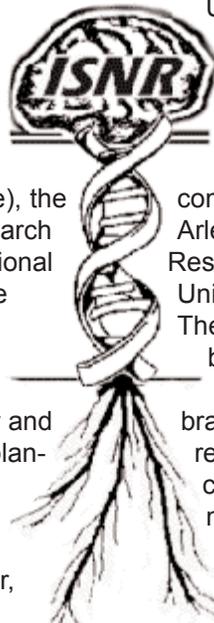




The view across the street from the Asilomar Conference Center

International Experts Lead Discussion Groups at Ninth ISNR Meeting

The Ninth International Symposium on Neural Regeneration (ISNR) was held at the Asilomar Conference Center in Pacific Grove, California from December 12-16, 2001. 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 Eastern Paralyzed Veterans Association. The symposium was organized by Dr. Roger Madison (Symposium Director, VA Medical Center and Duke University, Durham, NC), and the program planning committee included Drs. Susan Bryant (University of California, Irvine), Mary Bartlett Bunge (University of Miami, Florida), Edward Hall (Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan), Roger Madison (VAMC and Duke



University, Durham, NC), Marston Manthorpe (Vical, Inc., San Diego, California), Ken Muneoka (Tulane University, Louisiana), Fredrick Seil (VAMC, Portland, Oregon) and John Steeves (University of British Columbia, Canada). Guest attendees representing co-sponsoring institutions at the planning committee meeting were Drs. Vivian Beyda (EPVA), Arlene Chiu (NIH-NINDS), Michael Cohen (VA, Medical Research Service) and Jeffery Kocsis (VAMC and Yale University, West Haven, Connecticut).

The symposium was initiated with a keynote address by Dr. Marc Tessier-Lavigne (Stanford University, CA) entitled "Molecular studies of axon guidance, branching, and regeneration". Dr. Tessier-Lavigne reviewed recent studies describing the involvement of chemorepellents in shaping axonal growth, using the netrins, semaphorins and Slit proteins and their receptors as examples. Striking examples were given of the ability to modulate the response of

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The Director's Chair



Roger Madison

Call for Symposium Session Proposals

If your favorite topic has not 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 August 2 and 3, 2002, to formulate the program for the Tenth International Symposium on Neural Regeneration (ISNR) scheduled for December, 2003.

Proposals may be received in the ISNR Office as late as July 25, 2002 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).

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

Roger Madison, Ph.D., Director
International Symposium on Neural Regeneration
VA Medical Center (Bldg. 16/Room 38)
508 Fulton Street
Durham, NC 27705 USA

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www.vard.org/neural/neural.htm

Symposium Session Proposals for the International Symposium on Neural Regeneration

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.

The Faces of ISNR



The ISNR Planning Board -- Front row from left: Arlene Chiu, Fritz Seil, Ed Hall, Ken Muneoka, Sue Bryant
Back row from left: John Steeves, Michael Sofroniew, Roger Madison, Michael Cohen, Marston Manthorpe.



Theo Palmer Jack Parent Pasko Rakic Jeffrey Macklis and Anne Calof during roundtable discussion.



Featured Speaker Larry Benowitz.



Cold but scientifically satisfied.

growth cones to chemotropic molecules by modulating cyclic nucleotide levels (a topic that was also highlighted by Dr. Marie Filbin later in the meeting).

The two featured speakers of the symposium were Drs. Paul Letourneau (University of Minnesota) and Larry Benowitz (Harvard Medical School/Children's Hospital, Boston). Dr. Letourneau's talk entitled "Guiding growth cone navigation: stop and go in complex environments" reviewed almost three decades of work examining growth cone guidance. Dr. Benowitz's presentation ("A purine-sensitive switch regulates the axon growth program of CNS neurons") described data demonstrating that several trophic factors that stimulate axonal outgrowth of goldfish retinal ganglion cells converge on a purine-sensitive signaling mechanism that influences both axonal outgrowth and the expression of multiple growth-associated proteins.

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).

Targeted Axonal Growth/Regeneration in the PNS (Chaired by Dr. Ronald Oppenheim, Wake Forest University, NC)

The first speaker in this session was Dr. Wolfram Neiss (University of Cologne, Cologne, Germany) who discussed "The misdirection of reinnervation after peripheral nerve suture and chances of its therapy". Dr. Neiss reviewed anatomical (sequential double-labeling) and electromyographic studies to ascertain the ability of regenerating neurons to reinnervate their original targets. Dr. Neiss noted that although several manipulations (e.g. different surgical techniques, Ca-entry-blockers, etc.)

have been shown to influence overall axon regeneration, none of them has so far been shown to increase functional recovery.

Dr. Roger Madison (VA Medical Center and Duke University, North Carolina) followed with "Preferential motor reinnervation (PMR) and peripheral nervous system regeneration". PMR refers to the proven ability of regenerating motor axons in the rat femoral nerve to preferentially, albeit incompletely, reinnervate a distal terminal nerve branch to muscle vs. skin (cutaneous). Dr. Madison reviewed recent studies that demonstrated the existence of PMR in the non-human primate following median nerve regeneration, as well as gene expression studies aimed at elucidating the potential molecular targets that might be responsible for PMR.

Dr. Michael Laskowski (University of Idaho) presented evidence during his talk, "Reinnervation of muscle: Cues that guide synaptic choices", that a particular subfamily of tyrosine kinases and their cognate receptors (Eph A-ephrin A) is involved in the formation of the neuromuscular map during development and regeneration.

Dr. Christian Krarup's (University Hospital, Copenhagen, Denmark) talk, "The influence of the near-nerve environment on the rate of elongation in the cat", reviewed studies utilizing chronically implanted electrodes to measure the rate of nerve regeneration into normal or freeze/thawed distal nerve stumps. The findings indicated that the cellular environment of the endoneurium is of central importance for regeneration to occur.

Dr. William Snider's (University of North Carolina, Chapel Hill) talk, "Roles of growth factor signaling in axon development and regeneration", described studies utilizing BAX null mice crossed with neurotrophin-deficient mice to assess the role of neurotrophin signaling in regulating axon growth during development.

Dr. Julia Terzis (Eastern Virginia Medical School, Virginia) described clinical nerve repair studies in her talk enti-

tled "Neural regeneration following end-to-side coaptation: A basic science and clinical review". The technique of end-to-side neural coaptation has been used since the 19th century and Dr. Terzis reviewed recent success with the technique for brachial plexus and facial paralysis repairs.

Human Cells for Transplantation (Chaired by Mahendra Rao, University of Utah)

Dr. Stephen Goldman (Cornell University Medical Center, New York) was the first speaker in this session with his presentation of "Isolation and induction of adult neural progenitor cells". He discussed the recent ability to specifically harvest several progenitor cell types from the human CNS and to assess their lineage potential, functional capacity, and engraftment efficacy following transplantation. He found that each adult progenitor phenotype can mature to functional competence *ex vivo*, can successfully integrate upon xenograft, and can be induced *in vivo* by exogenous delivery of cognate neurotrophic cytokines.

Dr. Evan Snyder (Harvard Medical School / Children's Hospital, Massachusetts) followed with "The biology of neural stem cells may make them uniquely suited for neural regenerative processes". He presented data from studies using neural stem cells isolated from human fetal telencephalon and described their ability to migrate along established migratory pathways to disseminated CNS regions, differentiate into multiple developmentally- and regionally-appropriate cell types, and their non-disruptive interspersions with host progenitors.

Dr. Melissa Carpenter (Geron Corporation, California) described "Neural specific differentiation of human embryonic stem cells". She described the evaluation of culture conditions that maintain pluripotency and control differentiation of human ES (hES) cells and the ability to induce differentiation into the neural lineage using several paradigms. The data indicated that hES cells could provide an abundant cell

Continued next page

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In addition to chairing this session, Dr. Rakic presented a multimedia demonstration entitled "Adult neurogenesis: Promises and controversies", and showed exquisite movies of migrating neurons in vivo. Dr. Rakic stressed the need to apply stringent criteria for identification of cell proliferation and their identity, and reviewed the current controversy concerning the generation of new neurons in primate neocortex. Dr. Jeffrey Macklis (Harvard Medical School / Children's Hospital, Boston, Massachusetts) presented evidence for the "Induction of neurogenesis in the neocortex of adult mice". He reviewed prior work demonstrating that in regions of adult mouse cortex undergoing synchronous apoptosis of projection neurons, nearby cells upregulate genes that guide transplanted neuroblasts or precursors to undergo directed migration, differentiation, synaptic integration, and re-formation of long-distance projections.

More recently this work has shown that endogenous precursors can be induced in situ to differentiate into cortical neurons, survive for many months, and form appropriate long-distance connections in the adult mammalian brain. Dr. Anne Calof (University of California, Irvine) presented studies of "Bone morphogenetic proteins (BMPs): Multifunctional regulators of neurogenesis". Using the olfactory epithelium (OE) as a model system she demonstrated that BMPs exert both positive and negative effects on neurogenesis, depending on ligand identity, ligand concentration, and target cell type.

Dr. Jack Parent (University of Michigan) was the last speaker of the session with a talk entitled "Injury-induced neurogenesis in the adult mammalian forebrain subventricular zone (SVZ)". He presented studies on the effects of acute injury on adult rat forebrain SVZ neurogenesis using experimental models of two common neurological disorders, epilepsy and stroke. These results indicated that different forms of diffuse or focal brain injury exert remarkably similar effects on

endogenous neuronal precursors in the adult rat forebrain SVZ. Following the talk by Dr. Parent all of the speakers in this session participated in a lively round-table discussion of the issues involved in this emerging field of neurogenesis in the adult by taking questions from the audience.

Emerging Topics in Regeneration (Chaired by Dr. Oswald Steward, University of California, Irvine)

Because of a last minute cancellation for the first speaker in this session, two attendees were asked to each present a short (5 minute) talk about some recent new exciting data.

Dr. Scott Whittemore (University of Louisville, Kentucky) presented data suggesting a diffuse arrangement of axons within the ventral white matter from multiple descending pathways that subserve the behavior of spontaneous over-ground locomotion in the intact animal that must be kept in mind for spinal cord injury studies in the rat with apparent functional recovery.

Dr. Hans Keirstead (University of California, Irvine) spoke about preliminary findings of a replication of an experiment by Ramon-Cueto using olfactory ensheathing glia grafted to transected rat spinal cord; an experiment that was actually presented at the eighth ISNR meeting prior to publication in *Neuron*. Dr. Keirstead and colleagues replicated the findings of enhanced proprioceptive and tactile placing, as well as improved bladder function, but did not see functional enhancement on the climbing task.

Dr. Marie Filbin was the first scheduled speaker for this session and presented "Overcoming inhibitors of regeneration in myelin". Her laboratory has been instrumental in demonstrating that elevation of cAMP either with db cAMP or with neurotrophins, can overcome inhibitors of regeneration in myelin to encourage regrowth both in vitro and in vivo; a topic that was touched upon by the keynote speaker Dr. Tessier-Lavigne. Dr. Filbin presented new data that one downstream consequence of

this cAMP effect is the up-regulation of Arginase I (Arg I), a key enzyme in polyamine synthesis, and suggested that Arg I and polyamine synthesis represent more specific targets than direct manipulation of cAMP for potential therapeutic intervention to encourage regeneration after spinal cord injury.

Dr. James Fawcett's (Cambridge University Centre for Brain Repair, UK) talk was titled "The glial scar and glial boundaries". He presented evidence that various treatments that remove or modify the amount of chondroitin sulphate proteoglycans (especially neurocan, NG2, versican, brevican and phosphacan) can result in some axon regeneration in brain and spinal cord lesion models.

The last speaker of this session was Dr. Michael Sofroniew (UCLA School of Medicine, California) who presented "Astroglial cell roles in protection, repair, and neurogenesis". Dr. Sofroniew is utilizing a transgenic mouse line that allows the conditionally regulated ablation of reactive astroglia in the CNS and PNS of adult or developing mice. His results show that these cells exert important neuroprotective and anti-inflammatory functions.

In addition to the platform presentations, free communications were presented in the form of posters. Fifty-one 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 38, No. 6, November/December 2001 Supplement), 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).

ISNR NEWSLETTER PRODUCTION TEAM

ISNR Director.....Roger Madison
Administrative Asst.....Frances Stuart
DesignArvie Wrang

Asilomar After Hours



Ian Wishaw Bryan Kolb and Seth Finklestein agree with the night's wine choice.



Posters & drinks.



Lisa McKerracher Christian Krarup and Wolfram Neiss discussing the days science.



Os Steward and Sasha



Rod Williams, Fritz Seil and Roger Madison share a toast to Asilomar

source for neural progenitor cells and mature neurons for therapeutic and drug research and development uses.

Dr. Ian Duncan (University of Wisconsin) discussed "Myelinating cells for transplantation and myelin repair:

Comparative aspects of human versus animal cells". He reviewed studies showing that growth factors and mitogens for human oligodendrocyte precursors (OPs) appear different from those that have been known for animal OPs and highlighted some of the problems involved in trying to produce such human OPs in significant numbers for potential studies of human myelin repair.

Neuron-Glia Interactions and Synaptic Plasticity (Chaired by Dr. Fredrick Seil, VA Medical Center, Portland, Oregon)

Dr. Seil chaired this session in the absence of Dr. Platon Kostyuk of the Bogomoletz Institute of Physiology, Kiev, Ukraine) and also gave an overview of the field, drawing on several decades of work from his laboratory.

Dr. Ian Wishaw (University of Lethbridge, Canada) continued the session with his talk "Modification of skilled movement: Fixed circuits versus plastic changes". Dr. Wishaw reviewed studies demonstrating that neuron-glia changes underlying normal plasticity and compensatory process of skilled movements are widespread within motor circuits and in other circuits that influence the motor system. Dr. Bryan Kolb (also from the University of Lethbridge, Canada) followed with his talk "Neurotrophic factors, synaptic plasticity, and recovery from cortical injury". He presented data that showed that following cortical injury a combination of treatments, such as the infusion of Fibroblast Growth Factor-2 when animals are receiving intense training (i.e., therapy), appears to be more effective in stimulating functional recovery than either treatment alone, and furthermore that the timing of the administration of neurotrophic factors may either enhance or retard recovery.

Dr. Bruce Ransom's (University of Washington School of Medicine, Seattle,

Washington) presentation was entitled "Glial modulation of neural excitability mediated by extracellular pH". He reviewed data supporting the hypothesis that there exists a negative feedback loop whereby active neurons signal to nearby astrocytes the extent of their activity, in the form of graded changes in $[K^+]_o$, and astrocytes respond by producing graded degrees of extracellular acidification to dampen neuronal excitability. This feedback system can thus adjust local brain excitability in relationship to ongoing activity.

Dr. Harald Sontheimer (University of Alabama, Birmingham, Alabama) presented "Glial regulation of perisynaptic glutamate in health and disease". He demonstrated that the termination of postsynaptic currents requires removal of glutamate via glial transporters, and that cortical or hippocampal lesions downregulate the expression of glutamate transporters which is in turn correlated with the proliferation of glial cells. This sequence of events may contribute to increases in extracellular glutamate and possibly to excitotoxic neural injury.

Dr. Harry Goshgarian (Wayne State University, Michigan) was the final speaker of this session with his talk "Activity-dependant plasticity in rat phrenic nucleus after reversible hemispinalization of cervical spinal cord by a cooling device". He presented studies to differentiate between "injury-induced" and "activity-dependent" plasticity in the phrenic nucleus by utilizing a cooling device that allows reversible block of the inspiratory drive to phrenic motoneurons without injury to the spinal cord at the C2 level. He concluded that the induced changes are activity-dependent and are caused by interruption of the descending respiratory drive to the phrenic nucleus.

Signaling Pathways in Neural Plasticity (Chaired by Dr. Joseph Neary, VA Medical Center and University of Miami, Florida)

Dr. Joseph Avruch (Harvard Medical School, Massachusetts) began the session with his talk "Signal transduction through the Ras GTPase". He discussed recent work with NORE1, a

member of a small gene family that includes the tumor suppressor RASSF1A, and which is a noncatalytic protein recruited by Ras-GTP. These studies highlighted a new Ras regulated signaling pathway that controls cell survival in the presence of constitutively active Ras.

Dr. Bruce Gold (Oregon Health Sciences University, Portland, Oregon) presented "FKBP-52/Hsp-90 steroid receptor chaperones and ERK signaling in the regulation of nerve regeneration". He described work which grew out of the observation that the immunosuppressant drug FK506 dose-dependently accelerates functional recovery by increasing the rate of nerve regeneration following a peripheral nerve injury, using a mechanism that is distinct from that underlying immunosuppression which is mediated by binding to the immunophilin FK506-binding protein-12 (FKBP-12) and subsequent calcineurin inhibition. This data suggests that orally active non-FKBP-12 neuroimmunophilin ligands may be useful for the treatment of human neurological disorders without any potential side effects resulting from FKBP-12 binding (such as calcium regulation and cardiomyopathy).

Dr. Lisa McKerracher (University of Montreal, Canada) reported on "Overcoming growth inhibition in the CNS: Use of Rho antagonists". She used the C3 toxin from *C. botulinum* to inactivate Rho by application to crushed rat optic nerves and demonstrated that retinal ganglion cells axons were able to cross the lesion to extend in the distal optic nerve. Similar studies are ongoing in models of rat spinal cord injury.

Dr. Seth Finklestein's (ViaCell Neuroscience, Worcester, Massachusetts) talk was entitled "The role of growth factors in repair and recovery from brain injury and stroke", and he reviewed studies of bFGF administration alone, or in combination with neural and umbilical cord blood stem cells, in animal models of stroke.

Neurogenesis in the Adult (Chaired by Dr. Pasko Rakic, Yale University, Connecticut)

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Questionnaire Results from 2001

International Symposium on Neural Regeneration

Thank you to all who responded to the questionnaire that was handed out at the recent ISNR meeting at the Asilomar Conference Center. About a third of the 185 registered participants filled out a questionnaire. Overall, the comments were very positive. Below is a synopsis of the results.

Did the symposium meet your expectations?

Very Much	79%
Somewhat	33%
A Little	2%

Top 3 preferred months to hold the conference

1st choice -	December
2nd choice -	May
3rd choice -	April

Scientific quality of presentations:

Excellent	74%
Good	26%
Fair	4%

Asilomar Conference Center:

	Excellent	Good	OK	Poor	Very Poor
Conf. Rooms:	7%	54%	24%	4%	6%
Lodging:	17%	15%	9%	4%	4%
Food:	19%	41%	12%	9%	4%

Quantity of presentations:

Just right	78%
Too few	4%
Too many	21%

Move the location of the ISNR from Asilomar?

No	89%
Maybe	1%
Yes	9%

Preferred time of sessions:

Sessions in the evening with afternoons free	74%
Sessions in the afternoons with evenings free	13%

Comments:

Several of the written comments focused on the temperature of the conference room and lodging rooms (we agree it was a bit cold); others were adamant about maintaining the Asilomar location (you win - Asilomar it is!); others were concerned about the small name tags (we will make them larger next year)...some comments focused on the schedule of speakers and the length of talks. Of course, there were many, many helpful suggestions. We will take all the comments into consideration and if it isn't mentioned here that doesn't mean we didn't read it. See everyone in 2003 back at Asilomar.

Likely to attend in the future?

Very Likely	79%
Somewhat Likely	21%