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# Comparative analysis of Antigliotic Guiding Regenerative Gel (AGRG - LDP-916) for peripheral nerve reconstruction: Evidence from prospective randomized controlled studies

S. Rochkind [a,b,c,*], A. Goldlust [c], M. Almog [c]

[a] Tel Aviv University, Tel Aviv, Israel
[b] Microsurgical Center for Peripheral Nerve Reconstruction, Assuta Medical Center, Tel Aviv, Israel
[c] Maxonis Ltd., Israel

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ABSTRACT

*Introduction:* Peripheral nerve injuries (PNIs) with segmental defects remain a challenge. Autologous nerve grafts (ANG) are the gold standard but are limited by donor-site morbidity and variable outcomes in long-gap repairs. Processed allografts and synthetic conduits provide alternatives but lack biological cues for optimal regeneration.
*Research question:* This article presents a structured, author-driven narrative synthesis of published prospective randomized controlled preclinical studies evaluating the Antigliotic Guiding Regenerative Gel (AGRG), also known as LDP-916, a bioactive hydrogel designed to promote axonal growth and remyelination. It examines whether AGRG can achieve outcomes comparable to or exceeding ANG while avoiding donor-site morbidity.
*Methods:* Data were synthesized from two published prospective randomized controlled preclinical studies: (1) acute rat sciatic nerve transection with a 15-mm critical-size defect repaired using AGRG-filled collagen conduits versus ANG and empty tubes; and (2) chronic rabbit sciatic nerve injury with a 25-mm critical-size defect repaired using AGRG-filled NeuraGen® conduits versus ANG and empty NeuraGen®. Additional observations from a rat replication study are summarized qualitatively to provide context on sensory, neuromuscular, and muscle preservation outcomes.
*Results:* Across rat and rabbit models, AGRG supported regeneration comparable to ANG in structural outcomes. It demonstrated favorable electrophysiological and myelin-related outcomes compared with empty conduits, with histological analyses confirming organized remyelination and axonal maturation.
*Conclusion:* AGRG shows reproducible preclinical efficacy across critical-size models and represents a clinically oriented, donor-site-sparing candidate for bridging major peripheral nerve defects. Conclusions are based on published evidence and presented as a structured narrative synthesis rather than definitive practice-changing claims.

## 1. Introduction

Peripheral nerve injuries (PNIs) represent a substantial clinical challenge due to their often-devastating impact on motor and sensory function. (Bailey et al., 2009). Each year, thousands of patients suffer from traumatic nerve lesions arising from sharp trauma, stretch, crush, or iatrogenic injury. Such injuries frequently result in severe functional deficits and irreversible loss of sensory and motor function. When accompanied by neuropathic pain, they can impose significant psychological strain and socioeconomic burden (Rosberg et al., 2005). Emotional distress and depression are common sequelae after PNI (Wojtkiewicz et al., 2015), and approximately 2–5% of patients develop complex regional pain syndrome (Veldman et al., 1993). Despite significant advances in microsurgical technique, the recovery of function following long-gap nerve injury remains suboptimal (Skouras and Wiggins, 2000).

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* Corresponding author. Tel Aviv University, Maxonis Ltd., Israel.
*E-mail address:* rochkind@zahav.net.il (S. Rochkind).

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Current repair strategies – including autologous nerve grafts, processed allografts, and synthetic conduits – each carry distinct limitations that are examined in detail in Section 3.

Tissue-engineered hydrogel systems have emerged as a promising category of biomaterials that may overcome the limitations of existing repair strategies. These hydrogels can provide both mechanical scaffolding and biological modulation through the controlled delivery of neurotrophic, anti-inflammatory, and anti-fibrotic agents (Dodla and Bellamkonda, 2008; Yan et al., 2009; Dubey et al., 1999; Rosner et al., 2003; Rochkind et al., 2024). Within this category, the Antigliotic Guiding Regenerative Gel (AGRG) represents a clinically oriented bioactive hydrogel system specifically developed to support axonal growth and limit glial scar formation. AGRG combines an ECM-mimetic scaffold with antigliotic, anti-inflammatory, and antioxidant components and has been evaluated in published critical-size nerve defect models in rats and rabbits (Rochkind and Nevo, 2014; Rochkind et al., 2021). This review provides a comprehensive examination of hydrogel-based interventions in nerve repair, focusing particularly on AGRG, and situates them in the context of current and emerging treatment paradigms. Importantly, it is explicitly conceived as a narrative, author-driven evidence synthesis of our own preclinical program rather than as a conventional peer-reviewed original research article. This review is structured as a narrative synthesis of published prospective randomized controlled preclinical studies performed by our group, complemented by a contextual overview of contemporary nerve repair strategies. Rather than providing a systematic review of the field or claiming practice-changing conclusions, we focus on a structured comparison of AGRG versus autologous nerve grafts, empty conduits, and alternative bioactive approaches across acute and chronic rat and rabbit critical-size models, with emphasis on quantitative electrophysiological, histomorphometric, functional, and muscle preservation outcomes.

## 2. Biological Barriers to peripheral nerve regeneration

Peripheral nerve regeneration is impeded by a combination of structural and biological obstacles. Key challenges include fibrotic scar formation (Ghosh et al., 2020), axonal misdirection (Angius et al., 2012), inflammatory infiltration (Gaudet and Popovich, 2014), and degradation of the extracellular matrix (ECM) (Gaudet and Popovich, 2014). Moreover, the regeneration process is influenced by the length of the nerve gap, with longer gaps ($\geq$15 mm in rats and >20 mm in humans (Fregnan et al., 2020) showing significantly reduced success rates. This is primarily due to the inability of regenerating axons to maintain directionality, viability, and sufficient trophic support across large acellular zones. Furthermore, scar tissue formation within the endoneurial and epineurial compartments creates a mechanical and biochemical barrier to axonal penetration (Dy et al., 2018). Fibrosis not only impedes axonal progression but also alters the spatial organization of the nerve microenvironment, resulting in poor remyelination and incomplete target reinnervation. These biological challenges underscore the need for advanced repair strategies capable of modulating the injury environment and providing directional cues and trophic support to regenerating axons – objectives that hydrogel-based systems, particularly AGRG, are designed to address.

## 3. Conventional nerve repair strategies: comparative overview

Several established techniques are available for bridging nerve gaps and supporting regeneration, including autologous nerve grafts (ANG), processed allografts, and synthetic nerve conduits. Each method offers distinct advantages and has demonstrated clinical applicability; however, each is also associated with specific considerations and potential limitations that may influence its suitability in different clinical scenarios.

*Autologous Nerve Grafts (ANG)* remain the most widely used technique and offer histocompatibility, native extracellular matrix, and Schwann cells that can support regeneration. However, their use is restricted by donor site morbidity, finite tissue availability, surgical complexity, and inconsistent motor recovery across long gaps (Ijpma et al., 2006; Lans et al., 2023; Ducic et al., 2020; Zou et al., 2024; Chhabra et al., 2022; Xu et al., 2024; Zhou et al., 2024).

*Processed Allografts* eliminate the need for donor nerves but are associated with immune rejection risks, higher cost, and inferior performance in larger gaps. Decellularization techniques reduce antigenicity but also diminish the biological activity inherent to native nerve tissue (Moore et al., 2009a,b; Siemionow and Sonmez, 2007; Bradford et al., 2005; Whitlock et al., 2009; Brooks et al., 2012; Hudson et al., 2013; Cho et al., 2012).

*Synthetic Nerve Conduits* (e.g., collagen or polyglycolic acid tubes) provide a passive guide for axonal growth but lack intrinsic bioactivity. They are generally limited to small-gap repairs (<20 mm in humans), and complications such as fibrosis, neuroma formation, and conduit collapse are reported (Chhabra et al., 2022; Kehoe et al., 2012; Jiang et al., 2020; Gu et al., 2014; Moore et al., 2009a,b).

Given these challenges, the development of biomaterials such as hydrogels that combine physical guidance with biological cues represents a compelling next step in peripheral nerve repair.

## 4. Hydrogel-Based systems for peripheral nerve repair

Hydrogels combine tunable physicochemical properties with biological compatibility, making them promising scaffolds for peripheral nerve regeneration. Their high-water content mimics native extracellular matrix (ECM), supporting diffusion of nutrients, growth factors, and waste. When bioengineered to deliver therapeutic agents or structural cues, hydrogels can modulate neuroinflammation, promote axonal guidance, and enhance myelination (Zhang et al., 2025; Zhao et al., 2023).

Among clinically oriented examples, the Antigliotic Guiding Regenerative Gel (AGRG) – also known as LDP-916 - represents an advanced formulation. This injectable hydrogel integrates hyaluronic acid, synthetic laminin-derived peptides (containing the IKVAV and YIGSR pentapeptide motifs), D,L-α-tocopherol, and glatiramer acetate – components selected for synergistic effects on tissue hydration, oxidative protection, axonal guidance, and modulation of glial responses (Rochkind and Nevo, 2014; Rochkind et al., 2021, 2022).

### 4.1. Comparative context and development of AGRG

Several groups have explored bioactive hydrogels and regenerative matrices as alternatives to autografts and empty conduits (Zhang et al., 2025; Zhao et al., 2023; Lu et al., 2024; Chen et al., 2023; Boecker et al., 2019; Meyer et al., 2016). Common strategies include ECM-mimetic scaffolds enabling controlled release of growth factors, anti-inflammatory agents, or supportive cells such as Schwann or stem cells (Lu et al., Chen et al., 2023; Boecker et al., 2019). Many of these systems have shown promising results in short-gap or early-stage models but remain at preclinical proof-of-concept levels, often without replication or testing in chronic or critical-size defects (Zhang et al., 2025; Zhao et al., 2023).

By contrast, AGRG has undergone a structured, multi-step translational development. The original Guiding Regenerative Gel (GRG) demonstrated that a hyaluronic acid–based, laminin-mimetic matrix improved axonal counts across critical-size rat sciatic nerve gaps compared with empty conduits (Rochkind and Nevo, 2014). Subsequent iterations incorporated glatiramer acetate to reduce gliosis and D, L-α-tocopherol to enhance antioxidant capacity, leading to the current AGRG formulation (Rochkind et al., 2021). In chronic rabbit studies with 25-mm tibial nerve defects, AGRG-treated nerves exhibited axonal organization and myelination comparable to autografts and superior to empty NeuraGen® conduits, with significantly improved conduction parameters and myelin basic protein expression (Rochkind et al., 2021).

In addition to these published data, an internal rat replication experiment has been completed within our preclinical program and qualitatively supports the previously observed patterns of recovery; however, because this work has not yet undergone peer review, detailed results are not reported here and it is not cited as a formal reference. Together, the published studies provide a substantiated preclinical evidence base for AGRG's functional efficacy and translational potential.

## 5. Mechanistic basis of AGRG (LDP-916) function

The biological activity of AGRG is attributed to the coordinated functions of its four constituents. Experimental findings from AGRG-specific studies support several mechanisms, while others remain hypothesized based on related literature:

1. Anti-gliotic and anti-fibrotic modulation (experimentally supported). In AGRG-treated models, reduced glial and fibrotic responses have been observed (Rochkind et al., 2021, 2022). These effects are consistent with the known anti-scarring properties of hyaluronic acid in peripheral nerve settings (Ozgenel, 2003; Ikeda et al., 2003) and the antigliotic activity of glatiramer acetate (Luria et al., 2010, 2013).
2. Axonal guidance (experimentally supported). The laminin-derived peptides containing IKVAV and YIGSR motifs provide biochemical cues for aligned neurite extension, as demonstrated by the improved axonal alignment and increased neurite numbers observed in AGRG in vitro and in vivo studies (Rochkind et al., 2021,2021). These findings are consistent with extensive literature on laminin-mediated neurite outgrowth and guidance (Manthorpe et al., 1983; Hammarback et al., 1985; Yang et al., 2020).
3. Neuroprotection and antioxidant support (supported, partially inferred). D,L-α-tocopherol has been shown to protect neurons against oxidative cell death in vitro (Behl, 2000; Crouzin et al., 2010) and is known to mitigate lipid peroxidation in neural tissue (Seese and Xu, 2026). In AGRG-treated animals, improved axonal and Schwann cell integrity was observed (Rochkind et al., 2021, 2022), which may reflect, in part, the antioxidant contribution of tocopherol within the formulation; however, the direct protective contribution of tocopherol within AGRG has not been independently isolated from the composite gel's overall effect.
4. Immunomodulation (hypothesized, supported by external literature). Glatiramer acetate is known to shift immune polarization toward a trophic profile, downregulating pro-inflammatory cytokines and augmenting expression of neurotrophic factors such as BDNF, NT-3, and NT-4 in CNS injury models (Aharoni et al., 2005, 2024; Kasindi et al., 2022). This mechanism may contribute to the favorable regenerative microenvironment observed in AGRG-treated peripheral nerves; however, this specific immunomodulatory effect has not yet been directly confirmed in peripheral nerve AGRG studies. Systemic glatiramer acetate has been shown to augment peripheral nerve regeneration histologically and functionally in rat sciatic nerve models (Luria et al., 2010, 2013).
5. Hydration and ECM preservation (inferred from composition and outcomes). Hyaluronic acid retains water and stabilizes ECM structure (Ozgenel, 2003; Wang et al., 1998), facilitating cellular infiltration and axonal elongation. The observed tissue integration, reduced fibrosis, and maintained extracellular architecture in AGRG preclinical studies (Rochkind et al., 2021,2022) are consistent with this role, although the isolated contribution of HA within the AGRG formulation has not been separately quantified.

Collectively, these complementary actions are proposed to create a permissive, dynamic microenvironment that supports axonal regeneration and remyelination (Fig. 1).

## 6. Overview and comparative analysis of preclinical AGRG studies in acute and chronic peripheral nerve injury

All components of AGRG have been extensively evaluated in multiple in vitro studies to confirm their individual and combined biological activity. Fig. 2 presents one representative example, illustrating the effect of AGRG on neurite outgrowth in cultured cortical neurons. In these experiments, AGRG significantly enhanced neuronal growth, resulting in a mean neurite length of 449.13 ± 31.66 μm per cell compared with 260.77 ± 40.68 μm per cell for GRG alone ($p < 0.05$, one-way ANOVA followed by Dunnett's test), representing a 78% increase. The total

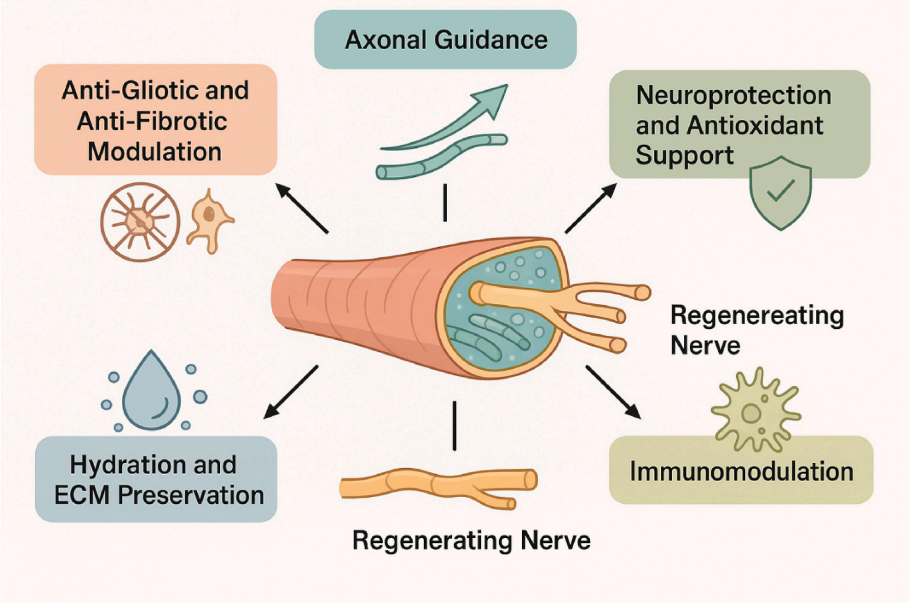


**Fig. 1.** Proposed mechanisms of action of AGRG (LDP-916) in peripheral nerve regeneration. AGRG engages five complementary pathways to support axonal regrowth and remyelination: anti-gliotic and anti-fibrotic modulation (experimentally supported), axonal guidance (experimentally supported), neuroprotection and antioxidant support (supported, partially inferred), immunomodulation (hypothesized, supported by external literature), and hydration with ECM preservation (inferred from composition and outcomes). Together, these mechanisms create a permissive, dynamic microenvironment within the regenerating nerve.

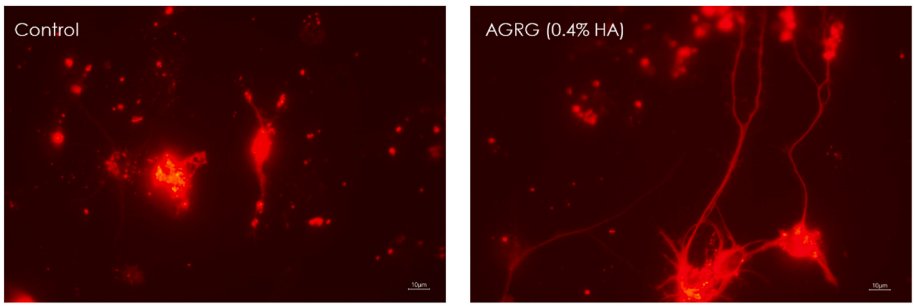


**Fig. 2.** AGRG-driven enhancement of neurite growth.

number of neurites increased approximately fourfold (186 vs. 46) (Rochkind et al., 2021). These findings provide direct evidence of AGRG's capacity to promote axonal extension and neuronal network formation under controlled laboratory conditions.

The regenerative potential of the AGRG has been systematically evaluated in three independent prospective randomized controlled experimental studies using peripheral nerve injury models: a 15-mm critical-size defect in an acute rat model (Fig. 3) and a 25-mm critical-size defect in a chronic rabbit model (Fig. 4), representing the human condition of chronic, large-gap injuries.

Each study was designed to address specific aspects of peripheral nerve reconstruction (see Table 1).

In these studies, AGRG was directly compared with autologous nerve grafts (ANG) and a clinically used FDA-approved conduit (NeuraGen®), enabling comprehensive assessment alongside established gold-standard and commercially available repair strategies. A consolidated overview of the study designs and principal findings is presented in Table 2.

As summarized in Table 2, AGRG matched autologous nerve grafts in key published structural metrics and exceeded empty conduits in several published functional and myelin-related outcomes. In the first study (Rochkind and Nevo, 2014), GRG-treated nerves showed myelinated axon growth across the 15-mm gap ($p < 0.001$ vs. empty tube), with no significant difference from autograft. In the second study (Rochkind et al., 2021), AGRG achieved distal MBP values comparable to healthy nerve and higher than empty NeuraGen, while CMAP normalized

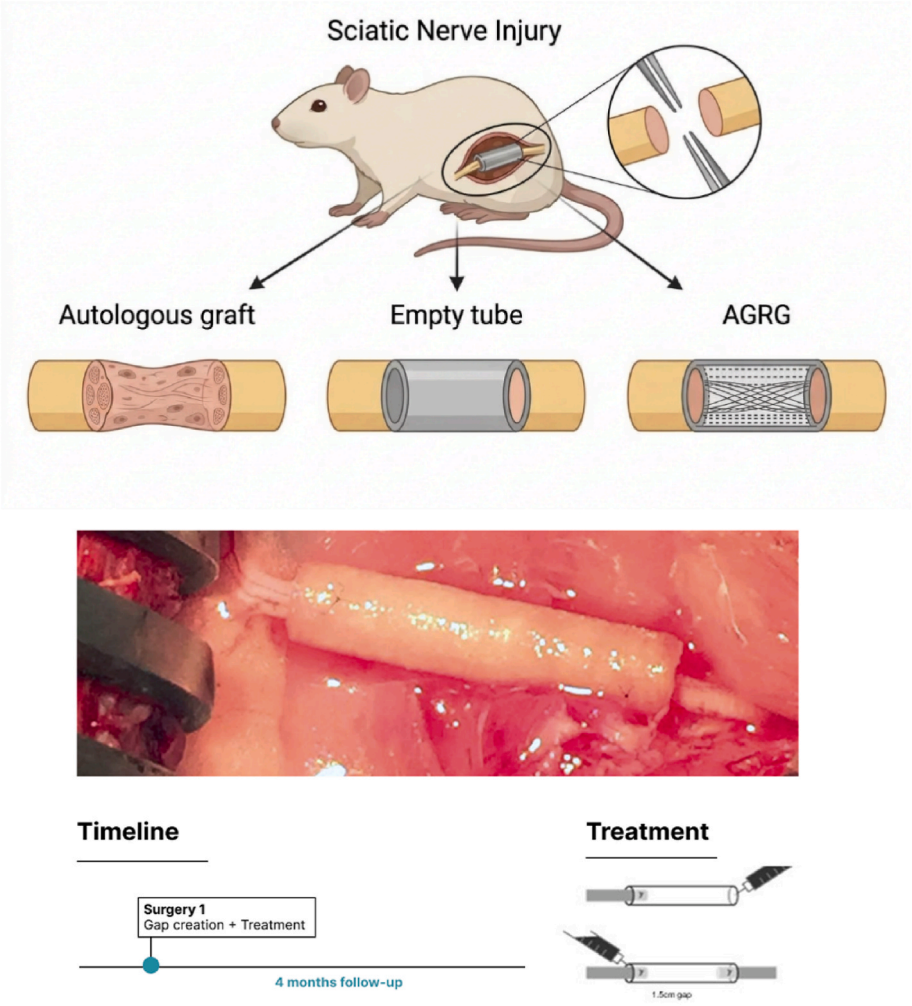


**Fig. 3.** PNI Rat Acute Model: Reconstruction of the Sciatic Nerve using NeuraGen® conduit.

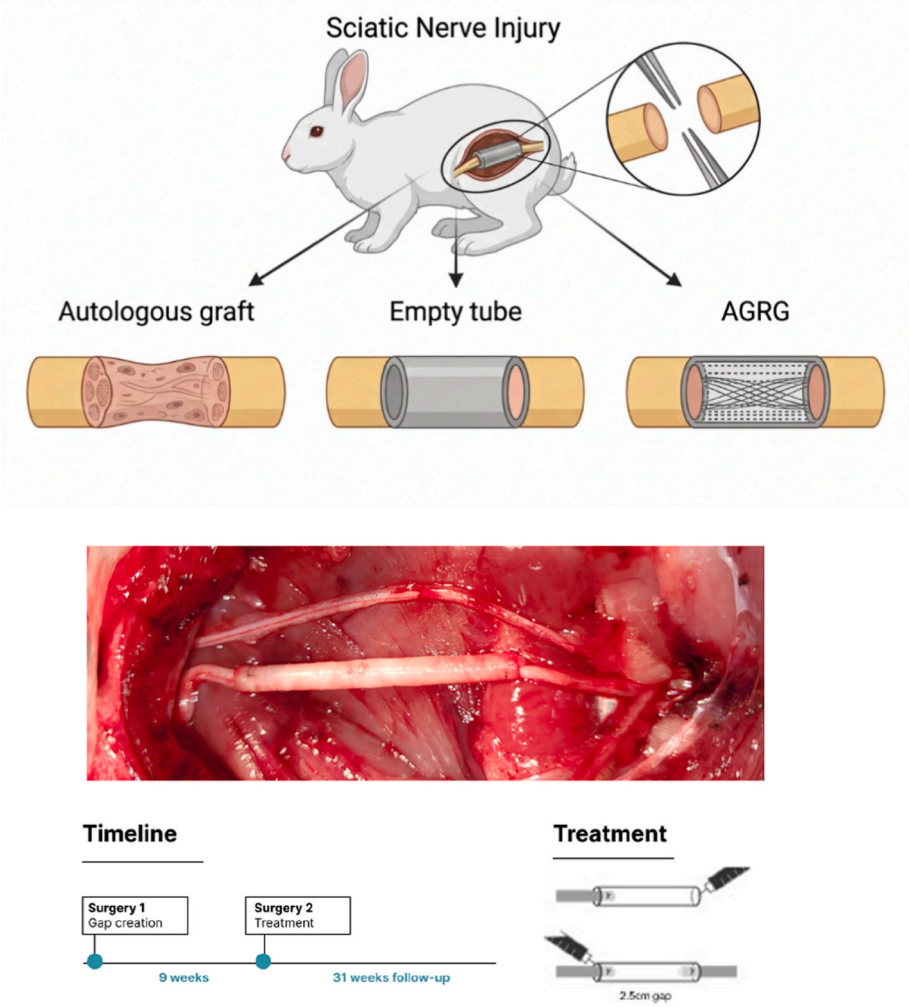


**Fig. 4.** PNI Rabbit Chronic Model: Reconstruction of the Sciatic Nerve using NeuraGen® conduit.

**Table 1**
Advantages and limitations of conventional peripheral nerve repair strategies.

| Strategy | Advantages | Limitations |
|---|---|---|
| **Autologous Nerve Graft** | Native ECM and Schwann cells; histocompatibility | Donor site morbidity; limited availability; complex surgery |
| **Processed Allograft** | No donor site needed; off-the-shelf availability | Costly; immunogenic risk; inferior in long-gap/motor repair |
| **Synthetic Conduit** | Easy to use; no donor site or immune response | No bioactivity; fibrosis risk; limited to short gaps |

amplitude was significantly greater in AGRG than in empty conduits at week 15.

### 6.1. *Integrated interpretation across published studies*

The published studies support AGRG as a reproducible and effective strategy for bridging critical-size nerve defects in both acute and chronic settings. Across the published studies, AGRG matched ANG in structural regeneration metrics and exceeded empty conduits in key electrophysiological and myelin-related outcomes. These advantages are achieved while avoiding donor-site morbidity and maintaining efficacy in both immediate and delayed repairs. The extended preclinical observations summarized in Section 6.1 are drawn from a completed independent rat experiment and are presented here as contextual evidence that complements, but does not replace, the formal published evidence base.

### 6.2. *Extended preclinical observations: sensory, NMJ, and muscle preservation outcomes*

The completed rat replication study (15-mm acute sciatic nerve gap; $n = 39$) generated several outcome categories that were not examined in the published studies, providing novel data on sensory function, neuromuscular reinnervation, and muscle preservation. Key findings are summarized below.

Electrophysiology: At 4 months, AGRG-treated animals achieved a mean CMAP latency of $1.59 \pm 0.09$ m, comparable to intact controls and significantly shorter than both ANG and NeuraGen® alone ($p < 0.01$), indicating normalization of conduction velocity. CMAP amplitude was highest in the ANG group ($0.70 \pm 0.05$ mV) followed by AGRG ($0.30 \pm 0.05$ mV) and NeuraGen® ($0.24 \pm 0.03$ mV). The combination of normalized latency with maintained amplitude in AGRG-treated animals suggests the predominance of well-myelinated axons capable of rapid conduction, consistent with the histological myelination data.

Sensory recovery: Von Frey monofilament testing at 4 months demonstrated markedly superior mechanical sensitivity thresholds in the AGRG group ($7.00 \pm 0.45$ g) compared with the ANG group ($4.67 \pm 0.45$ g; $p < 0.0001$), with intact controls at $26 \pm 0$ g. This finding represents the first demonstration of a sensory outcome advantage for AGRG over ANG within our preclinical program and suggests that the antigliotic and guidance properties of the gel may specifically benefit sensory fiber reinnervation.

Neuromuscular junction (NMJ) reinnervation: Synaptophysin

**Table 2**
Comparative overview of published prospective randomized controlled preclinical studies of AGRG (two published studies).

| Aspect | First Study (Rochkind and Nevo, 2014) | Second Study (Rochkind et al., 2021) |
|---|---|---|
| **Model** | Rat, 15-mm sciatic nerve gap, acute PNI (n = 32) | Rabbit, 25-mm tibial nerve gap, chronic PNI (n = 40) |
| **Groups** | GRG[a] vs. empty tube vs. HA-only tube vs. autograft | AGRG vs. GRG vs. empty NeuraGen® vs. autograft vs. healthy |
| **Electrophysiology** | Not assessed | CMAP normalized amplitude at week 15: AGRG = 6.20 ± 1.01 vs. NeuraGen® = 3.08 ± 0.69 ($p < 0.05$), with autograft and healthy intermediate. By week 23, AGRG had the highest recovery among all groups; overall comparable to autograft and healthy nerve |
| **Axonal Regrowth/ Myelination** | Histological score: GRG enabled myelinated axon growth across 15-mm gap ($p < 0.001$ vs. empty tube; $p < 0.014$ vs. HA-only); no significant difference vs. autograft | MBP mean relative area (distal): AGRG = 0.43 ± 0.05 vs. empty NeuraGen® = 0.17 ± 0.10 ($p < 0.1$); comparable to healthy = 0.50 ± 0.13 and autograft = 0.31 ± 0.09 |
| **Sensory Recovery** | Not assessed | Not assessed |
| **NMJ Reinnervation** | Not assessed | Not assessed |
| **Muscle Preservation** | Not assessed | Not assessed |
| **Interpretation of Conduction vs. Axon Quality** | Not deeply analyzed | Indirectly observed via histology |

* Note on the extended preclinical dataset: In addition to the two published randomized controlled studies, our preclinical program included a completed independent replication experiment in the acute rat sciatic nerve model (15-mm gap; n = 39; groups: intact control, ANG, NeuraGen®, NeuraGen®+AGRG). This study prospectively examined long-term functional and histological endpoints not addressed in the earlier published work, including quantitative sensory recovery (von Frey monofilament), neuromuscular junction (NMJ) reinnervation (synaptophysin immunostaining), target-muscle preservation (atrophy scoring), and detailed electrophysiological profiling (CMAP latency and amplitude at 4 months). Key summary-level outcomes from this study are incorporated in the extended observations presented in Section 6.1; full quantitative reporting of all endpoints will be provided in the dedicated primary study report.

[a] GRG (Guiding Regenerative Gel) has the same composition as AGRG, except it lacks antigliotic component (glatiramer acetate).

immunostaining yielded a mean score of 3.60 ± 0.24 in the AGRG group, statistically equivalent to the ANG group (3.83 ± 0.24; $p > 0.05$) and significantly superior to the empty NeuraGen® group (2.29 ± 0.18; $p < 0.01$). Intact controls scored 5.00 ± 0.00. These data provide the first direct evidence of functional synaptic reconnection in AGRG-treated animals and confirm that AGRG supports NMJ reformation at a level comparable to autologous grafts.

Muscle preservation: Target muscle atrophy score at 4 months was markedly lower in the AGRG group (0.50 ± 0.50) than in the ANG group (3.00 ± 0.00) and the NeuraGen® group (4.00 ± 0.00; $p < 0.01$ vs. both), approaching the intact control (0.00 ± 0.00). This finding suggests that AGRG-mediated reinnervation is sufficiently rapid and complete to prevent the progressive denervation atrophy observed with autograft and conduit repair alone.

* Note on the extended preclinical dataset: taken together, these extended observations indicate that the functional and structural benefits of AGRG over empty conduits and its equivalence to ANG in key outcome domains are robust across experimental replication and extend beyond the endpoints captured in the two published studies.

## 7. Comparative analysis of AGRG, autologous nerve grafts, nerve conduits, and allogeneic nerve grafts in complete peripheral nerve injuries

To better understand the clinical relevance of the findings, we performed a structured comparison of AGRG with established peripheral nerve repair approaches, including autologous nerve grafts, nerve conduits, and processed allogeneic nerve grafts.

### *7.1. Comparison between AGRG and autologous nerve grafting*

A side-by-side evaluation was conducted to compare AGRG and autologous nerve grafts across functional, biological, and surgical

**Table 3**
Comparative features of AGRG and autologous nerve grafting based on published evidence.

| Aspect | Autologous Nerve Graft | AGRG System |
|---|---|---|
| **Regenerative Capacity** | Provides native Schwann cells and ECM; satisfactory motor recovery (≥M4) reported in 50–80% of median/ulnar repairs (Ruijs et al., 2005) | Provides a bioactive scaffold supporting axonal guidance and remyelination in published preclinical studies; structural regeneration is comparable to ANG in the published rat and rabbit models |
| **Immunogenicity** | No immune rejection (autologous tissue) | Composed of biocompatible components with low immunogenic potential (Rochkind et al., 2014,2021, 2022) |
| **Surgical Considerations** | Requires donor nerve harvesting; increases operative time and causes donor-site morbidity in up to 19% of patients (Ducic et al., 2020) | Minimally invasive, injectable delivery; no donor tissue required |
| **Availability** | Limited by the patient's own nerve supply, especially in large-gap injuri or multiple injuries | Not dependent on donor tissue; manufactured as needed |
| **Biological Support** | Schwann cells promoting axonal growth and remyelination (Jessen & Mirsky, 2016; Nocera & Jacob, 2020. Preserved basal lamina (laminin, fibronectin, collagen IV) activates integrin signaling in regenerating axons (Chen et al., 2023) | Four FDA-approved bioactive agents (Rochkind et al., 2014,2021,2022): (1) laminin-derived peptide for axonal guidance; (2) hyaluronic acid – promotes Schwann cell migration (Fregnan et al., 2020; Zhong et al., 2024) (3) antioxidant for cellular protection; (4) glatiramer acetate – augments local BDNF/NT-3 expression (Aharoni et al., 2005). Antigliotic combination yielded 78% greater neurite length and 4× neurite number in vitro (Rochkind et al., 2014,2021) |
| **Limitations** | Donor site morbidity (Ducic et al., 2020) finite tissue, size mismatch | Long-term clinical performance still under investigation; currently preclinical only |
| **Muscle Preservation** | Not directly assessed in the published comparative AGRG evidence base | Not directly assessed in the published comparative AGRG evidence base |
| **Sensory Recovery** | Variable; age and delay significantly predict outcome (Ruijs et al., 2005)) | Not reported in the published AGRG studies included in this review |
| **Electrophysiology** | Standard conduction parameters; may show delays depending on gap and timing (Ruijs et al., 2005) | Published rabbit data show improved CMAP recovery versus empty conduit and outcomes comparable to autograft in key measures |

aspects. Table 3 summarizes the main similarities and differences, focusing on regenerative capacity, immunogenicity, surgical requirements, availability, and biological support. The analysis highlights the specific strengths and limitations of each approach (see Table 4).

### 7.2. Comparison between AGRG and nerve conduits

FDA-approved nerve conduits provide structural guidance but lack intrinsic bioactivity, with clinical utility generally limited to sensory nerve gaps ≤3 cm (Kehoe et al., 2012; 2 Deal et al., 2012). In a meta-analysis of over 1550 nerve repairs, conduits showed significantly lower meaningful sensory recovery (62.2%) compared with both autograft (81.6%) and allograft (87.1%) in short-gap repairs ($p < 0.05$) (Lans et al., 2023).

### 7.3. Comparison between AGRG and processed nerve allografts

Processed nerve allografts (PNA) provide ECM scaffolding with reduced immunogenicity and achieve meaningful recovery in 82–87% of sensory, mixed, and motor repairs in gaps up to 50–70 mm (Brooks et al., 2012; Safa et al., 2020). However, their efficacy in critical motor nerve repairs and long-gap defects (>50 mm) declines, and concerns regarding cost, residual immunogenicity, and disease transmission persist (Moore et al., 2009; Siemionow and Sonmez, 2007).

### 7.4. Positioning of AGRG relative to other bioactive strategies

Beyond conventional approaches, several bioactive strategies for nerve repair are under investigation (see Table 5). Table 6 positions AGRG within this broader landscape (see Table 7).

Unlike single-agent growth-factor hydrogels, AGRG integrates multiple biological activities (antigliotic, antioxidant, guidance, immunomodulatory) within a single injectable formulation (Rochkind et al., 2014,2021,2022). Unlike cell-based approaches, AGRG does not require cell harvesting or expansion, eliminating associated regulatory and logistical barriers (Burks et al., 2021). And unlike decellularized matrices, which serve primarily as passive ECM scaffolds (Lovati et al., 2018), AGRG actively modulates the regenerative microenvironment. However, direct head-to-head comparisons between AGRG and these emerging bioactive strategies have not yet been conducted, and such studies would further clarify AGRG's relative advantages.

**In conclusion**, AGRG technology represents a promising advancement in nerve repair biomaterials, enabling robust structural and functional regeneration across critical-size nerve defects with outcomes comparable to, and in some cases exceeding, those of autologous nerve grafts. Its bioactive, injectable design addresses key limitations of current grafting techniques, positioning it as a compelling next-generation option for clinical peripheral nerve repair. Overall, the AGRG (LDP-916) system combines targeted bioactivity, minimal invasiveness, and strong translational potential, offering clear advantages over traditional methods. Further clinical validation will be essential to confirm these benefits and support its adoption into standard surgical practice.

**Table 4**
Comparative features of AGRG and nerve conduits.

| Aspect | Nerve Conduits | AGRG System |
|---|---|---|
| **Regenerative Capacity** | Structural guidance only; lacks biological cues ( Kehoe et al., 2012; Deal et al., 2012) | Provides both structural support with active biological stimulation (antigliotic, neurotrophic, antioxidant) ( Rochkind et al., 2014,2021, 2022) |
| **Gap Bridging** | Effective in short gaps (≤3 cm); limited in longer defects (Kehoe et al., 2012; Deal et al., 2012); meaningful recovery 62.2% in short-gap sensory repairs (Lans et al., 2023) | Supports regeneration across 15-mm (rat) and 25-mm (rabbit) critical-size gaps with outcomes comparable to ANG ( Rochkind et al., 2014,2021) |
| **Immunogenicity** | Low (synthetic materials) | Similarly low; biocompatible components (Rochkind et al., 2014,2021,2022) |
| **Electrophysiology** | NeuraGen® alone: CMAP amplitude 0.24 ± 0.03 at 4 months; delayed latency (published AGRG studies) | NeuraGen®+AGRG: CMAP amplitude 0.30 ± 0.05; latency normalized to intact controls (1.59 ± 0.09 ms) (published AGRG studies) |
| **Myelination** | MBP intensity: 1.25 ± 0.25 (distal) (published AGRG studies); MBP relative area: 0.17 ± 0.10 | MBP intensity: 2.67 ± 0.37 (distal) (published AGRG studies); MBP relative area: 0.43 ± 0.05; both significantly superior to empty conduits |
| **Material Risks** | Risk of fibrosis, neuroma, or collapse depending on material (Kehoe et al., 2012) | Includes antigliotic elements (glatiramer acetate) intended to reduce scar formation ( Rochkind et al., 2014,2021, 2022; Luria et al., 2010, 2013) |
| **Customization** | Available in different diameters and lengths | Injectable, conformal, can be used as intraluminal filler within existing FDA-approved conduit platforms |

**Table 5**
Comparative features of AGRG and processed nerve allografts.

| Aspect | Allograft Nerve Graft | AGRG System |
|---|---|---|
| **Regenerative Capacity** | Preserves ECM architecture; meaningful recovery 82% across all nerve types in gaps up to 70 mm (Safa et al., 2020); inferior to autograft in long motor repairs (Moore et al., 2009) | Enhanced axonal regeneration and remyelination through bioactive scaffold; comparable to autograft in preclinical critical-size defects (Rochkind et al., 2014,2021) |
| **Immunogenicity** | Reduced via decellularization; residual immune risk remains (Moore et al., 2009; Siemionow and Sonmez, 2007) | Minimal immunogenicity; synthetic and biocompatible composition (Rochkind et al., 2014,2021,2022) |
| **Disease Transmission** | Very low risk, but not entirely eliminated (Moore et al., 2009) | No risk of disease transmission |
| **Availability** | Off-the-shelf; cadaveric supply chain mm (Brooks et al., 2012) | Fully synthetic; manufactured as needed with no donor dependency |
| **Cost** | Processing and cold-chain storage contribute to higher costs (Safa and Buncke, 2016) | Potential for lower overall costs due to inexpensive materials and simplified production |
| **Surgical Complexity** | No harvesting, but sizing and matching remain important ( Brooks et al., 2012) | Injectable system eliminates sizing issues; adapts to lesion morphology |
| **Biological Activity** | Passive ECM scaffold only; lacks bioactive components ( Moore et al., 2009; Siemionow and Sonmez, 2007) | Active biological modulation: antigliotic, anti-inflammatory, antioxidant, and guidance properties ( Rochkind et al., 2014,2021, 2022) |

## Informed consent statement

Not applicable.

## Author contributions

Conceptualization: S.R., M.A., A.G.; methodology: S.R., M.A., A.G.; formal analysis: S.R.; investigation: S.R., M.A.; writing-original draft preparation: S.R.; writing-review and editing: S.R.; supervision: S.R.

**Table 6**
AGRG in the context of emerging bioactive peripheral nerve repair strategies.

| Strategy | Mechanism | Preclinical Outcomes | Translational Status | Key Limitations |
|---|---|---|---|---|
| **Growth-factor-loaded hydrogels** (e.g., FGF-1, BDNF, GDNF) | Sustained local release of neurotrophins to promote axonal growth and Schwann cell activity | FGF-1/collagen-filled conduits achieved regeneration comparable to autograft in 10-mm rat gaps Midha et al., 2003; GDNF-gel and BDNF-chitosan conduits improved CMAP, myelination, and motor recovery in rat models ( Cai et al., 2024; Li et al. (2024) | Preclinical; no clinical approval for neurotrophic-loaded systems | Single-factor delivery; rapid degradation; dose optimization unresolved; limited replication across models |
| **Cell-based therapies** (Schwann cells, stem cells) | Provide living cellular support for axonal guidance, myelination, and trophic factor secretion | SC-seeded conduits improved regeneration in 7-mm rat gaps (Hadlock et al., 2000); VEGF-producing SC conduits enhanced nerve repair (Wu et al., 2021; SC-seeded systems comparable to autograft in short gaps (Burks et al., 2021) | Preclinical to early clinical; complex regulatory pathway | Cell harvesting, expansion, and quality control; immunogenicity of allogeneic cells; high cost and surgical complexity |
| **Decellularized nerve matrices** | Preserve native ECM architecture; may support guided regeneration | Effective in rat 15-mm gaps; functional and morphological regeneration demonstrated ( Lovati et al., 2018); 5–7 cm sheep peroneal nerve repair achieved, though slower than autograft ( Contreras et al., 2023) | Clinically available (Avance®) as processed allograft | Lack of cellularity delays regeneration vs. autograft; variable decellularization quality; limited bioactivity |
| **Tissue-engineered living grafts** (e.g., stretch-grown axon grafts) | Living axon fascicles provide pathway for axon-facilitated regeneration | 5-cm pig sciatic nerve repair with dense axon regeneration and electrophysiological recovery comparable to autograft. (Smith et al., 2022) | Late preclinical | Requires specialized bioreactor; logistical complexity; not yet replicated across labs |
| AGRG | Multifunctional injectable hydrogel combining antigliotic, antioxidant, neurotrophic, and ECM-mimetic properties | Structural regeneration comparable to ANG in 15-mm rat and 25-mm rabbit critical-size gaps; superior sensory recovery and muscle preservation vs. ANG (Rochkind et al.,2014, 2021,2022), published AGRG studies) | Preclinical with replicated RCT evidence | No human clinical data yet; long-term durability unknown |

**Table 7**
AGRG comparative advantage summary based on published evidence.

| Comparison | Advantages of AGRG |
|---|---|
| vs. Autologous Grafts | Avoids donor site morbidity (Rochkind et al., 2014,2021) |
| vs. Empty Conduits | Provides active biological support; significantly higher myelination (MBP $p < 0.05$) and NMJ reformation ($p < 0.01$); effective in critical-size gaps (Rochkind et al., 2014,2021) |
| vs. Allografts | No immune rejection or disease transmission risk; active bioactivity vs. passive ECM scaffold; lower projected cost ( Moore et al., 2009; Siemionow and Sonmez, 2007) |
| vs. Growth-factor hydrogels | Multimodal mechanism (not single-factor); replicated across species and injury models (Rochkind et al., 2014, 2021,2022) |
| vs. Cell-based therapies | No cell harvesting, expansion, or immunosuppression; simpler regulatory pathway; injectable delivery (Burks et al., 2021) |
| vs. Decellularized matrices | Active biological modulation vs. passive scaffold; no cadaveric supply dependency (Lovati et al., 2018) |

## Institutional review board statement

These studies including Protocol Study Number: MD-1-1072-4316 were conducted in the facility of MD Biosciences Innovalora Ltd., a preclinical Contract Research Organization.

## Ethical approval

National Animal Care and Use Committee (NACUC): This study was performed following an application form review by the National Council of Animal Experimentation after receiving their approval that the study complies with the rules and regulations set forth (Md-IL-2301-113).

The number of animals used was the minimum that is consistent with scientific integrity and regulatory acceptability, and consideration was given to the welfare of individual animals in terms of the number and extent of procedures that were carried out on each animal.

## Conflict of interest

S. Rochkind serves as the founder and scientific advisor of Maxonis Ltd., which has licensed the AGRG technology under an alternative trade name and may derive benefit from its clinical and commercial advancement. A. Goldlust and M. Almog are employees of Maxonis Ltd. The company provided general research support but had no influence on the editorial decision to submit this manuscript. All authors declare that they have no additional conflicts of interest related to this work. It should be noted that only the most recent study was conducted with the support of Maxonis Ltd., whereas the two preceding studies included in this review were carried out within the authors' academic and hospital affiliations.

The preclinical investigations were performed independently by MD Biosciences Innovalora Ltd. (Rehovot, Israel), a contract research organization (CRO), and by Patho-Logica (Ness Ziona, Israel), a pathology laboratory.

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Prof. Rochkind and the late Prof. Nevo are inventors of the Antigliotic Guiding Regenerative Gel (AGRG) evaluated in this work.

We dedicate this work to the memory of Prof. Zvi Nevo and Prof. Abraham Shachar, whose pioneering contributions to neural tissue engineering continue to inspire our research.

All authors have read and agreed to the published version of the manuscript.

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