Sensory nerve autografting is the standard of care for injuries resulting in a nerve gap. Recent work demonstrates inferior regeneration with sensory grafts compared to motor nerve grafts. Improved regeneration with motor grafting may be a result of the nerve’s cellular content, or architecture. To define the role of nerve architecture, our study evaluates regeneration through acellular motor and sensory nerve grafts. Methods: Twenty-four Lewis rats underwent bilateral tibial nerve injuries with 5mm motor or sensory nerve cervical cable grafts. Grafts were harvested and acellularized with 7 weeks of cold preservation in University of Wisconsin solution, leaving only the lamina tubes with the Schwann cells (SC) basal lamina tubes. Animals were sacrificed, and fresh motor or sensory nerves were harvested. Grafts were harvested after 4 weeks and histomorphometric analysis of the regenerating nerves was conducted for comparison. Results: Histomorphometric analysis distal to the repair revealed more robust nerve regeneration in both acellular and motor cellular grafts. In contrast, sensory grafts showed poorer regeneration with significantly decreased percent nerve, nerve fiber density, and percent nerve when compared to the motor graft groups (P < 0.05). Conclusions: Nerve architecture plays an important role in nerve regeneration through grafts of different nerve types. Determining the benefit seen with motor graft material was lost implying that nerve architecture (SC basal lamina tube size) may play an important role in nerve regeneration. Schwann cell basal lamina tubes are smaller in sensory nerves than in motor nerves (Fig 2A). Cold preservation in University of Wisconsin solution (UW) for 7 weeks completely decellularizes nerve grafts, leaving only intact the basal lamina tube architecture and laminin in the extracellular membrane. Thus, this study evaluates the impact of nerve architecture (size of Schwann cell basal lamina tubes) by studying nerve regeneration across acellular motor and sensory grafts.

Methods and Materials

Experimental Design: Twenty-four rats were randomized to each of 2 fresh graft recipient groups and 6 animals each were randomized to 2 acellular graft recipient groups. An additional 18 animals served as sensory graft donors. In all experimental animals, a 5 mm tibial nerve gap was created and immediately reconstructed with a nerve cable graft of equivalent length. Experimental groups were defined as an injury to the quadriceps and sensory nerve grafts were derived from the femoral saphenous branch.

Six animals per group were sacrificed at 4 weeks, and the nerve tissue was harvested for histomorphometric analysis. An additional 6 animals in the fresh nerve graft groups were used for weekly walking track analysis and at a 6 week endpoint, bilateral gastrocnemii were harvested for wet weight ratios as a measure of functional recovery. Table I: Experimental Design

Table 1: Experimental Design

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<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Outcome Measure(s)</th>
<th>Endpoint</th>
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<tbody>
<tr>
<td>I</td>
<td>Fresh Sensory Isograft</td>
<td>Histomorphometry</td>
<td>4 weeks</td>
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<tr>
<td>II</td>
<td>Fresh Motor Isograft</td>
<td>Histomorphometry, Weekly walking track, wet muscle mass ratio</td>
<td>6 weeks</td>
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<tr>
<td>III</td>
<td>Cold Sensory Isograft</td>
<td>Histomorphometry, Weekly walking track, wet muscle mass ratio</td>
<td>6 weeks</td>
</tr>
<tr>
<td>IV</td>
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Figure 1. Sensory and motor cable graft repair of the tibial nerve

Femoral cutaneous Motor Nerve Saphenous Nerve Sensory Figure 2. Nerve Histology

A. Normal Neurologly
B. Repair of Motor Nerve Gaps with Sensory Nerve Inhibits Regeneration in the Rat

Histology: Qualitative analysis of nerve sections distal to the cable graft site showed robust regeneration in motor graft groups compared to sensory graft groups (Fig 2B). Electron micrographs of the acellularized groups showed robust regeneration in the motor group, while in the sensory group, multiple empty SC basal lamina tubes suggest a possible size barrier to reinnervation. Nerve Histomorphometry: Analysis of the distal tibial nerve tissue harvested from each group revealed significant differences in multiple Histomorphometric parameters (Fig 4). The total number of fibers, nerve density, and percent nerve all showed significantly greater regeneration in the motor graft groups (p < 0.05).

Walking track analysis: Weekly analysis of the print length factor as an indicator of tibial functional recovery demonstrated a trend toward improved recovery with motor compared to sensory grafting.

Conclusions: This study demonstrates that motor nerve grafting has a clear functional advantage over sensory grafts, and that this can be attributed to motor nerve architecture. Regardless of cellularity, more fibers cross a motor nerve graft than a sensory graft. Motor nerve grafts have larger diameter endoneurial tubes which allow for more nerve fibers to cross a nerve defect. While the reason for improved axonal regeneration in motor compared with sensory grafts is likely multifactorial, this study suggests that motor nerve architecture, regardless of neurotranscopic or biochemical factors, has an independent beneficial effect on nerve grafting. Sensory nerves have a higher fiber count, indicating that more Schwann cell basal lamina tubes are available, and there is evidence that supports that regenerating axons prefer to grow along SC basal lamina tubes. However, the size of Schwann cell basal lamina tubes appears to be a crucial factor when nerve fibers are selecting an endoneurial tube. The use of musculoscutaneous flaps requiring sacrifice of the transferred motor nerve, illustrates that these accompanying motor nerves are functionally expendable. Multiple expendable motor nerves exist and can be harvested and used with limited morbidity to bridge short defects in nerves with critical function. This finding has implications for our immediate clinical management of nerve gaps, and can guide the future development of tissue engineered conduits constructed with SC basal lamina tubes at an “optimal” diameter for motor nerve regeneration.

References