

AMERICAN SOCIETY FOR PERIPHERAL NERVE

Newsletter



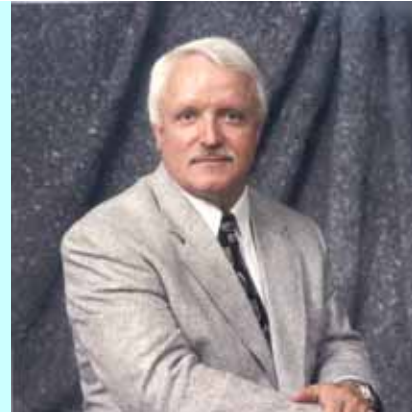
Spring 2008

President's Message

Dear Colleagues,

There are a number of issues facing ASPAN as we go forward as a specialty medical society and in preparation for the annual meeting on Maui in Hawaii. The most pressing issue for our long term sustainability is member retention and growth through recruitment of new members. The facts are these; we now have 203 active members. Last year we gained 10 new members, but dropped 21, mostly for lack of dues payment. This year we have streamlined the dues assessment process and asked the by-laws committee to consider dropping members after two years of dues non-payment. The by-laws committee will also be proposing that the requirement to have written a nerve related paper for acceptance to membership be dropped. I believe as an organization we need to strongly recruit new members to ASPAN from the ranks of our colleagues, residents, or basic scientists to increase new members by 10% a year. New members not only help sustain the organization financially, but also bring new ideas and innovative research and clinical expertise, which is the essence of any specialty medical society. All of us should make a concerted effort this year to recruit one new member. The meeting being in Hawaii should help peak interest.

We are working closely with Richard D'Amico, M.D., and Linda Phillips, M.D., the ASPS/PSEF presidents, to obtain a permanent seat on the ASPS/PSEF board for ASPAN, as well as money dedicated to nerve research each year. Hopefully, I will be able to make this a reality by Hawaii.



The meeting program for Hawaii is coming together nicely under the direction of Dr. Nash Naam. The over all theme for the meeting will be pain management with panels, courses, and guest lectures by experts from a variety of medical fields. None of us particularly like patients whose pain won't go away, but we often need to use the patient's pain response to make the diagnosis, or determine the effectiveness of our procedures. We hope to gain a better understanding of pain pathophysiology, stimulate discussion, and perhaps learn new ways to approach pain management. I look forward to seeing you in Maui January 9-11, 2009. Registration materials will be available online and in the mail in early fall.

On behalf of the ASPAN, I extend our heartfelt congratulations to Dr. Susan Mackinnon for her wonderful achievement. It is an honor to our society and its members that she has been elected to the institute of medicine.

Robert C. Russell, M.D.
President

From The Editor's Desk

This issue of the ASPN Newsletter comes in between the last annual meeting in Los Angeles and the next meeting in Maui, Hawaii. Our last annual meeting in Los Angeles was very successful. We had the largest number of attendees. The next meeting's theme will be "Pain" as suggested by our president, Bob Russell, M.D. Pain, which is an important issue related to peripheral nerve surgery, has often been ignored. In the last few years there has been a significant amount of research into the pathophysiology, mechanism, and management of pain. I am glad that our president thought of making "Pain" as the main theme for our next meeting.

We have a new ASPN Newsletter committee that consists of Randy Bindra, A. Lee Dellon, Mike Neumeister, and Robert Russell as Ex-Officio. I am very excited to be working

with the new committee. We are still greatly interested in the feedback from the membership. Please take a moment or two to go through the newsletter and drop us a note regarding your ideas, criticism, suggestions, and recommendations. We definitely appreciate your input.

Again, our sincere thanks are extended to Alice Romano for her excellent work and dedication to the newsletter and to our society as a whole. Good job Alice!

I join Dr. Russell in congratulating our former president Susan Mackinnon, MD for here election to the institute of medicine.

Congrats, Susan!! We are proud of you!!!

Nash Naam, MD

drnaam@handdocs.com

Call for New Members - Bring us your brightest and best!

The ASPN is keen to welcome new members to the Society. We are revising the bylaws to allow easier access to Active Membership for young surgeons and investigators and have waived the requirement for a published paper in nerve regeneration. Researchers beginning an independent career will be allowed a smooth transition from the new Candidate Membership category to Active Membership. We wish to attract bright, young members to the Society and will be pleased to facilitate this in any way possible.

We would also like to extend our membership internationally. A focus of the 2010 meeting in Florida will be our European colleagues and the major contributions they have made in nerve regeneration. With this in mind, please consider inviting your European friends to join you at the meeting in either Hawaii or Florida and to consider becoming members in the future.

Yours sincerely,

Howard M. Clarke, M.D., Ph.D., F.R.C.S.(C), F.A.C.S., F.A.A.P.,

howard.clarke@utoronto.ca

2008 Annual Meeting Recap

A final postscript to this year's meeting. First of all, thanks to Greg Evans and to all of the council members and the program committee members for helping to make this such a wonderful meeting. Beverly Hills was the best attended meeting thus far for ASPN with 135 attendees.

Our first speaker on Friday, Professor Andrew Schwartz, from the University of Pittsburgh, gave an outstanding presentation of his work on cortical control of movement. Our second speaker, Professor Jeffrey Lichtman, a return speaker to ASPN, began Saturday's session with a fascinating update on his work with neural development using fluorescent transgenic mice. His presentation was very well received. Our final speaker, Dr. John Beck, a clinician with a unique perspective on postural neuromuscular function, provided our group with insight into an often neglected aspect of the peripheral nervous system. Our panels from the combined sessions drew on the strengths of their multidisciplinary faculties. Nerve transfers vs. tendon transfers provided new insight into the growing applications of nerve transfers for common nerve palsies. The panel on the treatment of the mangled hand gave a broad coverage of a very complex topic in hand surgery.

Finally, the heart of our meeting, the scientific papers, were truly outstanding. The 2008 program included 53 abstract presentations. Congratulations to all of the presenters for the very high quality of their work.

Thanks again to all who contributed and thanks for the opportunity of being the meeting program chairperson. See you next year in Maui.

Jonathan Winograd, MD



Best Resident/Fellow Clinical Paper:

Morphological Analysis of the Carpal Tunnel and Median Nerve Following Endoscopic and Open Carpal Tunnel Release

Institution where the work was prepared:
University of Manitoba, Winnipeg, MB, Canada
Avinash Islur, MD, FRCSC

Best Resident/Fellow Basic Research Paper:

Repairing Peripheral Nerve Injuries Using Skin-Derived Precursor Cells

Institution where the work was prepared:
University of Calgary, Hotchkiss Brain Institute, Calgary, AB, Canada
Sarah K. Walsh, BSc

Congratulations!!

Annual Meeting Photos



*President
Greg Evans*



*Program Chair
Jonathan Winograd*



*Invited Speaker
Jeff Lichtman, MD*



Dan Nagle and wife Jan



Best Resident/Fellow Paper Award



Attendees at the reception



*President Evans congratulating
Dr. Winograd, the program chair*



*Passing of the Presidential
Medallion to incoming
President Bob Russell*




*Presidential plaque presented
to Greg Evans*

The ASPN Council and 2008 Annual Meeting Program Committee would like to thank the following companies for their support and participation:

- *A.M. Surgical, Inc.*
- *American Society of Plastic Surgeons*
- *Aptis*
- *Ascension Orthopedics*
- *ASSI - Accurate Surgical*
- *Axogen*
- *BioMet Trauma*
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- *Cook Medical*
- *DePuy Hand Innovations*
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- *Elsevier/Saunders/Mosby*
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- *Synthes*
- *TeleEMG, LLC*
- *The Guatemala Healing Hands Foundation*
- *Tornier*
- *TriMed, Inc.*
- *TrueVision Systems Inc*

An additional thank you to the *ASSI-Accurate Surgical* for their generous sponsorship of the ASPN Welcome Reception, and to *Ethicon, Inc.* for their support of the ASPN 2008 Invited Speakers.



**ASPN CALL FOR ABSTRACTS
2009 ANNUAL MEETING
JANUARY 9-11, 2009
WAILEA, MAUI, HAWAII**

SUBMISSION DEADLINE: JUNE 1, 2008

VISIT WWW.PERIPHERALNERVE.ORG TO
SUBMIT YOUR ABSTRACT TODAY!! DEADLINE
FOR SUBMISSION IS JUNE 1, 2008. PLEASE
SPREAD THE WORD AND ENCOURAGE YOUR
COLLEAGUES TO SUBMIT AN ABSTRACT.



AMERICAN ASSOCIATION FOR HAND SURGERY
AMERICAN SOCIETY FOR PERIPHERAL NERVES
AMERICAN SOCIETY FOR PERIPHERIC MICROSURGERY
NOW ACCEPTING ABSTRACTS

Bylaws Committee News for 2008.

Melanie Urbancek, Paul S. Cederna, William M. Kuzon, Jr, and Warren Schubert, who served as Bylaws Committee members for 2007, will serve again in 2008. Melanie Urbancek continues as the Chairperson. Ex-Officio 2007 member, Gregory R. D. Evans is replaced by Robert C. Russell, Ex-Officio for 2008.

The 2007 Committee proposed three changes to the Bylaws. Briefly the changes included easing membership requirements for Senior and Candidate Members and adding the new Grants Generating and Distribution (GGD) Committee. Senior membership is now available to anyone who has retired from active practice and Candidate membership may continue while a candidate is in training such as a research or clinical fellowship. The Society Treasurer will serve as the Chairperson of the GGD Committee. The GGD Committee consists of six (6) active member named to the Committee by the President. The GGD Committee is charged with developing policy, exploring funding sources, and establishing a mechanism for requesting and evaluating grant applications. The 2007 Bylaws Committee submitted these proposed changes to the Society's Secretary, they were reviewed by the Executive Council, and approved by the membership at the Business Meeting held during the January 2008 Scientific Meeting in Century City, CA.

The 2008 Bylaws Committee is already responding to Council's charges for additional changes. The Council indicated a need to streamline the process to move candidate members to active status. The Council feels the requirements of active

membership; specifically the need to have at least one paper published is too restrictive. The Council agreed publication should not be mandatory for active membership. The council also charged the Bylaws Committee with updating the active requirement to include candidates that have an interest in peripheral nerve. You will soon receive additional correspondence regarding these proposed changes.

We request your input regarding Bylaws changes. The Bylaws are a dynamic for keeping the Society in touch with current practices in contemporary associations. We especially seek your input regarding the bylaws which pertain to the Grants Generating and Distribution Committee. For the current set, we felt it best to give the GGD Committee freedom to decide how to distribute the work among the committee members rather than the Bylaws Committee establishing and imposing a highly structured hierarchy of responsibilities. Please send your comments and suggestions to: Melanie Urbancek, Chairperson, melurban@umich.edu

Very truly yours,

Melanie Urbancek

Research Grants

The ASPN's commitment to education is demonstrated by the initiation of a new seed grant for young investigators designed to support either basic or clinic research related to peripheral nerve disorders. We were pleased to recognize Terence M. Myckatyn, M.D., from Washington University School of Medicine as the first recipient at the annual meeting. Dr Myckatyn received \$5,000 for his project entitled "The Effects of Controlled Release GDNF on Motor Nerve Regeneration." His submission was one of 8 quality grant applications received – all of which underwent rigorous peer review. This grant, sponsored by Integra Life Sciences, is intended to support early-phase innovative research that will potentially lead to larger, extramural funding. Full details for the seed grant (i.e., preamble, eligibility criteria, application information) are available on the ASPN website. Applications for next year's funding cycle are due November 1, 2008.

Robert J. Spinner, MD
Research Grant Committee

American Society for Peripheral Nerve 2008 Committee Roster

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Melanie Urbanchek, PhD
Paul S. Cederna, M.D.
William Kuzon, Jr, M.D.
Warren Schubert, M.D.
Robert C. Russell, MD, Ex-Officio

Coding & Reimbursement

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Terence M. Myckatyn, MD
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Robert C. Russell, MD, Ex-Officio

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Gedge D. Rosson, MD
Robert C. Russell, MD
Robert Spinner, M.D.
Thomas H.H. Tung, M.D.
Jonathan M. Winograd, MD

Welcome New Members

Active

Antonia Barm pitsioti MD
Gregory Borschel MD
Ida Fox MD
David Halpern MD
Kirsten Westberg MD, FRCSC
Eric Williams MD

Candidate

Nitin Engineer MD
Michael Obeng MD
Milan Sen MD

Associate

Karen Zaderej BSCHE, MD

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Past President- Rajiv Midha, MD
Council Member at Large- Loree K. Kalliainen, MD
Council Member at Large- Gedge D. Rosson, MD
Council Member at Large- Jonathan M. Winograd, MD

Honoring Dr. Kline

A Festschrift was held in David G. Kline's honor at the LSU Medical Center and in the Neuroscience Center of Excellence on October 19th and 20th, 2007. Fifty papers were given by physicians and scientists working in the field of peripheral nerve. In attendance were workers from the U.S., Canada, Great Britain, Belgium, Netherlands, Germany, Italy, Brazil, and India.

Many of these 80 or so individuals were former Nerve Fellows, Faculty, or Residents.

It is hoped that the proceedings will be published during the coming year.

The occasion was also marked by the printing and release of the second edition of Kline and Hudson's Nerve Injuries: Operative Results for Major Nerve Injuries, Entrapments, and Tumors edited by Daniel H. Kim, Rajiv Midha, Judith A. Murovic, and Robert J. Spinner.

Congratulations!!

Susan Mackinnon elected to Institute of Medicine

By Beth Miller



Oct. 9, 2007 -- **Susan Mackinnon, M.D.**, has been elected to the Institute of Medicine of the National Academy of Sciences, one of the highest honors medical scientists in the United States can receive. Mackinnon was honored for her professional achievement in the health sciences.

Mackinnon is the Sydney M. Jr. and Robert H. Shoenberg Professor and chief of the Division of Plastic and Reconstructive Surgery at Washington University School of Medicine in St. Louis.

The Institute of Medicine serves as a national resource for independent analysis and recommendations on issues related to medicine, biomedical sciences and health. It was established in 1970 as part of the National Academy of Sciences, which advises the federal government on science and technology issues. Members are selected based on their professional achievement and commitment to service.

Mackinnon, a surgeon at Barnes-Jewish and St. Louis Children's hospitals, is considered an international authority on nerve regeneration, nerve transfer and on the use of limited immunosuppression in transplant patients. She established her international reputation as a surgeon in 1988 by completing the first donor nerve transplant, a procedure that can restore function to severely injured limbs that previously were considered irreparable.

She has been named among the Best Doctors in America by Best Doctors Inc. and among America's Top Doctors by Castle Connolly Medical Ltd. She was the first recipient of the outstanding clinician award given by the School of Medicine's Humanity Program. She also received the Medal Award in Surgery from the Royal College of Physicians and Surgeons of Canada in 1988.

She is president of the American Association of Plastic Surgeons for the 2007-08 term and was president of the American Association of Hand Surgery in 2005.

Mackinnon earned her medical degree from Queens University in Kingston, Ontario, Canada, in 1975. She did a surgical residency at Queen's University in 1978 and a residency in plastic surgery at the University in Toronto in 1980. She did a neurosurgery research fellowship at the University of Toronto in 1981 and a fellowship in hand surgery at Raymond Curtis Hand Center at Union Memorial Hospital in Baltimore in 1982.

Mackinnon is among 65 members whose elections to the Institute of Medicine were announced by the National Academy of Sciences Oct. 8. As a member, Mackinnon makes a commitment to devote a significant amount of volunteer time on committees engaged in a broad range of health-policy issues.

What's New in Peripheral Nerve Surgery and Research

Neurotization improves contractile forces of tissue-engineered skeletal muscle

Dhawan V, Lytle IF, Dow DE, Huang YC, Brown DL.

Tissue Eng. 2007 Nov; 13(11):2813-21

Section of Plastic and Reconstructive Surgery, University of Michigan, Ann Arbor, Michigan 48109, USA.

Engineered functional skeletal muscle would be beneficial in reconstructive surgery. Our previous work successfully generated 3-dimensional vascularized skeletal muscle in vivo. Because neural signals direct muscle maturation, we hypothesized that neurotization of these constructs would increase their contractile force. Additionally, should neuromuscular junctions (NMJs) develop, indirect stimulation (via the nerve) would be possible, allowing for directed control. Rat myoblasts were cultured, suspended in fibrin gel, and implanted within silicone chambers around the femoral vessels and transected femoral nerve of

syngeneic rats for 4 weeks. Neurotized constructs generated contractile forces 5 times as high as the non-neurotized controls. Indirect stimulation via the nerve elicited contractions of neurotized constructs. Curare administration ceased contraction in these constructs, providing physiologic evidence of NMJ formation. Histology demonstrated intact muscle fibers, and immunostaining positively identified NMJs. These results indicate that neurotization of engineered skeletal muscle significantly increases force generation and causes NMJs to develop, allowing indirect muscle stimulation

In Vivo Electrophysiologic Properties of Poly 3,4-ethylenedioxythiophene (PEDOT) in a Biosynthetic Nerve Interface

Brent M. Egeland M.D.¹

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Sarah M. Richardson-Burns Ph.D.^{2,3}

David C. Martin, Ph.D.^{2,3,5}

Daryl R. Kipke, Ph.D.^{3,4}

William M. Kuzon Jr., M.D., Ph.D.¹

Paul S. Cederna, M.D.¹

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5.) Macromolecular Science and Engineering Center, University of Michigan, Ann Arbor, MI 48109, USA

Abstract:

Trauma and disease related upper extremity amputation causes substantial disability due to functional and tactile deficits which limit the ability to perform basic activities of daily living. Prosthetic-based restoration of mechanical and sensory function following amputation is critically important. To date, the development of a

biointegrated, durable, high fidelity, permanent prosthesis with bidirectional neural motor and sensory function, combined with refined robotics to effect or trigger these responses remains elusive. Existing capacitive and myoelectrical peripheral interface devices have poor durability and fidelity for detecting small specialized physiologic action-potentials. We wish to develop a novel interface addressing these previous limitations using the biocompatible electroconductive polymer PEDOT (poly(3,4-ethylenedioxythiophene)) on acellular muscle (ACM) scaffolds capable of biointegration. Here we show that an efferent action potential in the peripheral nerve can be electrically detected and delivered to downstream target organs and electronic circuitry using a biosynthetic PEDOT-ACM scaffold with electrophysiologic characteristics similar to intact nerve. This is the first study describing the in-vivo use of PEDOT polymerized on biologic scaffolds for implantation. Furthermore, PEDOT conductivity and electrical compatibility had not previously been tested in vivo. Given the peripheral nervous system electrical compatibility, we feel that these composite constructs may be crucial for long term peripheral nervous system. We are evaluating the long term integration and long-term compatibility of these constructs with the regenerating peripheral nerve. Furthermore, given our previous observations that acellularized tissues can repopulate in vivo, we are evaluating whether these constructs may provide a permanent neurotization target allowing successful synaptogenesis with coordinated action potentials coupled with electronic circuitry.

Introduction

Spinal cord injury, neuromuscular disease and amputation affect millions of people in the United States alone resulting in significant disability or loss of independence [1, 2]. Advanced robotically controlled prosthetics may have the capacity for significant restoration of this function but are often limited by the interface components [3-5]. Converting biologic neural signals to signals capable of controlling modern advanced prosthetics or native tissue for these individuals remains a major focus of neuroscience research [5-9]. A recent Functional Electrical Stimulation Society meeting identified one of the areas of greatest potential for restoring function after neurological damage was the development of hybrid neural interfaces combining synthetic and biologically derived elements [10].

Saltatory conduction in myelinated axons is distinctly different from pure electron currents utilized in conventional electronic devices [11]. Detecting these unique, discrete, low current biologic signals requires an interface which addresses the unique characteristics of living neural tissue [9, 10, 12-17]. Current neural implants are placed in the central or peripheral nervous system and utilize either invasive, penetrating probes, perineural cuffs, or sieve electrodes to detect action potentials [5, 8, 14, 18-21]. These devices utilize capacitive, high-impedance, non-integrated interfaces which suffer from time-related foreign body response, scarring, encapsulation and biofouling; all which lead to time-related signal degradation [5, 13, 14, 18, 22]. Monitoring the complex, bidirectional, central neural sensory and motor electrophysiologic interconnections requires an expensive, high-risk, invasive array of monitors and complicated, individualized computer algorithms, precluding their widespread clinical use at present [5].

Peripheral nerve action potentials reflect complex central signal integration and output and may allow less invasive and less complex signal detection approaches, while simultaneously achieving fidelity [16]. Peripheral nerve monitors (probes) exist, but suffer the same fate as their central counterparts, namely signal degradation, limiting their utility [20]. Peripheral nerve integration of complex central cellular communication is demonstrated clinically by targeted muscle reinnervation techniques, which are effective in human patients who have had an amputation [23, 24]. Previously severed peripheral nerves may be neurotized with an alternate target muscle leading to the creation of a myoneurosome, defined as a single muscle segment under voluntary cortical control which can be isolated from other surrounding muscles by electromyography (EMG) [25]. The directed nerve subsequently undergoes synaptogenesis and forms functional neuromuscular units with its new target muscle. Whole muscles may be partitioned to produce several individually innervated myoneurosomes. These myoneurosomes may be controlled by voluntary action potential generation within the severed nerves allowing discretely identifiable muscle depolarization. EMG on the myoneurosomes provides an indirect, amplified electrical representation of peripheral neural output. Furthermore, the peripheral nerves, neuromuscular junctions and muscles retain normal cellular maintenance machinery and are biologically stable.

Despite these promising clinical results, there are limited donor muscles suitable for the myoneurosome use, precluding individual axonal fidelity and subsequent fine motor control deficiencies [3]. .

We aim to develop a hybrid peripheral nerve interface utilizing a biologically derived muscle array capable of converting the saltatory conduction into electron currents useful in electronic circuitry. We have previously shown that acellular muscle lacks antigenicity and is capable of myoblast repopulation (unpublished data). When acellularized muscles (ACM) have been neurotized, successful synaptogenesis with coordinated action potential-contraction coupling has been achieved and quantified. Thus, ACM can be used as a target for directed reinnervation, forming biosynthetic myoneurosome. A distinct advantage to note is that these tissue engineered muscle constructs are not limited by availability, which permits fabrication of muscular arrays and higher fidelity fascicular, or possibly even axonal, neurotization necessary for fine motor control.

Our collaborators have recently begun using the electroconductive polymer poly(3,4-ethylenedioxythiophene) (PEDOT) (Baytron, Newton, MA) to enhance the electrical characteristics of centrally-placed silicone electrodes [14]. Further investigations of this highly electroconductive polymer have revealed that PEDOT can be deposited on biologic substrates through electric or chemical deposition processes [26]. In situ deposition of PEDOT around living neural cells initiated apoptosis in some cell populations [27]. However, initial data suggests that prefabricated implanted PEDOT constructs do not cause deleterious effects on nerve viability or myoblast migration (preliminary data).

In this experiment, we wished to determine if peripherally integrated neural action potentials could be detected and propagated in vivo by a hybrid device composed of PEDOT deposited on biologically derived acellular muscle. Here, we describe the production, implantation, and in vivo electrophysiologic properties of these hybrid neural constructs and their ability to detect action potentials proximally and deliver electronic signals distally.

Methods:

Preparation of the neural interface constructs began with acellularization of whole rat lower limb vastus lateralis muscles using techniques developed in our lab [28]. The acellular muscles were then prepared under a Nikon Zoom Stereomicroscope at 10x magnification (Nikon Instruments Inc. USA, Melville, NY) to create an acellular construct with the macroscopic morphologic characteristics of an intact rat peroneal nerve in the upper leg. Muscle bundles were dissected parallel to the fiber orientation to avoid disrupting the muscle fibers structure; tendon and fascial components were avoided where possible. The maximum fiber length was approximately 2.0 centimeters with an average diameter of 2.0-3.0mm. These fibers were subsequently coated with chemically polymerized EDOT using anhydrous iron(III) chloride powder (98%) (Acros Organics, Geel, Belgium) counterion treatment [26]. Although these constructs undergo multiple cycles of polymerization, increasing polymer surface area and electrical performance, we found that these repeated cycles reduced handling characteristics. Increasing polymerization cycles increased the brittleness of the constructs and had deleterious effects on suturing characteristics in preliminary studies. We chose to test the electrical characteristics after one polymerization cycle, where the constructs maintained some flexibility and sutures could penetrate and hold the constructs effectively. These polymerized constructs are subsequently referred to as ACM-PEDOT. Given the iron(III) chloride counterion treatment, we felt it necessary to treat a group of ACM fibers using the polymerization technique without addition of the EDOT monomer to evaluate the conductivity contribution of iron alone. These constructs are subsequently referred to as ACM-Fe. Untreated ACM was also used as a third construct group. Construct lengths included 5mm, 10mm, 15mm and 20mm for each group.

A hindlimb peroneal nerve model in retired-breeder F344 rats (Charles River, Wilmington, MA) was used for all experiments, in compliance with institutional UCUC guidelines. General anesthesia was achieved using 50mg/ml pentobarbital sodium injection, USP (Abbott Laboratories, North Chicago, IL) at 0.1 gram/kg dosing. Animals were prepped and the sciatic nerve was exposed through a lateral leg approach with care to avoid damage to the nerve. The peroneal division of the sciatic nerve was identified, isolated, and preserved. All branches of the sciatic nerve were divided so that only action potentials through the peroneal nerve would

propagate distally. Baseline electrophysiologic measurements were obtained on the intact peroneal nerve using clinical nerve conduction velocity (NCV) and EMG in the extensor digitorum longus (EDL) muscle using a Viasys EMG machine (Viasys Healthcare, Madison, WI). Generation of action potentials following application of nerve stimulator currents was confirmed by chemically blocking voltage gated sodium using 1% lidocaine HCL (Hospira Inc, Lake Forest, IL). After treatment with lidocaine, nerve conduction was completely eliminated in intact nerves (see Intact-Lido results).

To study efferent action potential propagation through the constructs, the peroneal nerve was divided and a segment was removed to correspond with the length of the construct to be utilized for reconstruction. The construct was then sutured to the proximal nerve stump with care to ensure that the exposed axons were held in close proximity to the construct by splaying and suturing the epineurium to the perimeter of the construct end. Although the distal nerve will undergo anterograde (Wallerian) degeneration, it remains excitable immediately after nerve division. This excitability was confirmed by stimulating the distal nerve and observing nerve conduction velocities and EMG responses indistinguishable from intact nerve (data not shown). The distal end of the construct was sutured to the distal nerve stump in a manner similar to the proximal attachment (see Image 1). The nerve was then stimulated proximal to this construct interposition and NCV and EMG measurements obtained (see Image 2). Control groups for this experiment included intact nerve, divided nerve which underwent a single epineural repair, and divided nerve which underwent nerve autografts repair with identical graft lengths to the test constructs.

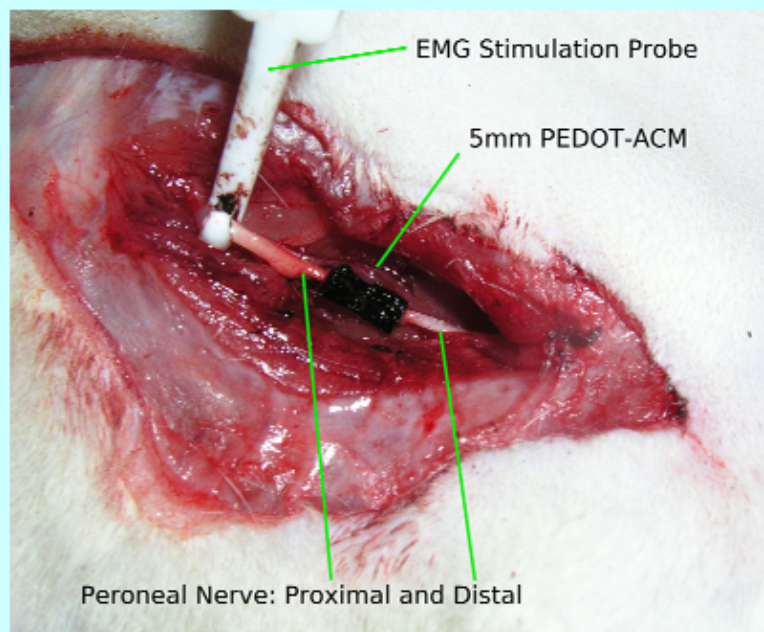


Figure 1: 5mm PEDOT Coated Acellular Muscle (PEDOT-ACM) hybrid neural interface in place in rat peroneal nerve. Note the non-invasive nerve stimulator. EMG electrodes are not visible.

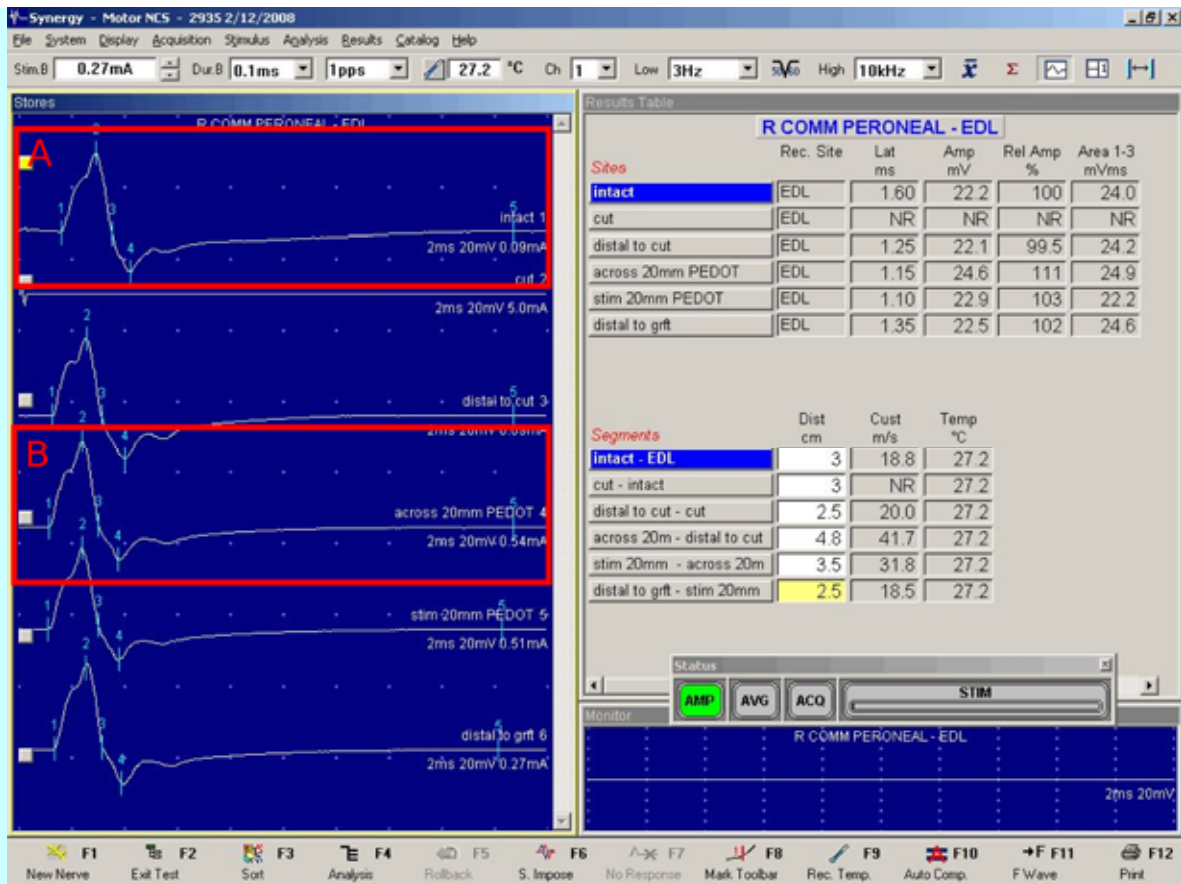


Figure 2: Typical EMGuser interface data output using the **Viasys Healthcare EMG**. This example is from testing a 20mm PEDOT construct. Note the similar EMG results obtained comparing intact nerve (A) with a 20mm PEDOT interposition (B).

Results:

Nerve autografts, epineural nerve repairs and PEDOT-ACM constructs conducted physiologic currents at all lengths tested. 10mm ACM and ACM-Fe constructs were non-conductive and thus, longer lengths were not tested. NCV/EMG results (Table 1) demonstrate ACM-PEDOT constructs conduct physiologic currents (0.53 ± 0.19 mA) up to 20mm with maximal amplitude of 16.60 ± 5.29 mV, and latency of 1.09 ± 0.15 ms. Furthermore, statistical analysis using One-Way ANOVA with post-tests shows that ACM-PEDOT data are not different from NCV/EMG values for intact nerve or from similar length nerve autografts. ACM-PEDOT constructs showed a statistical increase in conductive velocity (40.22 ± 8.71 m/s) compared with intact nerve (22.15 ± 3.68 m/s). See Table 1 for complete test results.

Table 1: In Vivo Electrophysiologic Properties of Poly 3,4-ethylenedioxythiophene (PEDOT) in a Biosynthetic Nerve Interface

Construct Studies (n=5 in each group)						
Length	EMG Measurement	Nerve Gap	ACM	ACM-Fe	ACM-PEDOT	Nerve Graft
5mm	Stimulation (mA)	No Response	2.58 ± 2.20	1.43 ± 2.00	0.86 ± 0.37	0.80 ± 0.82
	Amplitude (mV)	No Response	16.57 ± 9.57	15.48 ± 3.44	12.62 ± 4.28	13.38 ± 6.16
	Latency (ms)	No Response	1.20 ± 0.10	1.14 ± 0.24	1.18 ± 0.16	1.24 ± 0.18
	Velocity (m/s)	No Response	26.30 ± 9.44	26.18 ± 8.91	28.6 ± 3.12 *	20.40 ± 8.42
10mm	Stimulation (mA)	No Response	No Response	No Response	2.45 ± 4.22 *	0.44 ± 0.23
	Amplitude (mV)	No Response	No Response	No Response	13.22 ± 7.65	16.04 ± 5.68
	Latency (ms)	No Response	No Response	No Response	1.33 ± 0.33	1.27 ± 0.07
	Velocity (m/s)	No Response	No Response	No Response	28.62 ± 8.64	23.40 ± 5.35
15mm	Stimulation (mA)	No Response			3.66 ± 6.28 *	1.61 ± 1.87
	Amplitude (mV)	No Response			16.00 ± 3.54	17.12 ± 3.21
	Latency (ms)	No Response			1.21 ± 0.14	1.24 ± 0.19
	Velocity (m/s)	No Response			35.64 ± 3.81 *	22.22 ± 6.18
20mm	Stimulation (mA)	No Response			0.53 ± 0.19	1.06 ± 1.52
	Amplitude (mV)	No Response			16.6 ± 5.29	18.60 ± 2.59
	Latency (ms)	No Response			1.09 ± 0.15	1.20 ± 0.17
	Velocity (m/s)	No Response			40.22 ± 8.71 *	26.90 ± 3.36
Nerve Studies						
EMG Measurement	Intact (n=70)	Intact-Lido (n=5)	Epineural (0mm Gap) (n=5)			
Stimulation (mA)	0.20 ± 0.14	No Response	0.36 ± 0.14			
Amplitude (mV)	16.63 ± 5.20	No Response	17.70 ± 2.72			
Latency (ms)	1.34 ± 0.23	No Response	1.12 ± 0.24			
Velocity (m/s)	22.19 ± 3.62	No Response	29.77 ± 2.77 *			

mA = milliamps, mV=millivolts, ms= milliseconds, m/s=meters per second.

No Response=No EMG or NCV response.

n=5 in all groups (except intact nerve: n=65)

(*) denotes statistically significant difference compared to intact nerve (p<0.05)

The views expressed in this work are those of the authors and do not necessarily reflect official Army policy. This work was supported by the Department of Defense Multidisciplinary University Research Initiative (MURI) program administered by the Army Research Office under grant W911NF0810218

Conclusions:

This study has demonstrated that PEDOT coated acellular muscle constructs can transmit the small currents (<1 mA) associated with physiologic action potentials in vivo. Further, the proximal nerve action potential can be electrically coupled across an interface coated with PEDOT. Interestingly, the efferent action potentials are transmitted across the peroneal nerve - ACM-PEDOT interface proximally without detectable degradation in the signal amplitude or conduction delay. Distally, the electron mediated signal within the ACM-PEDOT construct is then propagated across the ACM-PEDOT -peroneal nerve interface to generate a distal action potential. This is proof of concept that an electronic signal in the biosynthetic ACM-PEDOT construct can be utilized to stimulate a peripheral nerve from an exogenously generated electrical impulse, which may be useful for sensory feedback in a prosthetic device. We are now conducting studies aimed at further understanding the electrical conduction properties and interactions of axons with the polymer in vivo. A major focus of these studies is integrating conventional wires with the hybrid construct which maintain continuity with the PEDOT. One approach currently being optimized is using electrical EDOT polymerization techniques whereby the polymerization electrode is simultaneously coated with polymer and remains permanently implanted for use as a recording lead. Furthermore, additional studies are underway on sensory nerve coupling using a sural nerve model. We hope that continued studies will allow these constructs to be used for permanent biologic interfaces for prosthetic control.

Department of Defense Disclaimer: The views expressed in this work are those of the authors and do not necessarily reflect official Army policy. This work was generously supported by the Department of Defense Multidisciplinary University Research Initiative (MURI) program administered by the Army Research Office under grant W911NF-06-1-0218.

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Double Transgenic Mice Are a Useful Tool in Peripheral Nerve Research

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Introduction

Schwann cell (SC)-axonal relationships at the neuromuscular junction (NMJ) are poorly understood in the context of traumatic nerve injury. With the aid of confocal microscopy, and a

double transgenic thy1-CFP(23)/S100-GFP mouse model, we simultaneously imaged SCs and axons to study these relationships and establish baseline data.

Thy1-CFP (23)/S100-GFP Double Transgenic Model

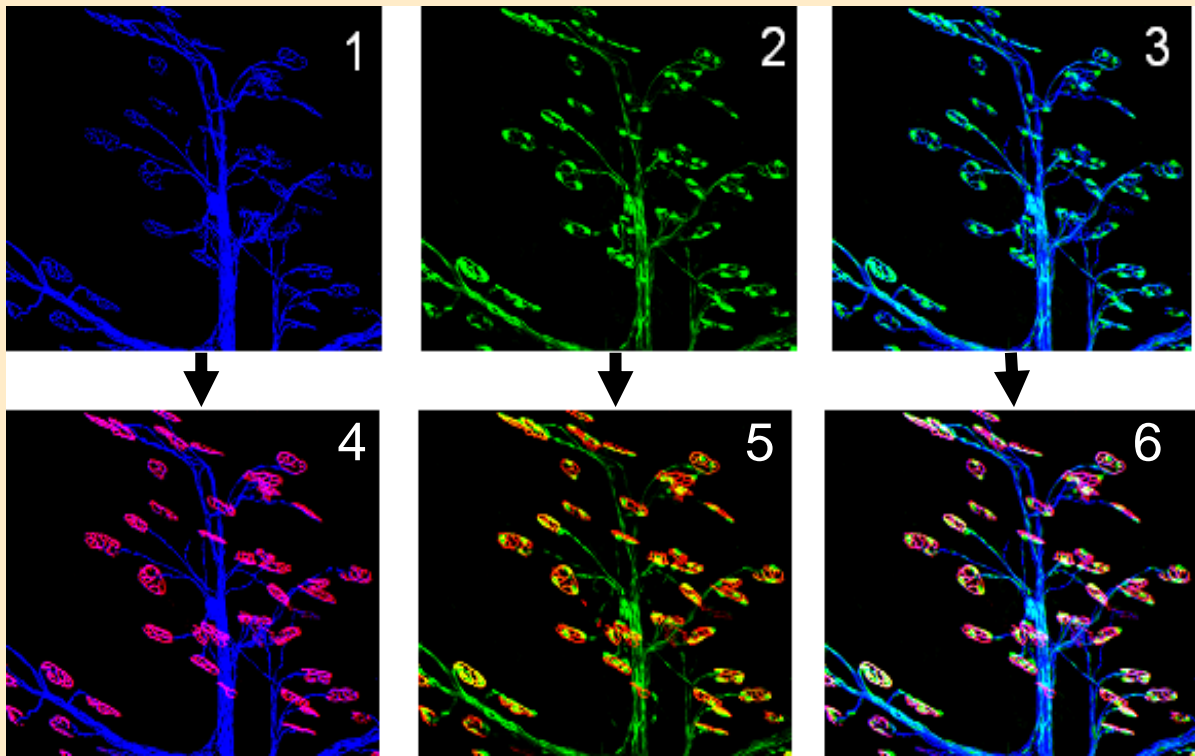


Figure 1. 1-6: Extensor digitorum longus (EDL) muscle of uninjured adult mice
1. Thy1-CFP (23) line –Axons express Cyan Fluorescent Protein (CFP) - Blue.
2. S100/GFP line – SCs express Green Fluorescent Protein (GFP) - Green.
3. Breeding these two lines produced double transgenic Thy1-CFP (23)/S100-GFP mice.
Row 2: All motor endplates were stained with red (alpha-bungarotoxin (BTX)).
4. Blue motor axons innervate red endplates; superimposition is magenta. The axon:endplate ratio is 1:1.
5. Green terminal SCs overlie red endplates to produce yellow. The average terminal SC:endplate ratio is approximately 3:1.
6. Superimposition of blue (axons), green (SCs) and red (motor endplates) produces white.

Results:

1. EDL Muscles

Axonal and SC changes in a crush injury paradigm using simultaneous imaging.

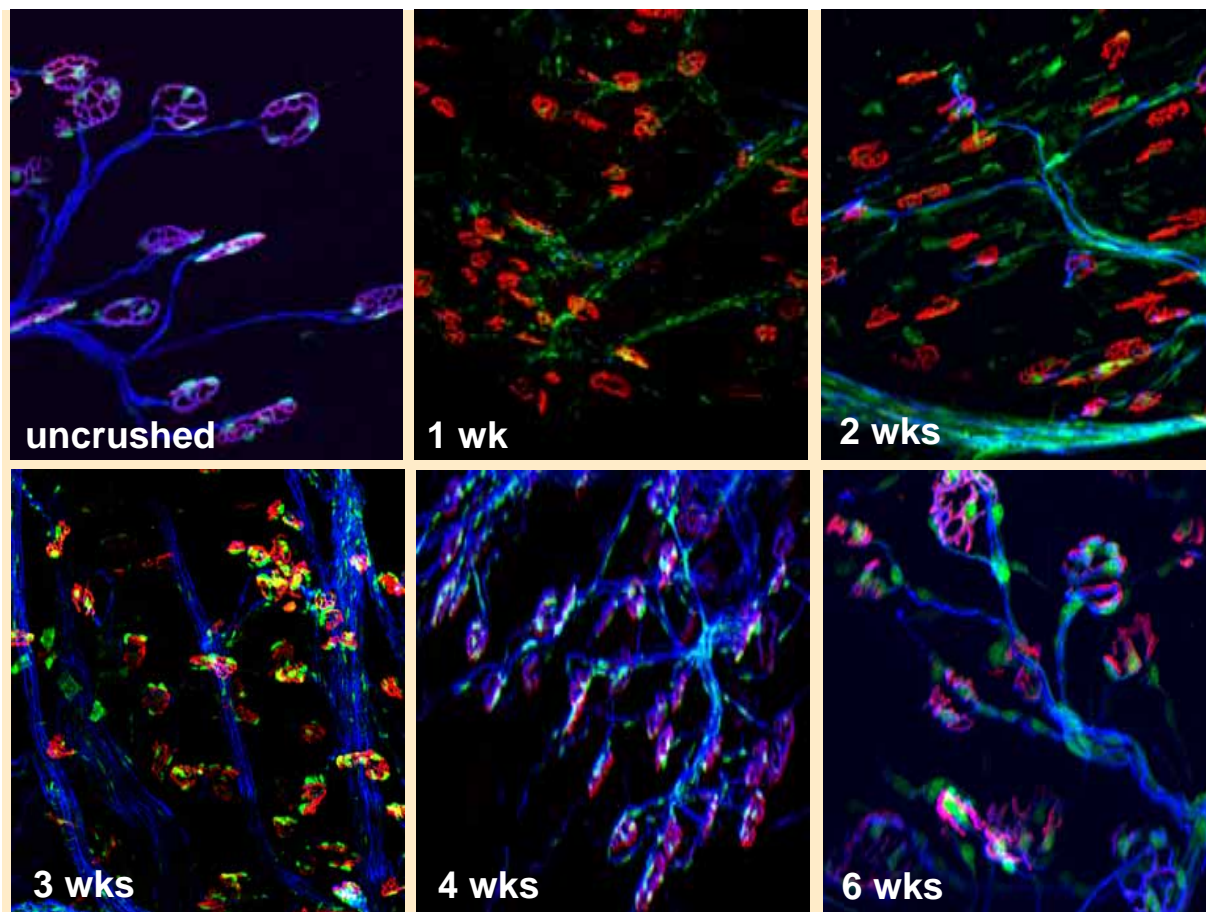


Figure 2. Experimental animals were harvested 1-6 weeks after sciatic crush injury, and axonal-SC relationships were evaluated with confocal microscopy.

Axons: Uninjured (0 wk) shows a 1:1 ratio between terminal axons and motor endplates. One week after crush (1 wk) 100% show denervation and no merged pink. Partially reinnervation is shown at 2 wks and is seen to be increasing at 3 and 4 wks. A return to a 1:1 ratio is seen at 6 weeks (wk 6).

SCs: The number of terminal SCs per endplate approximates a 3:1 ratio in a normal mouse. Terminal SC ratios decrease to 1.5:1 at one week after injury, and gradually increase over the next two weeks. By 6 weeks, the accepted recovery timepoint from crush injury, the ratio has returned to 3:1.

2. Sciatic Nerve Cross Section

Simultaneous imaging of SC-axonal relationships in the sciatic nerve after crush injury, combined with immunohistochemical evaluation of laminin.

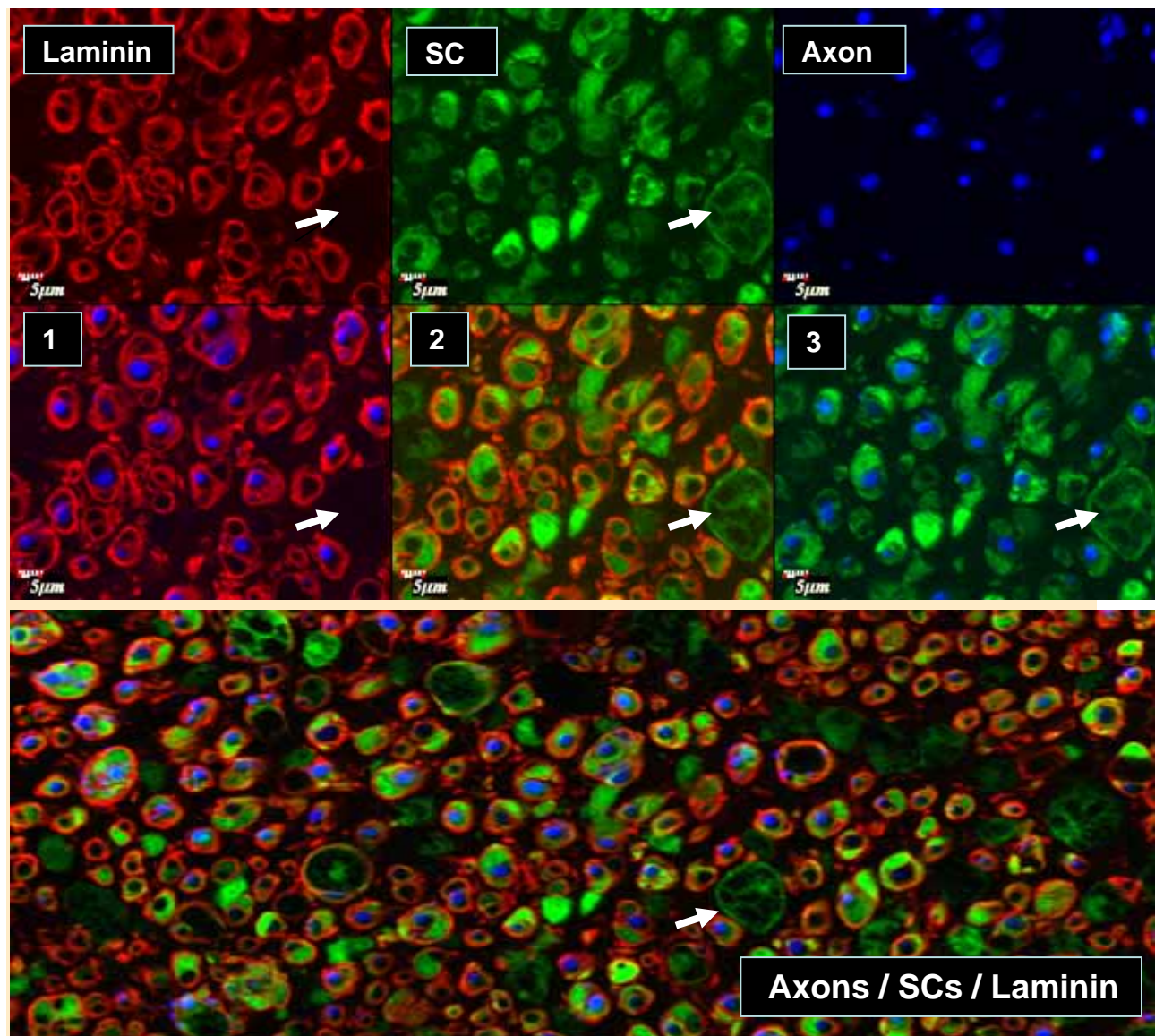


Figure 3. Two weeks after crush injury, the sciatic nerve was evaluated with confocal microscopy for native CFP and GFP fluorescence in axons and SCs, respectively, and a polyclonal anti-laminin antibody stain was used to image laminin on the same sections. Two-color merged images are labeled 1, 2 and 3.

In the context of Wallerian degeneration after crush injury, simultaneous imaging of these features provides information that might be lost with other staining techniques. For example, SC basal lamina tubes, visible with laminin staining, are frequently unoccupied by regenerating axons.

Arrows indicate a macrophage, which in the S100-GFP line produces GFP fluorescence, which can be distinguished from a Schwann cell because of its lack of close association with a basal lamina tube.

OUTCOMES OF A MULTICENTER STUDY OF DECOMPRESSION OF CHRONIC TIBIAL NERVE COMPRESSION IN DIABETICS WITH NEUROPATHY

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At the American Diabetes Association meeting in San Francisco, on June 6 to 8th, 2008, this poster on decompression of lower extremity peripheral nerves will be presented. This is the first time the American Diabetes Association has recognized this work in this format. This poster is a visual representation of the data available on-line at NeuropathyRegistry.com, a multicenter, prospective study comprised of surgeons who have taken the Advanced Lower Extremity Peripheral Nerve Workshop. The 30th Workshop will be given in Baltimore on July 15-18, 2008 (Delon.com). For diabetics with compression of the peroneal and tibial nerves, decompression can relieve pain in 80% and restore sensation in 80%. This leads to prevention of ulceration and amputation, and reduced admissions to the hospital for foot infections.

NeuropathyRegistry.com

is a multicenter study to evaluate outcomes from surgical decompression of chronic compression of the tibial nerve and its branches at the ankle and foot in patients with neuropathy. 37 surgeons contribute to this registry.

INCLUSION CRITERIA:

- 1) Diabetic patients with symptomatic neuropathy who were in good glycemic control and had not responded to neuropathic pain medication.**
- 2) There was sufficient blood supply (ABI \geq 0.7)**
- 3) There was no pedal edema.**
- 4) Nerve compression was determined by the presence of a positive Tinel sign over the tibial nerve in the tarsal tunnel.**
- 5) All surgeons used the same surgical technique to decompress the four medial ankle tunnels. ***

POPULATION:

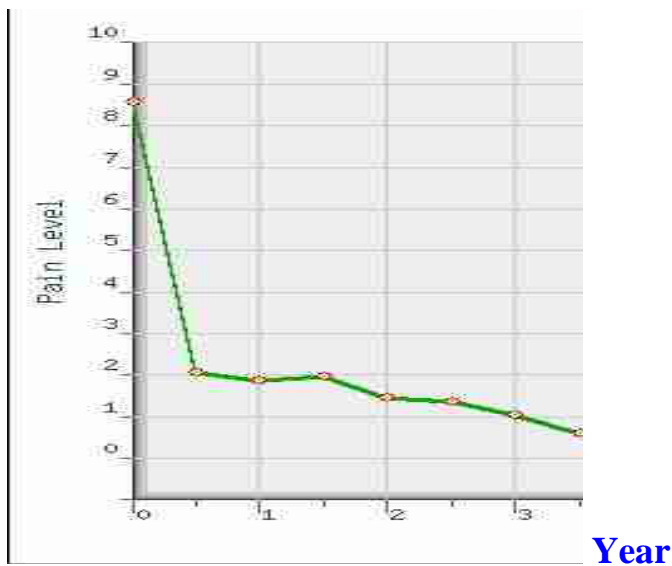
Study includes, as of July 1, 2007, 628 patients, of whom 211 had a second, contralateral, foot decompressed, for a total of 839 operations.

DATA ANALYSIS:

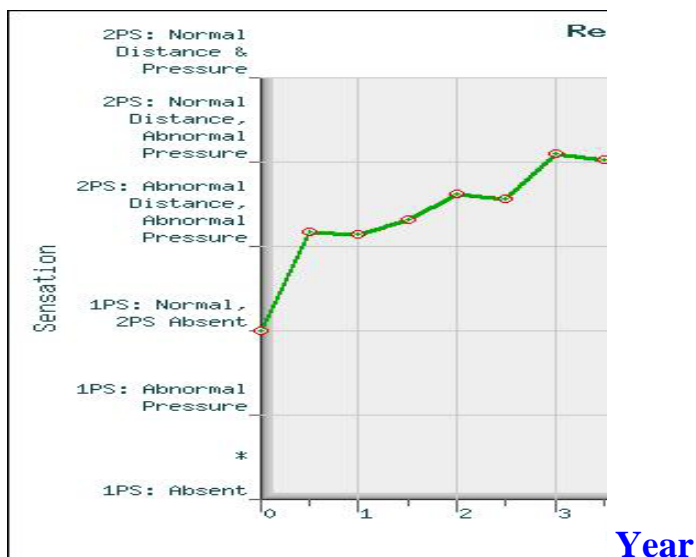
Kaplan-Meier proportional hazard analysis was applied to prospectively collected data. These data were reviewed retrospectively for this study.

CONCLUSIONS:

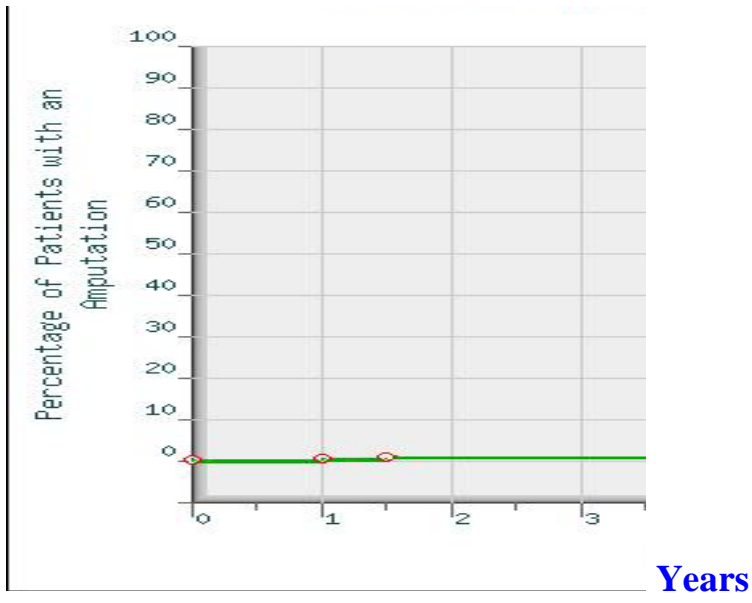
Decompression of the tibial nerve in patients with diabetic neuropathy, in whom tibial nerve compression is identified by the presence of a positive Tinel sign over the tibial nerve in the tarsal tunnel, results in 1) decreased pain, 2) increased sensation, 3) prevention of amputation, 4) prevention of ulceration in those patients with and without a history of previous ulceration, and 5) reduces hospitalization for treatment of foot infection.



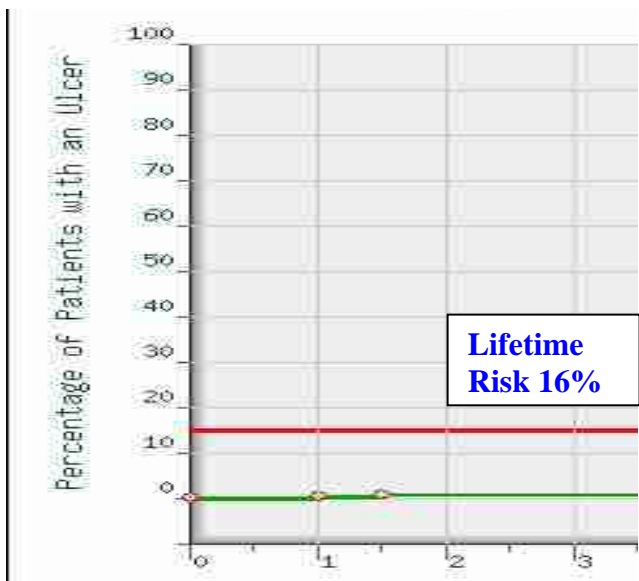
CHANGES IN MEAN PAIN LEVEL



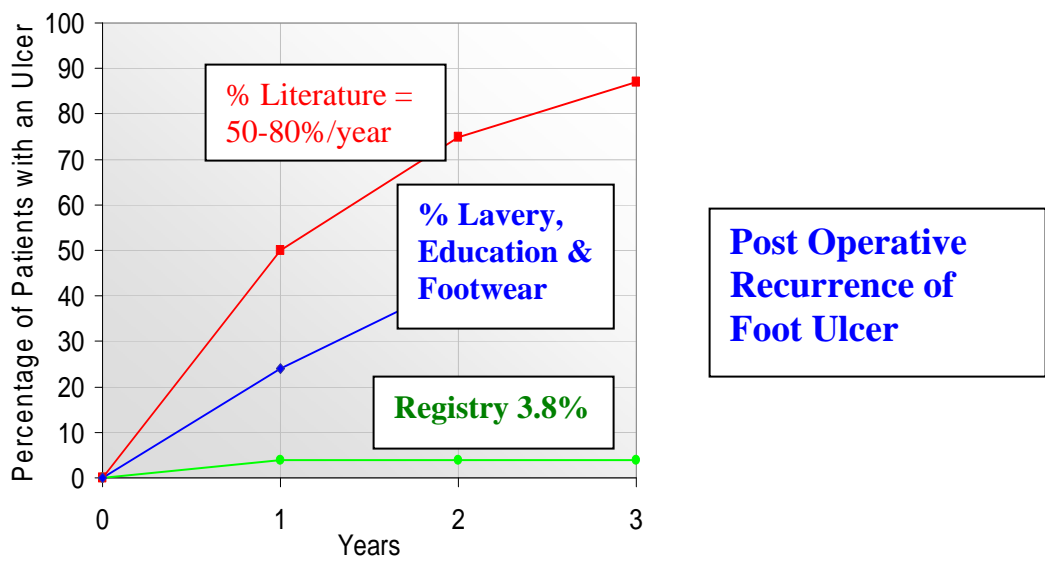
RECOVERY OF 1 PT & 2 PT SENSATION



AMPUTATION EVENTS



FIRST ULCERATION



Post Operative Recurrence of Foot Ulcer

FOOT RELATED HOSPITALIZATION

