Acellularized Peripheral Nerve Allograft Repopulated with Isogenic Schwann Cells: A Non-Immunogenic Construct that Supports Axonal Growth Across Short Nerve Gaps

Jason Rovak BS, Steve Haase MD, Leslie Boxer BA, Robert Dennis PhD, Keith Bishop PhD, William Kuzon Jr. MD PhD, Paul Cederna MD

University of Michigan Department of Surgery, Ann Arbor, MI

Introduction: Reconstructive options for peripheral nerve gaps are currently limited. Autogenous nerve grafts continue to be the gold standard, but are limited by the availability of graft material. All other methods of nerve grafting are either experimental or have limited clinical applicability. We propose developing a tissue engineered peripheral nerve allograft that is non-immunogenic but can support axonal regeneration across peripheral nerve gaps.

Methods: The local and systemic immune response to cellular allografts, acellular allografts, and cellular isografts was measured by placing a graft in a subcutaneous tunnel on the dorsal surface of a mouse. Allografts were transplanted across a MHC barrier from Balb C to C57BL6 mice, while isografts were transplanted between C57BL6 mice. The nerve was harvested at either 7 or 21 days, embedded, stained, and the local inflammatory cell infiltrate was quantified. Systemic response was measured at 14 days by quantifying systemic INF- , IL-2, IL-4, and IL-5. To evaluate the acellular graft's ability to support axonal regeneration, and whether reintroducing isogenic Schwann cells (SCs) to the acellular graft improves axonal regeneration, two centimeter gaps in rat peroneal nerve were repaired using an autograft, acellular isograft, or acellular isograft repopulated with isogenic SCs. Force generating capabilities of the rat EDL muscle were evaluated with standard techniques.

Results: At 7 and 21 days post transplant, cellular allografts demonstrated a substantial inflammatory cell infiltrate as compared with acellular allografts and isografts. (Table 1)

Table 1: Inflammatory Cell Counts/High Power Field

	7 days post transplant		21 days post transplant	
	Autograft	Allograft	Autograft	Allograft
Cellular	55±20	131±30	67±20	84±30
Acellular	21±10*	43±20*	20±10*	15±10*

*denotes statistical significance related to cellular counterparts ($p < 0.05$)

A dramatic systemic response was seen 14 days post transplant with cellular allografts as compared with acellular allografts and isografts. (Table 2)

Table 2: Systemic Immunologic Response to Transplanted

	IFN-gamma	IL-5	IL-4	IL-2
Cellular Allograft	1268	43	268	1432
Cellular Isograft	26	18	25	46
Acell. Allograft	6	12	21	86

Acellular grafts repopulated with isogenic SCs provided reinnervation comparable to autografts and significantly better than acellular grafts (Table 3).

Table 3: Functional Recovery Following Peripheral Nerve Reconstruction

	Force generation (mN)
Autograft	1886 ± 363
Acellular graft	597 ± 600*
Schwann cell repopulated acellular graft	1167 ± 832

* denotes statistical significance related to autograft ($p<0.05$)

Conclusion: Chemically acellularized peripheral nerve allografts are non-immunogenic and when repopulated with isogenic SCs can support axonal regeneration across short peripheral nerve gaps.