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

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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

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<th>Prox.</th>
<th>Mid.</th>
<th>Dist.</th>
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<td>2.5cm</td>
<td>1cm</td>
<td>2.5cm</td>
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<td>P. ANA ISO or ANA ANA D.</td>
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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).

Cellular senescence markers

- 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.

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.