

REGENERATION RESEARCH NEWSLETTER



The Eleventh International Symposium on Neural Regeneration

The Eleventh International Symposium on Neural Regeneration (ISNR) was held at the Asilomar Conference Center in Pacific Grove, California from December 14-18, 2005. The meeting was co-sponsored by the U. S. Department of Veterans Affairs (Medical Research Service and Rehabilitation Research and Development Service), the Paralyzed Veterans of America (Spinal Cord Research Foundation), the National Institutes of Health (National Institute of Neurological Disorders and Stroke, Office of Rare Diseases), the Christopher Reeve Paralysis Foundation and the United Spinal Association. Additionally, a generous donation was received from the Shapiro Spinal Cord Research Foundation.

The symposium was organized by Dr. Roger Madison (Symposium Director, VA Medical Center and Duke University, Durham, NC), and the program planning committee which included Drs. Marie Filbin (Hunter College), David Gardiner (University of Cal-

ifornia, Irvine), Jane Lebkowski (Geron Corporation), Michael Sofroniew (University of California, Los Angeles) and John Steeves (University of British Columbia/International Collaboration on Repair Discoveries). Guest attendees representing co-sponsoring institutions at the planning committee meeting were Drs. Vivian Beyda (United Spinal Association), Naomi Kleitman (NIH-NINDS) and Patricia Dorn (VA, Rehabilitation Research and Development).

The keynote speaker for this year's symposium was Jerry Silver from Case Western Reserve University. Featured talks were given by John Steeves from the University of British Columbia/ICORD, Miguel Nicolelis from Duke University, Steven Goldman from The University of Rochester, Edward Wirth, III from Geron Corporation, Jeff

REGENERATION RESEARCH STAFF

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Participants comment on ISNR 2005...

“It was my hope that the information presented at the meeting would be beneficial in focusing my research efforts. I indeed returned enthusiastic, inspired, energized, and motivated to contribute a small piece to such an extraordinary cause. Thank you!”

“Word of mouth indicated that this was absolutely the best meeting on regeneration, and that proved true.”

“It is my favorite conference of the year and brings together a great crowd in a relaxed atmosphere to share very exciting science.”

“The various social interactions with colleagues [are] as beneficial as they are enjoyable.”

“Bravo!, what a wonderful symposium! The setting at Asilomar coupled with the warmth and friendliness displayed by one and all was extremely heartwarming...I was able meet some wonderful people that I would like to consider friends and indeed as I later found out from their presentations were also some of today's most influential and inspiring researchers. I only wish other symposia and gatherings could even begin to attain the lofty heights set by this meeting.”

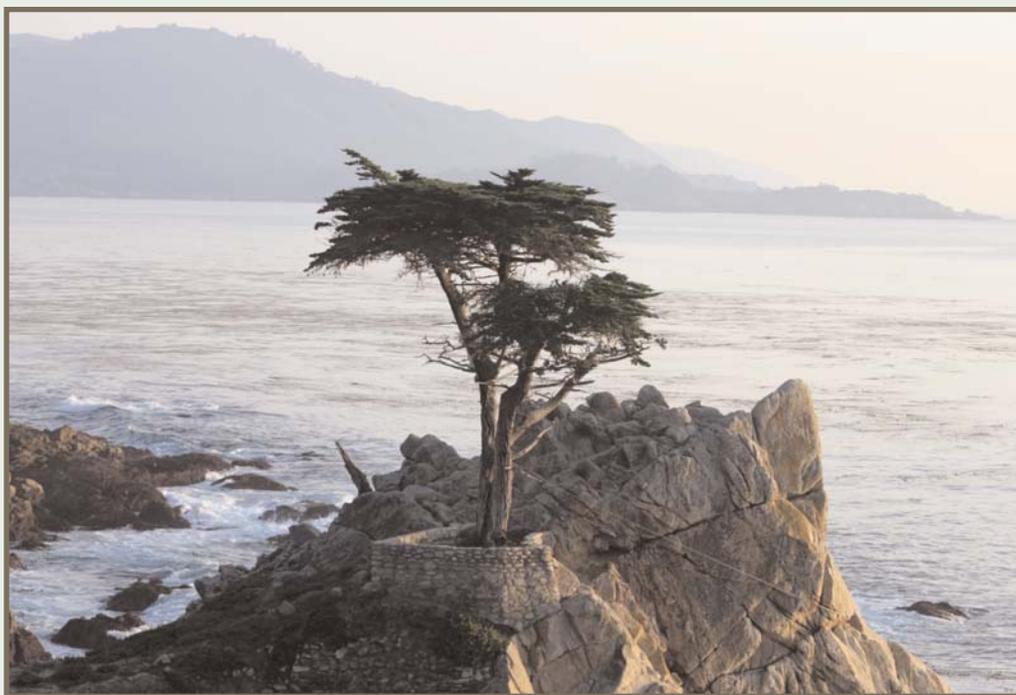
“It is our lab's conference of choice. I appreciate the quality of speakers and attendees, as well as the wonderful surroundings and social atmosphere.”

“Well-organized, good program. Topical, diverse. Good spirit.”

“It is one of the best symposia on regeneration research and the informal format is especially conducive for learning and interactions—an excellent experience for my graduate students.”

“I really enjoyed this meeting and the casual atmosphere. I especially enjoyed getting to know a number of the participants. The meeting has definitely increased my interest in the topic and in doing experiments related to regeneration.”

“I love this symposium!”



The “Lone Cypress”, a short drive from the Asilomar Conference Grounds

The Director's Chair

From the Office of the International
Symposium on Neural Regeneration

Roger D. Madison, Ph.D., Director



2005 Highlights

ISNR 2005 was attended by 232 participants, a 23% increase in overall participation from 2003, and an all-time high for the symposium. Seventy-nine students attended, creating a 41% increase in student participation, and 107 posters were presented, a 30% increase in free communications since the last symposium.

This year's event began with a moment of tribute to the late Christopher Reeve and his contributions to neural regeneration research. Keynote speaker Jerry Silver of Case Western Reserve University received an award provided by the Christopher Reeve Paralysis Foundation for his presentation entitled "Regeneration Beyond the Glial Scar."

An exciting symposium "first" this year was the "Increasing Inflammation Is Beneficial for Neural Repair and Outcome" debate chaired by Keith Crutcher (University of Cincinnati). Jonathan Kipnis and Howard Gendleman (University of Nebraska) and J. Regino Perez-Polo (University of Texas-Medical Branch) argued the "pro" side of the issue, while the "con" side was represented by Lynne Weaver (Robarts Research Institute), V. Hugh Perry (University of Southampton) and Phillip Popovich (The Ohio State University). The format included a group presentation of each side's argument followed by a rebuttal period. The debate sparked much conversation on inflammation throughout the remainder of the symposium, and due to the overwhelmingly positive audience response we are planning another debate for 2007.

The Frederick Seil Trainee Award, established in 2003 to honor the first director and founder of ISNR, was awarded this year to Fang Sun of The Ohio State University and Maarten Leyssen of The University of Leuven. Sun and Leyssen each received a \$250 cash award, and their names have been engraved on the Frederick Seil Trainee Award perpetual plaque. Additionally, five poster presenters were recognized with the "United Spinal Association Poster Finalist Award." Recipients were Jennifer Fleming (Robarts Research Institute), Kristina Kigerl (The Ohio State University), Julia Herrmann (University of California-Los Angeles) Ward Plunet (University of British Columbia/ICORD) and Erin McDaniel (The Ohio State University). The United Spinal Association generously provided a \$50 cash award and a certificate for each of these winners. All awards were chosen by planning board members who reviewed the poster sessions.



**Roger Madison and Frederick Seil
Trainee Award winner Maarten Leyssen**

In addition to these awards, two individuals were selected to give platform presentations based on the abstracts they submitted. Candace Floyd of The University of California-Davis and Damien Pearse of The University of Miami were chosen to give these talks in the final "Emerging Topics" conference session, and were presented with certificates. ISNR congratulates all of these winners.



Symposium Session Proposals

If your favorite topic has not recently been presented at one of the international symposia, we encourage you to submit a proposal for a symposium session. The program planning committee is meeting on July 15 and 16, 2006, to formulate the program for the Twelfth International Symposium on Neural Regeneration (ISNR) scheduled for December 2007. Proposals may be received in the ISNR Office as late as June 9, 2006 and still be considered, but earlier submission is recommended for advance distribution to committee members. Proposals will not be considered, however, if they are not submitted in an appropriate format (see guidelines below).

Submission Guidelines

Symposium sessions are chosen for their timeliness, current interest and recent progress. One of the goals of these symposia is to cover the field of neural regeneration as broadly as possible. This cannot be done in a single year, and therefore an attempt is made to vary the programs in successive symposia so that eventually the spectrum of neural regeneration research is covered. A symposium session proposal should define a session topic and include a few words about why the topic should be presented. A chairman should be identified (often the symposium proposer), along with four or six first choice speakers. Information on the speakers should include institutional affiliation, address, telephone number (if available), and a few words on what area this speaker would cover. In addition, at least one (preferably more) alternate should be listed for each speaker or chairman, along with institutional affiliation and other identifying data, as the first choice speaker is not always available because of some conflict. Potential speakers should not be contacted in advance, as invitations are issued by the Director's office if the program planning committee accepts the session. Some thought should also be given to whether a potential speaker has previously been a symposium presenter, especially in a recent symposium, as an attempt is made to vary the individuals participating in the program. Lists of speakers in past symposia are available from the ISNR office and are also posted on our web site: <http://www.vard.org/neural/neural.htm>.

Please submit session proposals via email to:

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Director, International Symposium on
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SYMPOSIUM, cont.

Lichtman from Harvard University and Paul Martin from The Ohio State University. Following the format of preceding neural regeneration symposia, the program was divided into six sessions, which included: 1) Autonomic Dysfunctions and the Long-Term Effects on the Aging Spinal Cord-Injured Population, chaired by Kimberly Anderson; 2) Growth/Plasticity and Functional Outcome, chaired by Harry Goshgarian; 3) Intrinsic Mechanisms Underlying the Initiation of Nerve Regeneration, chaired by Larry Benowitz; 4) Increasing Inflammation Is Beneficial for Neural Repair and Outcome (debate), chaired by Keith Crutcher; 5) Convergent Signaling Regulating Axon Growth, chaired by Marie Filbin; and 6) Emerging Topics, chaired by Michael Sofroniew.

The other platform presentations were given under six topic headings (see below), each featuring talks by invited speakers. Each topic session was chaired by an internationally recognized expert in the field who gave an overview of the session topic as well as introductory remarks. The abstracts of the platform and poster presentations are available online at the ISNR web site (www.vard.org/neural/neural.htm).

Brief summaries of the keynote and featured speaker presentations are given below followed by a listing of session chairmen and speakers.

Regeneration Beyond the Glial Scar (Jerry Silver, Case Western Reserve University)



Jerry Silver

Dr. Silver's keynote address reviewed his career-length work studying the cellular and molecular interactions that occur between the "growth cones" that form at the end of the cut axon and the various types of reactive glial cells which they interact, especially focusing on the spinal cord. For the past several years, Dr. Silver's laboratory has begun to clarify whether a particular family of boundary molecules produced by astroglia during normal development, the proteoglycans, are also critical after injury. The

proteoglycans appear to create both developmental as well as regenerative boundaries. Using a micro-transplantation technique to reduce the formation of reactive astroglia, Dr. Silver's laboratory has demonstrated that adult nerve cells can regenerate their axons with high efficiency and at high rates of speed, challenging long held beliefs that this is impossible. Recently, his laboratory has shown the ability to promote robust functional regeneration of severed sensory roots into the adult rodent spinal cord using a combinatorial strategy that maximally stimulates an intrinsic growth response in the sensory neurons while at the same time using chondroitinase to remove inhibitory sugar chains from proteoglycans. This exciting finding is being pursued by other labs with the combination of various cellular bridging techniques to enhance axonal regeneration in the damaged rodent spinal cord.

Guidelines for the Conduct of SCI Clinical Trials (John Steeves, University of British Columbia/International Collaboration on Repair Discoveries)



John Steeves

Dr. Steeves reported on the 2004 Vancouver meeting of the International Campaign for Cures of spinal cord injury Paralysis (ICCP) which was the first international clinical trials workshop on spinal cord injury. The main achievement of the meeting was to bring the varied international teams together and introduce them to the progress in clinical trials and the complexities involved in effective clinical trial design. A report of this meeting has been published (Steeves J, Fawcett J, & Tuszynski M. 2004. *Spinal Cord* 42: 591-597). Another outcome of the ICCP Clinical Trials Workshop in Vancouver was a vote by the participants to establish a working panel to bring forward more detailed guidelines for how to conduct valid SCI clinical trials. Given the rising number of SCI therapeutic interventions, where both the benefits and risks are large, the ICCP Clinical Trials

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Guidelines Panel determined that the initial focus should be on pharmaceutical drug interventions and cellular transplants directed to facilitating enhanced spinal function. Among the large number of clinical trial issues, the panel has initially identified four primary concerns:

1. Degree and level of injury, timing of clinical intervention, statistical power needed to achieve a valid outcome.
2. Determination of appropriate clinical outcome measures for different interventions.
3. Participant selection criteria (inclusion/exclusion) and ethics.
4. Trial Design, the control of potential confounding variables, standardization of adjunct treatments, and the organization of multicenter trials.

The latest recommendations of the panel can be found on the web at www.icord.org.

Computing with Neural Ensembles (Miguel Nicolelis, Duke University)



Miguel Nicolelis reviewed a series of exciting recent experiments demonstrating the possibility of using real-time computational models to investigate how ensembles of neurons encode motor information. These experiments have revealed that brain-machine interfaces can be used not only to study fundamental aspects of neural ensemble physiology, but they can also serve as an experimental paradigm aimed at testing the design of modern neuroprosthetic devices. He also reviewed exciting recent work from his laboratory indicating that continuous operation of a closed-loop brain machine interface, which utilizes a robotic arm as its main actuator, can induce significant changes in the physiological properties of neurons located in multiple motor and sensory cortical areas. This raises the question of whether the properties of a robot arm, or any other tool, can be assimilated by neuronal representations as if they were simple extensions of the subject's own body.

Isolation, Induction and Use of Neural Progenitor Cells (Steven A. Goldman, University of Rochester)



Steven Goldman

Dr. Goldman presented an update in the rapidly progressing field of stem cell research (a topic of one of the ISNR sessions in 2003). His presentation highlighted parenchymal glial progenitor cells. When isolated and transplanted into neonatal shiverer mice, whose brains lack myelin basic protein, these cells can mediate quantitatively substantial and geographically extensive myelination. Remarkably, whereas adult glial progenitor cells only generate oligodendrocytes and astrocytes within the normal white matter, upon removal from the tissue environment they expand to generate neurons as well as glia. Thus, an abundant pool of glial progenitors retains both multilineage capacity and mitotic competence in adult brain parenchyma, suggesting the potential for substantial cell replacement in the human CNS.

Dr. Goldman also reviewed research showing that endogenous stem and progenitor cells may be induced to generate new neurons by over-expressing cognate neuronal differentiation agents, such as BDNF. The concurrent suppression of astroglial differentiation by resident stem cells, accomplished by over-expressing the bone morphogenetic protein (BMP) inhibitor noggin, can potentiate the BDNF-mediated addition of new neurons to the adult rat neostriatum. The new neurons mature as medium spiny neurons, and successfully project to the globus pallidus, extending processes over several mm of normal adult striatum. R6-2 mice (a model of Huntington's disease, HD) treated with adenoviral BDNF and noggin exhibit both improved motor performance and longer survival than untreated controls, suggesting the potential therapeutic efficacy of this strategy for replacing medium spiny neurons lost to HD.

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Clinical Trials in Spinal Cord Injury: How Can We Link Imaging to Functional Outcome? (Edward Wirth, III, Geron Corporation)



Edward Wirth, III

Dr. Wirth reviewed the role of radiological imaging in diagnosing the severity of tissue damage following traumatic spinal cord injury (SCI). Although x-ray plain films and computed tomography (CT) are used to determine spinal column misalignment and instability, magnetic resonance imaging (MRI) has assumed an increasingly important role in the evaluation of spinal trauma. Routine MRI enables detailed evaluation of the spinal cord, nerve roots, intervertebral discs, and adjacent vascular structures. Typical MRI protocols include the acquisition of T1- and T2-weighted spin-echo images in both the sagittal and transverse planes. Additional images with gradient-echo weighting are also acquired frequently. These imaging sequences can reveal several important details that are associated with neurological impairment and functional recovery following SCI. Specifically, MRI can demonstrate the presence, location and extent of hemorrhage and edema in the spinal cord, as well as the degree of cord compression.

More recently, advanced MR methods such as diffusion-weighted imaging (DWI), diffusion-tensor imaging (DTI), and functional MRI (fMRI) have shown promise for providing additional information about the anatomical and functional integrity of the spinal cord. For example, DWI/DTI can reveal continuity in white matter tracts by visualizing the anisotropy of water motion. This anisotropy is related to both the parallel arrangement of axonal components (e.g. neurofilaments) and to myelin. Accordingly, MRI may serve as an important surrogate outcome measure for clinical trials of therapies that are intended to mitigate tissue damage following acute SCI or to facilitate repair of the spinal cord at later stages.



Jeff Lichtman

Dr. Lichtman's talk was considered by many of those present as the Monet-of-Neuroscience presentation. It was an extraordinarily colorful review of the use of transgenic mice that express fluorescent proteins in neurons to monitor the behavior of axons in vivo. He reviewed the recent finding that regenerating peripheral motor axons not only reestablish their original branching patterns in former Schwann cell tubes, but also that once axons reach their postsynaptic sites they show a marked preference for growth along the basal lamina that coincides with the location of postsynaptic acetylcholine receptors. His laboratory is also helping to pioneer the ability to follow damage to central axons in the dorsal columns of the spinal cord. They have found that both the proximal and distal segments of the axons undergo an acute die-back from the site of the lesion, and that although these axons appear to make an attempt at regrowth, it is always misdirected. Finally, newly engineered transgenic "rainbow" mice in which many different spectral variants of GFP are expressed in the same animal are beginning to make it possible to track many axons and axonal organelles simultaneously in development and regeneration.

New Roles for Glycosylation in Neuromuscular Development, Regeneration, and Disease (Paul T. Martin, The Ohio State University)

Dr. Martin reviewed his extensive work identifying several carbohydrate structures that are uniquely present at the neuromuscular synapse in skeletal muscle, including the cytotoxic T cell (CT) carbohydrate antigen. The CT carbohydrate is made by CT GalNAc transferase, which is itself localized to the neuromuscular junction in skeletal muscle. Transgenic overexpression of this glycosyltransferase

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Paul Martin

ase in skeletal muscle causes the ectopic expression of a complex of synaptic proteins known to interact with dystroglycan, the principal glycoprotein target of this enzyme in skeletal muscle. CT transgenic mice demonstrate roles for this carbohydrate in muscle growth, axon guidance, and neuromuscular structure. Evidence suggests roles for follistatin and NCAM in the muscle growth and axon guidance phenotypes, respectively. In addition, CT overexpression in skeletal muscle stimulates the ectopic expression of utrophin, a synaptic homologue of dystrophin, the protein missing in Duchenne muscular dystrophy (DMD), and laminin alpha 4 and alpha 5, the synaptic homologues of laminin alpha 2, the protein defective in congenital muscular dystrophy IA (MDCIA). The ectopic expression of these molecules in CT transgenic mice inhibits the development of muscular dystrophy in mdx mice, a model for DMD, as well as in dyW mice, a model for MDCIA. This therapeutic effect can be accomplished using gene therapy approaches both in mdx and dyW animals in ways that bypass the developmental effects on muscle growth and neuromuscular development. All of this work highlights the roles of carbohydrate structures in neuromuscular development, disease, and regeneration.

Autonomic Dysfunctions (AD) and the Long-Term Effects on the Aging Spinal-Cord-Injured Population (Chaired by Kimberly Anderson, University of California, Irvine)

Michael Craggs (Royal National Orthopaedic Hospital, NHS Trust) was the first speaker in this session, presenting “Repeated Autonomic Dysreflexia Episodes Stimulated by Bladder and Bowel Dysfunction: Implications for the Aging SCI Population.” Stacy Elliott (University of British Columbia) presented “Autonomic Dysreflexia with Sexual Activity: Do the Benefits Outweigh the Risks?” Christopher Mathias (Imperial College of Science, Technology and Medicine) presented



From back left: John Steeves and AD session speakers Michael Craggs, Stacy Elliott and Christopher Mathias. Front: Kim Anderson, Session Chair.

“Hypotension and Hypertension in SCI: Short- and Long-Term Implications.”

Growth/Plasticity and Functional Outcome (Chaired by Harry Goshgarian, Wayne State University School of Medicine)

John H. Martin (Columbia University) presented “Bypassing Spinal Injury to Promote Motor Function.” John Houle (Drexel University College of Medicine) presented “Combinatorial Treatment Strategy to Overcome Astroglial Barriers and Promote Functional Axonal Regeneration After Spinal Cord Injury.” Gwendolyn Kartje (Edward Hines Jr. VA Hospital) presented “Recovery and Structural Plasticity After Stroke and Anti-Nogo Antibody Therapy in Adult and Aged Rats.” Blair Calancie (SUNY Upstate Medical University) presented “Neurophysiologic Testing for Predicting Outcome After Acute Spinal Cord Injury: Simple, Well-Tolerated and Accurate...But Is it Useful?”

Convergent Signaling Regulating Axon Growth (Chaired by Marie Filbin, Hunter College)

Zhigang He (Harvard University) presented “Signaling Mechanisms for Myelin Inhibitors.” Toshihide Yamashita (Chiba University) presented “Cell Signaling Cascades Regulating Axon Growth Inhibition.” Britta Eickholt (King’s College) presented “PI 3-kinase Signaling Controlling Axon Growth and Guidance.”

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ISNR 2005



Audience at ISNR session



Yimin Zou, speaker



Inflammation Debate teams square off



Mike Fainzilber, speaker



ISNR poster presentations

ISNR 2005



John Bollinger, PVA representative



ISNR poster presentations



USA Poster Finalist Awardees with Madison



Rao Chadaram and Rod Williams, ISNR support



Britta Eickholt, speaker

SESSIONS, cont.

DEBATE: Increasing Inflammation Is Beneficial for Neural Repair and Outcome (Chaired by Keith Crutcher, University of Cincinnati Medical Center)

Howard Gendelman (University of Nebraska Medical Center), Jonathan Kipnis (University of Nebraska Medical Center) and J. Regino Perez-Polo (University of Texas Medical Branch) presented a position of support for the statement.

Phillip Popovich (The Ohio State University), Lynne Weaver (Robarts Research Institute) and V. Hugh Perry (University of Southampton) presented a position of opposition to the statement.

Intrinsic Mechanisms Underlying the Initiation of Nerve Regeneration (Chaired by Larry Benowitz, Children's Hospital/Harvard Medical School)

Richard Ambron (Columbia University) presented "Intrinsic Kinase Pathways Regulate the Excitability of Regenerating Nociceptive Neurons Following Nerve Trauma: Role in Chronic Pain." Mike Fainzilber (Weizmann Institute of Science) presented "Retrograde Injury Signaling in Lesioned Nerve." Jeffery Twiss (Al duPont Hospital for Children) presented "Regulation of Protein Synthesis in Regenerating Axons." Gennadij Raivich (The Ohio State University) presented "New Roles for Glycosylation in Neuromuscular Development, Regeneration and Disease."

Emerging Topics (Chaired by Michael Sofroniew, University of California—Los Angeles)

Damien Pearse (University of Miami) was selected to present "Gene Transfer of Constitutively-activated MEK or ERK at the Neuronal Soma by Adeno-associated Viral Vectors to Induce Axonal Regrowth across Schwann Cell Bridges Implanted into the Completely Transected Rat Thoracic Cord."

Yimin Zou (University of Chicago) presented "Axon Guidance Cues Along the Rostral-Caudal Axis of the Spinal Cord." Molly Shoichet (University

of Toronto) presented "Neural Tissue Engineering and Drug Delivery Strategies for Spinal Cord Injury Repair."

In addition to the platform presentations, free communications were presented in the form of posters. 107 posters were displayed in two sessions. Abstracts of both speaker and poster presentations were published in the symposium booklet, courtesy of Springer Press under the auspices of the Journal of Neuroimmune Pharmacology, Ed. Howard Gendelman. In addition, the abstracts will be published as a supplement to the June 2006 issue of Neurorehabilitation and Neural Repair, Ed. Bruce Dobkin. The abstracts can also be found on the ISNR web site, along with a listing of all the meeting participants and photos of the event (www.vard.org/neural/neural.htm).



For more information about the International Symposium on Neural Regeneration, please contact:

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