Interposing an auto/isograft between a long ANA fails to rescue nerve regeneration across long nerve gaps

Ying Yan, Daniel A. Hunter, Lauren M. Schellhardt, Xueping Ee, Alison Snyder-Warwick, Amy M. Moore, Susan E. Mackinnon, and Matthew D. Wood

Division of Plastic and Reconstructive Surgery, Washington University School of Medicine, St. Louis, MO 63110, USA

Washington University in St. Louis School of Medicine

Peripheral Nerve Surgical Research Laboratory

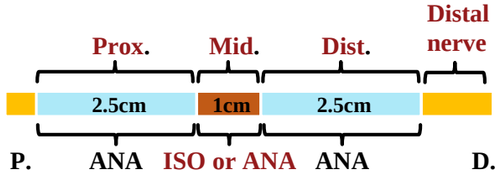
Introduction and Objectives

- Nerve grafting is often necessary to reconstruct nerve gaps.
- While auto/isografts facilitate adequate recovery, the use of graft alternatives is desirable for long gaps.
- The most promising graft alternative, acellular nerve allografts (ANAs), still fail to consistently facilitate axonal regeneration across long gaps (>3cm).
- We generated ANA hybrids by interposing a short isograft ("stepping stone") between shorter ANAs.
- We evaluated potential benefits this hybrid has on axonal regeneration.

Methods

- Rat sciatic nerve was transected and repaired with 6cm nerve grafts.
- Nerve grafts consisted of either ANA hybrids or ANA controls (Figure 1).
- 4 week endpoint: cellular phenotypes and neurotrophic factor expression were assessed at spatial locations.
- 20 week endpoint: nerve regeneration outcome metrics were performed.

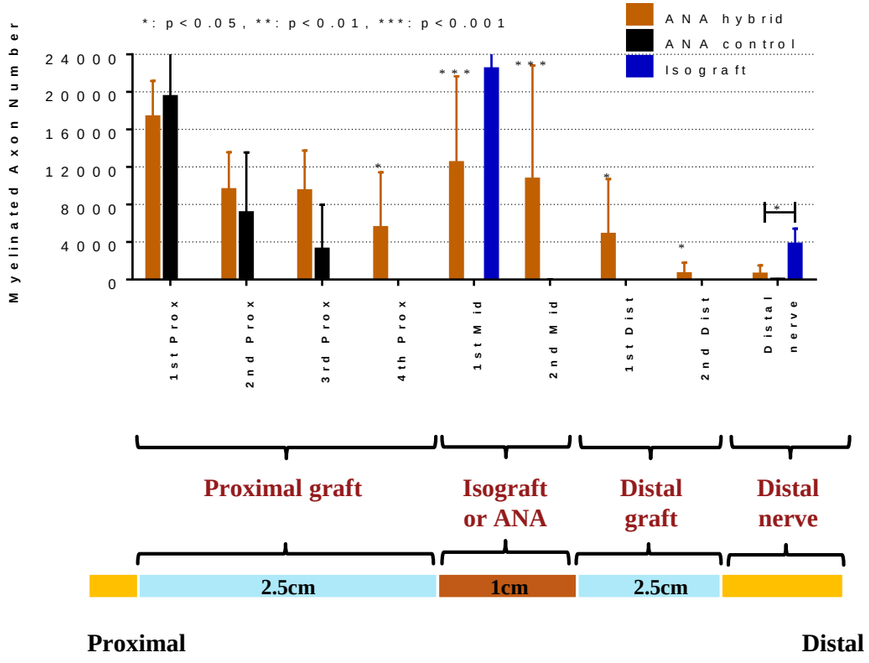
Surgery model



Results

- Myelinated axon numbers were quantified at spatial locations throughout the grafts (regions 1-4 or 1-2) and the distal nerve.
- The ANA hybrid received modest benefits from the isograft interposed between the ANAs, where locations within the proximal and distal graft contained more axons.
- The isograft region promoted an increase in axonal regeneration.
- The ANA hybrid failed to rescue regeneration across the long gap (Myelinated axon number: 578 ANA hybrid vs 3777 Isograft).

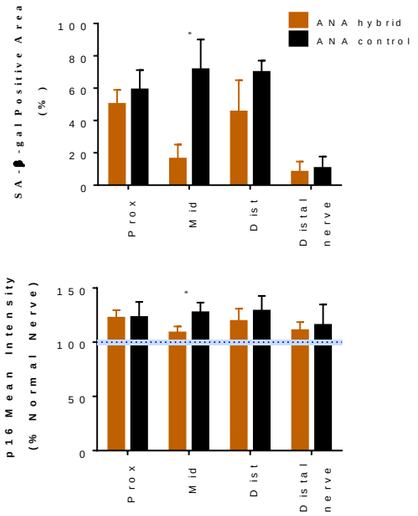
Histomorphometric analysis of axonal regeneration



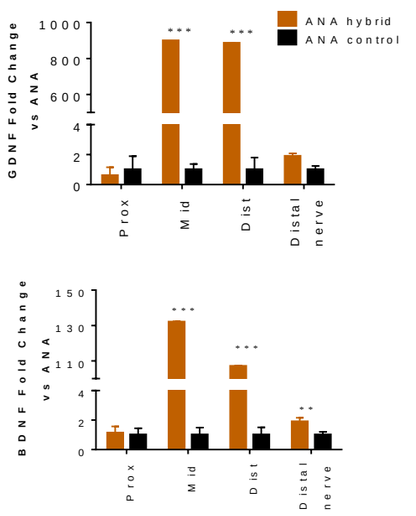
Results

- Senescence onset in neural support cells reduces nerve regeneration.
- The isograft region has reduced cellular senescence.
- The interposition of an isograft within ANA hybrids had minimal ability to rescue the onset of cellular senescence within the ANA regions despite improved neurotrophic factor expression.

Cellular senescence markers



Neurotrophic factor expression



Conclusions

- The interposition of an isograft to generate a hybrid graft:
  - increased axonal regeneration at the isograft spatial location.
  - conferred modest benefits to the paired ANAs.
- While axonal regeneration across the long hybrid graft was achieved, the outcome was considerably worse compared to an auto/isograft.
- The onset of cellular senescence within ANAs cannot be offset by the beneficial factors provided by isografts.