



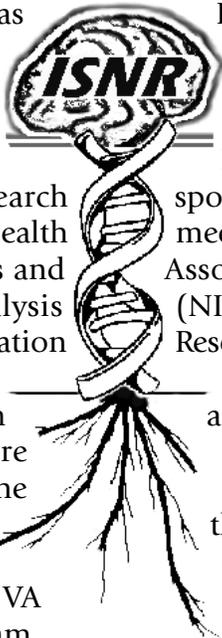
# Regeneration Research NEWSLETTER



## Tenth International Symposium on Neural Regeneration

The Tenth International Symposium on Neural Regeneration (ISNR) was held at the Asilomar Conference Center in Pacific Grove, California from December 10-14, 2003. The meeting was co-sponsored by the US Department of Veterans Affairs (Medical Research Service and the 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), the Christopher Reeve Paralysis Foundation and the United Spinal Association (formerly the Eastern Paralyzed Veterans Association). In addition to these long term sponsors, two generous donations were received from Richard and Gail Siegal and 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. Susan Bryant (University of California, Irvine), Edward Hall (University of Kentucky), Roger Madison (VAMC and Duke University), Ken Muneoka (Tulane University), John Steeves (University of British Columbia) and Michael Sofroniew (University of California, Los Angeles). Guest attendees representing co-sponsoring institutions at the planning committee meeting were Drs. Vivian Beyda (United Spinal Association, formerly EPVA), Naomi Kleitman (NIH-NINDS) and Adam Richman (VA, Medical Research Service).

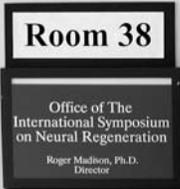
The symposium was initiated with a keynote address by Dr. Mary Bartlett Bunge (University of Miami, FL) entitled "Neuroprotection and regeneration strategies to promote repair of the injured spinal cord". The four featured speakers of the symposium were Drs. Hunter Peckham (VA Medical Center and Case Western Reserve University, Cleveland, OH),

See **SYMPOSIUM** continued on page 4

**OFFICE OF THE INTERNATIONAL SYMPOSIUM ON NEURAL REGENERATION – MAY, 2004**

[www.vard.org/neural/neural.htm](http://www.vard.org/neural/neural.htm)

# The Director's Chair



*Roger Madison*

## Call for Symposium Session Proposals

The program planning committee is meeting on July 23 and 24, 2004, to formulate the program for the Eleventh International Symposium on Neural Regeneration (ISNR) scheduled for December, 2005. We encourage you to submit a proposal for a session topic. Proposals may be received in the ISNR Office as late as July 16, 2004 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).

### **Symposium Session Proposals for the International Symposium on Neural Regeneration (ISNR)**

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 recently been a symposium presenter, as an attempt is made to vary the individuals participating in the program. Lists of speakers and topics in recent symposia are available on the Symposium website ([www.vard.org/neural/neural.htm](http://www.vard.org/neural/neural.htm)).

### **Please submit Session Proposals via email to:**

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## **New Components to the 2003 Symposium**

The Fredrick Seil Trainee Award was established in 2003 to honor the first director and founder of this symposia series for his dedication and long-term commitment to the symposium itself and the students and fellows who attend the meetings. The awards were given to the two best poster presentations chosen by the ISNR planning board members who reviewed the poster presentations. The two winners were chosen out of 82 posters presented at the 10th ISNR, all of which were very deserving of the award. Each winner received a \$250 cash award and their names have been engraved on the Fredrick Seil Trainee Award perpetual plaque. The recipients of the 2003 Fredrick Seil Trainee Award were Yuqin Yin (Larry Benowitz Lab, Children's Hospital/Harvard Medical School, Boston, MA) and Angelo Lepore (Itzhak Fischer Lab, Drexel University, Philadelphia, PA).

In addition to the trainee award, two individuals were selected from the poster abstract submissions for a short platform presentation based on the high degree of interest in the abstract material and were presented during the final session of the conference. The selected presenters were Lowell McPhail (University of British Columbia, Canada - "The astrocytic barrier to regeneration at the dorsal root entry zone is induced by injury") and Bruce Dobkin (University of California, Los Angeles - "Randomized trial of weight-supported treadmill training versus conventional training for rehabilitation after incomplete traumatic spinal cord injury"). The complete abstracts are available online at the symposium website.

Congratulations to each individual selected for the trainee award and platform presentation.

# A Look At Asilomar



Trainee Award Recipients  
(left - right) Yuqin Yin, Fredrick Seil,  
Roger Madison and Angelo Lepore



Poster Session



More at the Poster Session



Susan Bryant (L) and Mary Bunge (R)

## A Glance at Asilomar Wildlife



Questions about the symposium should be sent to the following address:

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Michael Fehlings (University of Toronto, Canada), Ellen Heber-Katz (The Wistar Institute, Philadelphia, PA) and Stephen Strittmatter (Yale University, New Haven, CT). Dr. Peckham's talk was entitled "Neuroprostheses for functional restoration: Current status and future directions". Dr. Fehlings' talk was entitled "Neuroprotection of the injured spinal cord: From bench to clinical application". Dr. Heber-Katz' talk was entitled "A model of mammalian regeneration - The MRL mouse", and Dr. Strittmatter's talk was entitled "The role of Nogo and Nogo receptor in axonal regeneration".

The other platform presentations were given under six topic headings (see below), each with 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](http://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.

**"Neuroprotection and regeneration strategies to promote repair of the injured spinal cord" (Dr. Mary Bartlett Bunge, University of Miami, FL)**



**Mary Bunge**  
Keynote Speaker

Mary Bunge introduced her keynote address by considering interventions that may be necessary to combine to effectively improve outcome after spinal cord injury, including: halt development of numerous deleterious cascades initiated by the initial injury (neuroprotection); curb inflammation; reduce scar formation; neutralize inhibitory

factors; awaken nerve cells to regrow fibers; provide sustenance to nerve cells; promote fiber growth across the injury; guide growth to appropriate areas; and, finally, enable the formation of appropriate connections. Dr. Bunge reviewed work with two models of thoracic spinal cord injury studied in her laboratory: the complete transection model and the contusion model, which leads to cavity formation. Cavity formation also occurs in humans after a contusion injury.

Her group has studied the efficacy of

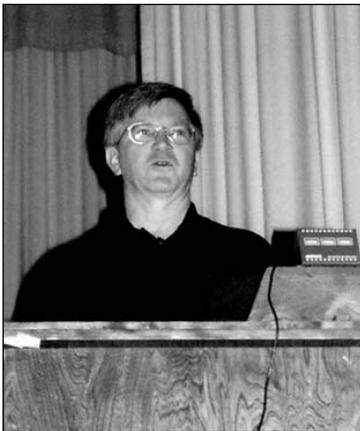
transplanted Schwann cells, these being responsible for regeneration in the peripheral nervous system. In the complete transection model, with a Schwann cell bridge interposed between the stumps, there is regeneration of axons onto the bridge from both stumps. In combination with Schwann cell bridges, three additional strategies improved the regenerative response: the administration of both methylprednisolone and neurotrophins, and the transplantation of olfactory ensheathing glia at the ends of the bridge. The improvements to the regenerative response included regeneration of axons from brainstem neurons into the bridge, more myelinated axons in the bridge, and fiber growth from the bridge into the spinal cord. Provision of a trail of Schwann cells engineered to produce BDNF enabled fibers to cross the transection site and grow the length of the trail. Ensheathing glia at either end of the bridge led to long-distance axonal regeneration, regeneration of raphespinal fibers across the lesion and into the caudal cord, and numerous fibers exiting the Schwann cell bridge.

Transplanting Schwann cells and/or olfactory ensheathing glia into a site of contusion injury has also been investigated. Cavitation was largely abolished, tissue loss was reduced, substantial axonal growth into the graft was seen, axonal sparing and regeneration of spinal and supraspinal axons were significantly improved, and there was a modest improvement in hindlimb function. A recent combination strategy tested in the contusion model has been to elevate cyclic AMP levels in concert with Schwann cell transplantation. Spinal cord cyclic AMP levels plummet after injury. The best outcome was seen with a combination of Schwann cell transplantation, a one-time injection of cyclic AMP into the cord near the transplant, and a two-week administration of a phosphodiesterase inhibitor to prevent the breakdown of cyclic AMP. With this triple strategy, the drop in cyclic AMP levels was prevented, and levels increased above uninjured controls. There was a 230% increase in lateral white matter sparing, 500% increase in the number of myelinated axons in the bridge, raphespinal fiber growth onto the Schwann cell bridge and beyond, and more fibers from brainstem nuclei below the injury/transplant. There also was a striking improvement in gross and fine motor control of the hindlimbs.

Additional combination strategies must be sought to further repair the spinal cord after injury, among them neuroprotection interventions, cellular

bridges or scaffolds, genetically engineered cells to provide additional growth factors, inflammation modification, neutralization of inhibitory molecules, scar formation prevention, and, finally, rehabilitation and training to enable full utilization of the new interventions.

**"Neuroprostheses for Restoration of Motor Function: Current Status and Future Directions" (Dr. P. Hunter Peckham, Case Western Reserve University/Cleveland VA Medical Center, OH)**



**Hunter Peckham**  
Featured Speaker

Major advances have been made over the past decade in use of neuroprostheses for restoration of motor function. Two systems have received FDA approval; one for hand/arm control and a second for providing bladder and bowel management. These advances have been built on the fundamental science of neural excitation and the technologies for implantable stimulation. This presentation overviewed these advancements, and suggested the future directions of research in this area, including areas of convergence of study between fields of endeavor that currently are progressing in parallel.

The advances of fundamental knowledge of neurostimulation include the ability to generate selectively action potentials in nerves for reliable and safe control of muscle activation, and the ability to create unidirectional action potentials and selectively activate regions of the nerve. More recent advances are enabling activation of populations of neurons in the spinal cord. Technologies have advanced to provide implants that function in the body for decades, and include electrodes for reliable and repeatable stimulation, implantable stimulation sources, and implantable sensors for control. Distributed implantable systems that will provide greater flexibility in implementation and performance are currently in development.

The clinical manifestation of these findings is the available systems that have been created and are being developed to restore function. These include many areas of the body for people with spinal cord

injury, including hand grasp, standing and walking, breathing, and bladder and bowel control. The presentation provided examples of both upper and lower extremity neuroprostheses. Upper extremity systems include first generation FDA approved systems for hand control and second generation systems that are currently in clinical trials for restoring full arm control. Lower extremity systems include a system for standing and transfer currently in a clinical trial, and advancement to more complete ambulation systems. Several areas for possible integration of regeneration and neuroprosthetic approaches were also discussed.

**"Neuroprotection of the injured spinal cord: from bench to clinical application" (Dr. Michael G. Fehlings, University of Toronto, Canada)**

The featured talk by Michael Fehlings began by reviewing the pathophysiology of acute spinal cord injury, including the initial mechanical insult which is usually due to a fracture-dislocation of the spine. This initial or primary injury is followed by a series of secondary injury processes which include instability and mechanical compression, ischemia, derangements of ionic homeostasis, glutamatergic excitotoxicity, free radical mediated cell death, inflammation and apoptosis (Sekhon and Fehlings, 2001; Park et al., 2003). Dr. Fehlings reviewed the clinical trials with methylprednisolone and GM-1 ganglioside that have shown the potential for neuroprotection in acute spinal cord injury; however, these therapies are associated with only modest clinical benefit. Thus, more effective therapeutic approaches to target the acute injury are required. Accordingly, Dr. Fehlings critically evaluated new promising neuroprotective approaches and discussed efforts to examine the role and timing of acute surgical decompression (STASCIS trial) (Fehlings et al., 2001). The talk ended with the take-home-message that a key aspect of promoting successful repair and regeneration of the injured spinal cord is the reduction of the impact of the acute injury (Sekhon and Fehlings, 2001; Park et al., 2003). Fehlings MG, Sekhon LH, Tator C (2001) The role and timing of decompression in acute spinal cord injury: what do we know? What should we do? Spine



**Michael Fehlings**  
Featured Speaker

26:S101-110.

Park E, Liu Y, Fehlings MG (2003) Changes in glial cell white matter AMPA receptor expression after spinal cord injury and relationship to apoptotic cell death. *Exp Neurol* 182:35-48.

Sekhon LH, Fehlings MG (2001) Epidemiology, demographics, and pathophysiology of acute spinal cord injury. *Spine* 26:S2-S12.

**"A model of mammalian regeneration: The MRL Mouse" (Dr. Ellen Heber-Katz, The Wistar Institute, Philadelphia, PA)**



**Ellen Heber-Katz**  
*Featured Speaker*

The MRL mouse has been shown to have a unique ability to regenerate complex tissue. This was first shown with the MRL's ability to completely close ear holes within 30 days without scarring and with the complete replacement of cartilage and hair follicles. This is unlike any other mouse strain where the ear hole does not close and scarring occurs. The genetic analysis of this hole closure has revealed a complex genetic trait with at least 20 loci identified so far by multiple laboratories.

Dr. Heber-Katz's laboratory has also found that the heart has the capacity to regenerate in this mouse strain. To show this, they made a cryoinjury to the right ventricle of the heart. Such an injury leads to a process of local cardiomyocyte cell death, replacement by fibroblasts, and finally replacement by BrdU-positive cardiomyocytes. Analysis of the cells involved in this healing using bone marrow chimeras revealed that the cells in the healing area are derived predominantly from the recipient and that the phenotype of healing is recipient-like as well.

Remodeling is a major area of difference in regenerating and nonregenerating tissue. They found that MRL and control ear and heart tissue after injury differ in the inflammatory response as well as the accompanying matrix metalloproteinase (MMP) response. The MRL tissue displays elevated neutrophil infiltrates and these cells express elevated levels of activated MMPs and reduced levels of their inhibitors or TIMPs. This is a major focus of their current research.

Finally, they examined various CNS injuries. In a cortical stab injury model carried out in collabora-

tion with D Hampton and J. Fawcett, they found that the MRL showed significant differences during the first few days after injury compared to a nonhealer control. However, by day 7, the two injuries looked the same. They proposed that the healing differences seen were due to a differential protease and remodeling response which is dampened in the cortex by day 7. This was supported by their finding that the MMP response is in fact elevated both at the RNA and protein levels in the MRL, but that was true only on day 2. By day 7, the control and MRL levels were quite similar.

Thus, in the MRL mouse, regeneration in various tissues is readily seen. In the cortex of the brain, however, though the MRL is able to express the beginnings of a regenerative response, this appears to be quickly changed to a normal nonregenerating phenotype.

**"The Role of Nogo and Nogo Receptor in Axonal Regeneration" (Dr. Stephen M. Strittmatter, Yale University, New Haven, CT)**

Axonal regeneration after traumatic spinal cord injury is minimal. In part, this may be due to myelin-derived inhibitors such as Nogo. Dr. Strittmatter's laboratory has shown that a NEP1-40 peptide blocker of Nogo action at the Nogo-66 receptor (NgR) increases corticospinal (CST) and raphespinal axonal sprouting and functional recovery after spinal cord injury (SCI). This peptide is also effective when delivered systemically up to a week after injury. Similarly, genetic ablation of Nogo-A expression yielded a degree of CST axonal regeneration and functional improvement after SCI. However, the NgR is also a receptor for MAG and OMgp. To block all NgR function, they delivered the extracellular domain of the receptor to mice with SCI by transgenic means and to rats with SCI intrathecally. The degree of fiber sprouting was moderately greater than with the selective NEP1-40 blockade. Overall, several lines of evidence demonstrate a role for NgR in limiting axonal sprouting after SCI



**Stephen Strittmatter**  
*Featured Speaker*

Optic Nerve Regeneration (Chaired by Dr. Kwok-Fai So, University of Hong Kong)

*continued on page 8...*

# A Few of the Session Speakers



**Sarah Dunlop**



**Jane Roskams**



**Matt Ramer**



**Mark Tuszynski**



**George Smith**



**Catherina Becker**



**Vivian Mushahwar**



**David Gardiner**



**Martin Oudega**

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The first speaker in this session was Dr. Ben Barres (Stanford University, CA) who discussed "Amacrine-signaled loss of intrinsic axon growth ability by retinal ganglion cells". Prof. Martin Berry (Centre for Neuroscience, Neural Damage and Repair, King's College, London) followed with "Acute and delayed optic nerve regeneration in the adult rat: sleeping fibres awakened, putative CNS inhibitory signals ignored, de novo scar formation inhibited and established scars dispersed". Prof. Sarah Dunlop (University of Western Australia) presented "Molecular and behavioral correlates of optic nerve regeneration". Dr. Peter Hitchcock (University of Michigan) presented "Persistent and injury-induced neuronal regeneration in the vertebrate retina". Dr. Joseph Rizzo (MIT, Cambridge and VA Medical Center, Boston, MA) presented "Development of a retinal prosthesis to restore vision to blind patients".

#### **Biological and Translational Potential of Olfactory Ensheathing Glial Cells (Chaired by Dr. Almudena Ramon-Cueto, Spanish Council for Scientific Research, Valencia, Spain)**

Dr. Jeffery Kocsis (Yale University, New Haven and VA Medical Center, West Haven, CT) presented "Bone marrow stromal cells (MSCs) as a potential source for neural repair". Dr. Susan Barnett (University of Glasgow, Scotland) presented "The pros and cons of olfactory ensheathing cells (OECs) in CNS repair". Dr. Jane Roskams (University of British Columbia, Canada) presented "Lamina propria-derived olfactory ensheathing cells in spinal cord regeneration". Dr. Martin Oudega (University of Miami, FL) presented "Schwann cells and olfactory ensheathing glia for repair of the injured spinal cord".

#### **Visceral Function and Pain in SCI (Chaired by Dr. Alexander Rabchevsky, University of Kentucky, Lexington, Kentucky)**

Dr. Lynne Weaver (John P. Robarts Research Institute, Ontario, Canada) presented "An early anti-inflammatory strategy markedly reduces autonomic dysreflexia and chronic pain after clip-compression spinal cord injury in rats". Dr. Matt Ramer (University of British Columbia, Canada) presented "Intraspinal sprouting and neuropathic pain following dorsal rhizotomy". Dr. George Smith (University of Kentucky) presented "Growth and guidance factors modulating nociceptive afferent sprouting with in the adult spinal cord". Dr. Vivian Mushahwar

(University of Alberta, Canada) presented "Novel electrical stimulation techniques for restoring limb function".

#### **Regeneration in Complex Systems (Chaired by Dr. Susan Bryant, University of California, Irvine, California)**

Dr. David Gardiner (University of California, Irvine) presented "Vertebrate limb regeneration and the origin of limb stem cells". Dr. Ken Muneoka (Tulane University, New Orleans, Louisiana) presented "Msx genes and BMP signaling in mammalian digit regeneration". Dr. Catherina Becker (University of Hamburg, Germany) presented "Molecular determinants of successful regeneration in the CNS of adult zebrafish".

#### **Molecular Correlates of Nerve Regeneration (Chaired by Dr. Marie Filbin, Hunter College, New York, New York)**

Dr. Melitta Schachner (University of Hamburg, Germany) presented "The neural recognition molecule L1 and functional recovery in mammals". Dr. Wolfram Tetzlaff (University of British Columbia, Canada) presented "Cell body treatment strategies to promote axonal regeneration after acute and chronic spinal cord injury".

#### **Emerging Topics in Regeneration (Chaired by Dr. John Steeves, University of British Columbia, Vancouver, British Columbia, Canada)**

Dr. Malcolm Maden (King's College, London) presented "The induction of neurite regeneration in adult spinal cord using equine infectious anaemia based lentiviral vector". Two special platform presentations were given by Lowell McPhail (University of British Columbia, Canada) and Bruce Dobkin (University of California, Los Angeles).

In addition to the platform presentations, free communications were presented in the form of posters. Eighty-two posters were displayed in two sessions. Abstracts of both speaker and poster presentations were published as a supplement to the Journal of Rehabilitation Research and Development (Volume 40, No. 6, November/December 2003), and are also available on the ISNR web site, along with a listing of all of the meeting participants ([www.vard.org/neural/neural.htm](http://www.vard.org/neural/neural.htm)). ■