurectomy and nerve transposition into bone or muscle are standard techniques. Transposition is not always anatomically possible and requires the dissection of otherwise healthy tissue. Neuroma can still form and become dislodged from muscle [9], [10]. Success rates vary from 40% – 81% and 33% – 91% intraosseous and intramuscular transposition, respectively [11], [12]. Neurectomy is favored for its simplicity but is associated with neuroma recurrence ranging from 15% – 50% and incidence of reoperation reported at 47% [1], [13]. The American Society for Peripheral Nerve concluded traction neurectomy was not optimal, and the efforts of many groups to seek better treatments for this problem are justified to reduce dependence on postoperative opioid pain management and to improve outcomes for patients [4].

II. Project Objective Statement

The objective is to design a medical device to prevent painful neuroma in patients with a terminal or transected nerve end.

III. Documentation of the Final Design

The authors referred to International Standard ISO 10993-1 and FDA guidance on ISO 10993-1 during the design process and verification literature searches. International Standards ISO 14971 and ISO 22442-1 were considered in developing risk (refer Appendix A Hazard Traceability Matrix).

The nerve cap is a surgical implant indicated to protect a peripheral nerve stump and to separate the nerve from the surrounding environment to inhibit the formation of symptomatic neuroma. This device is intended for use by trained medical professionals. The nerve cap is derived from a bovine source and should not be used for patients with known sensitivity to bovine derived materials. The nerve cap is contraindicated for use in any patient for whom soft tissue implants are contraindicated. This device should not be implanted directly under the skin. This device is not intended for use in vascular applications.

This device is designed for single use only and should not be re-sterilized. The nerve cap is sterile provided its package is dry, unopened, and undamaged; if mishandling has caused possible damage or contamination, or if the device is past its expiration date, the device should be discarded. The nerve cap should be hydrated with sterile saline or sterile Lactated Ringer's solution prior to implantation.

Potential complications of the surgical procedure can include pain, infection, allergic reaction, acute or chronic inflammation, and complications associated with the use of anesthesia. Adverse events may include but are not limited to failure to prevent painful neuroma, irritation, infection, allergy, protrusion and wound dehiscence.

This device should be stored in a dark, dry environment between 10 ºC – 30 ºC. The nerve cap is sterilized with ethylene oxide and supplied in a plastic tray within a sterile pouch. This device should always be handled using aseptic technique. Damage to the device; *e.g.*, crimping, kinking, or puncturing, due to the application of surgical instruments such as forceps, needle holders, or scissors should be avoided.

TABLE I
VERIFICATION MATRIX

User Need	Design Input	Design Output	Verification
Biocompatibility	Device performs with an appropriate host response as a permanent implant device in tissue/bone (refer to FDA guidance on use of ISO 10993-1)	Material: crosslinked bovine pericardium	Literature search and/or *in vitro* testing
Different Sizes	Variety of device diameters to fit 1 mm – 8 mm range of nerve sizes [14], [15]	Device inner diameters of 1.5 mm, 2 mm, 2.5 mm, 3 mm, 4 mm, 5 mm, 6 mm, 7 mm, and 8 mm	Verify with plastic surgeon(s)
Durability	Device remodels; does not degrade. Device is elastic and strong to comply with soft tissue during joint movement	Material: crosslinked bovine pericardium	Literature search and/or bench-top testing
Ease of clinical implementation	Storage life of at least one year. Easily implanted	Device is sterile packaged dry. Secures to nerve via suture	Literature search
Prevent painful neuroma	Measureable reduction in post-operative pain and neuroma	Tubular device with one open end and one closed end to envelop and isolate nerve stump	*In vivo* study with histological testing and pain measurement
Sterilization	Device is sterile; no contaminates or residues	Device is sterilized by ethylene oxide (EtO) and sterile packaged in a Tyvek 1073B 109P pouch	Chemical characterization of final finished form

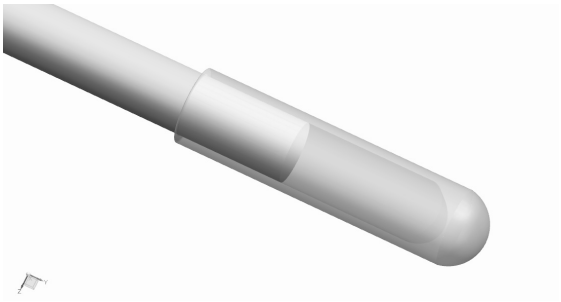

Fig. 1. Nerve cap and nerve end assembly.

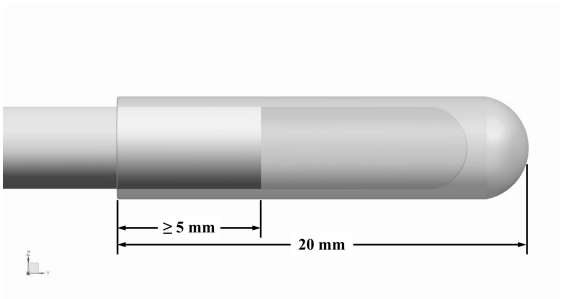

Fig. 2. Side view.

IV. PROTOTYPE OF THE FINAL DESIGN

The final design is a tubular device with one open end and one sealed end. The sealed end is buttressed to permit the surgeon to suture the device deep within soft tissue away from the lesion site. This device is composed of acellular bovine pericardium, and is fully remodeled during the healing process. When hydrated, the nerve cap is flexible, pliable, and non-friable, and can accommodate joint and soft tissue movement. The nerve cap has sufficient strength to be held by forceps as the nerve is pulled through, and to hold appropriately sized non-absorbable suture[1].

This device is available with inner diameters of 1.5 mm – 8 mm to fit the range of nerve diameters measured in the limbs [14], [15]. Thickness is preferably 0.5 mm and the sealed end thickened to 3 mm. The total length is 20 mm, providing for 8 mm – 12 mm of gap length, or "runway", to exhaust

[1]Recommended needle and suture size: #5-0 or #6-0 Polypropylene or monofilament with tapered needle 9 mm – 11 mm.

regenerating axons. Gap length was informed on research which found minimal axon outgrowth past 5 mm in hollow tubes [16].

The basic surgical technique involves selection of the appropriate diameter nerve cap after debridement and measurement of the nerve stump, accounting for post-operative swelling. Once hydrated, the nerve cap is ready for implantation. Hemostasis of the nerve end must be attained before beginning entubulation. The stump should be entubulated by passing suture through the wall of the nerve cap and transversely through the nerve epineurium. The suture is then reversed back through the epineurium and wall of the nerve cap, and the nerve stump is pulled into the cap to a length of 5 mm – 9 mm, ensuring that the nerve is aligned within the cap. The suture is tied securely. A suture may be passed through the distal end of the cap to anchor the device.

TABLE II
COMPARISON WITH MARKETED NERVE CAPS

Device	**This Device**	**Axoguard Nerve Cap**	**Polyganics Nerve Capping Device**
Material	Bovine pericardium	Porcine small intestinal submucosa	Bioabsorbable synthetic polymer
Internal guidance structures	None	Single partition	None
Distal suturing	Thickened distal end	Distal end tab	Distal end tab

Refering to Table II, synthetic polymer elicits a significant foreign body response when implanted, and may allow neuroma recurrence after degradation of the device [17]. The authors hypothesize that the addition of a thin distal end tab to the device may be a potential source of mechanical failure, especially when sutured into. Moreover, internal guidance structures may adversely direct pathophysiologic axonal regeneration instead of suppressing it (no supporting or refuting data exists).

V. PROOF THAT THE DESIGN IS FUNCTIONAL AND WILL SOLVE THE PROBLEM

Research and clinical data on the use of acellular bovine pericardium demonstrates its biocompatibility in permanent implant applications; *e.g.*, bioprosthetic heart valves, dental membrane, hernia repair, staple line reinforcement, and vascular patches. Principally composed of collagen, pericardial tissue is a strong, double-layered membrane which may effectively isolate regenerating axons, and comply with surrounding soft tissue during joint motion or subjugation to pressures [18]. Validation of this design should require an *in vivo* study where histological analysis and pain measurement could inform device effectiveness in reducing symptomatic neuroma pain. A preclinical rodent model of a porcine small intestinal submucosa (pSIS) cap effectively reduced hyperalgesia associated with mechanical stimulation of neuroma compared to neurectomy. At two, eight, and twelve weeks, the pain response in the nerve cap group was statistically lower than the neurectomy group [3].

VI. RESULTS OF A PATENT SEARCH AND/OR SEARCH FOR PRIOR ART, ASSESSMENT, AND PATENTABILITY

Axogen Corporation holds a U.S. patent, “Materials and methods for protecting against neuromas.” Axogen claims a sterile cap with “an internal chamber between the distal end and the proximal end... wherein the biomaterial is selected from the group consisting of: small intestine submucosa, amnion, dermis, collagen and decellularized fascia” [19]. Polyganics BV holds a WIPO patent, “Nerve cap and production thereof” [20]. Neither patent claims pericardium.

An alternative capping method is autologous capping, which has demonstrated promising results, but the harvest of vein or epineurium demands additional operative time, and a potential limitation is degradation of the tissue leading to failure of the cap [2], [21]. Newer surgical techniques to prevent neuroma are targeted muscle reinnervation (TMR) and regenerative peipheral nerve interface (RPNI), both techniques have shown promising results in limited human trials but are complex surgeries that require additional training and operative time [2].

VII. Anticipated Regulatory Pathway

The anticipated regulatory pathway in the U.S. is an FDA Premarket Notification as a Class II medical device within the nerve cuff regulation name.

VIII. Estimated Manufacturing Costs

Manufacturing costs are primarily vested in material, production and sterilization, and packaging. Production cost is not able to be accurately assessed. Production costs may involve resources for de-cellularization, cutting, rolling, crosslinking, welding, and sterilization of bovine tissue.

TABLE III
Estimated Manufacturing Costs Per Unit

Description	Cost ($)
Material	100[1]
Production	1000
Packaging	25[2]
Total	**1125**

[1] Quote for 7x4x0.05 cm minimally processed bovine pericardium
[2] Plastic tray packed in Tyvek 1073B 109P pouch

IX. Potential Market and Impact

The patient population essentially comprises all persons with a nerve amputation or transection injury. Neuroma is a leading cause of pain in amputees, with post-amputation symptomatic neuroma incidence of 15% and 185,000 limb amputations performed annually [8]. Federal law should restrict this device to sale by or on the order of a physician. The planned sale price is $2500 and may be amended as necessary.

Appendix A
Hazard Traceability Matrix

Rating	Definition	Value
Extreme	Requires immediate medical attention	5
Major	Requires explant surgery	4
Moderate	Chronic inflammation or pain	3
Minor	Acute inflammation or pain	2
Least concern	Minor symptoms	1

Rating	Probability (%)	Value
Frequent	$50 \leq x < 100$	5
Probable	$20 \leq x < 50$	4
Occasional	$5 \leq x < 20$	3
Improbable	$0.5 \leq x < 5$	2
Rare	$0 \leq x < 0.5$	1

Rating	Definition
N ACC	Not acceptable. Requires design change
ACC	Acceptable with mitigation(s) to decrease severity and/or probability
ACC	Acceptable

Hazard	Hazardous Situation	Harm	Severity	Probability	Acceptable	Mitigation(s)
Biological	Allergy or other immune response	Allergic reaction, rejection	4	1	ACC	Warning on package and instructions for use
Chemical	Contaminates or residues	Infection, inflammation	3	2	ACC	Administrative control of supply, production, sterilization and packaging
Loss or deterioration of function	Device is damaged or dislodged during or after surgery	Delayed wound healing, failure to prevent symptomatic neuroma	4	1	ACC	Specify proper handling of device in instructions for use
Use error	Nerve pulled too far into device	Acute or chronic pain	3	1	ACC	
User error	Implanted too close to skin	Protrusion, wound dehiscence	4	1	ACC	Warning on package and instructions for use

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