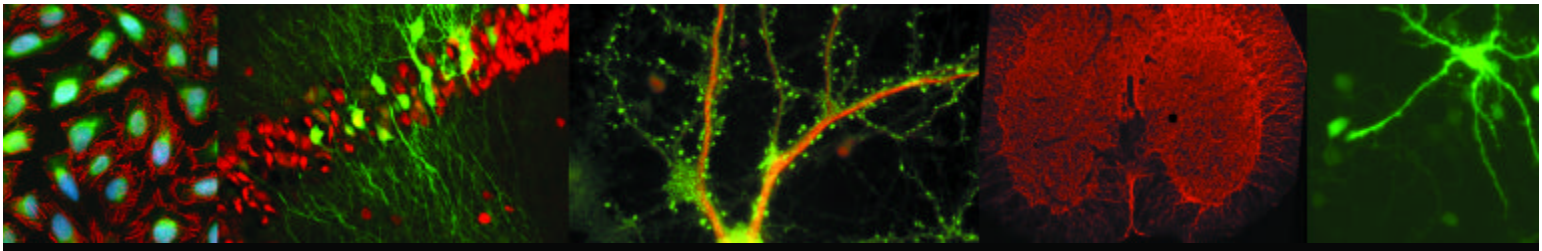

Molecular Approaches to Neuronal Regeneration: Opportunities in Neurodegenerative Diseases

Aula Magna
Oratorio San Filippo Neri
Bologna, Italy
October 27th 2006

ASSOCIAZIONE ITALIANA SCLEROSI MULTIPLA

Wyeth Research

ALMA MATER STUDIORUM UNIVERSITÀ DI BOLOGNA

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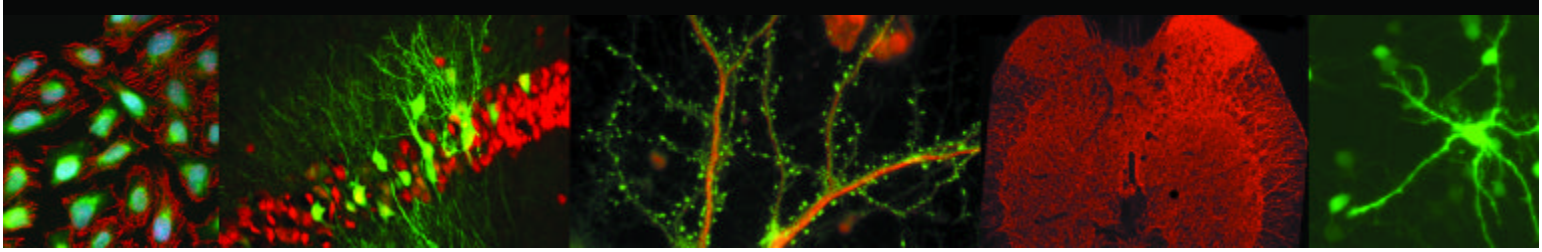
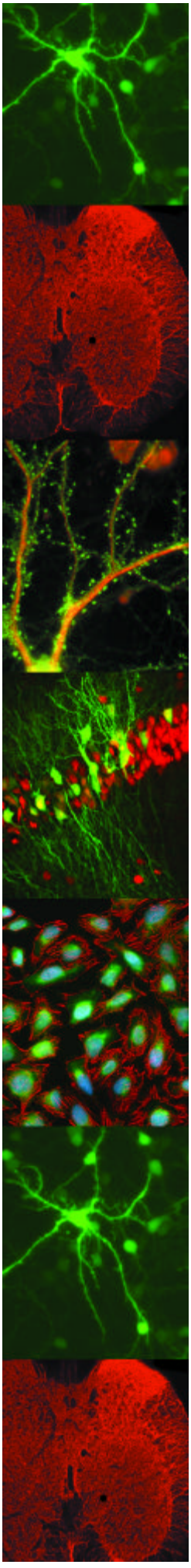




Introduction

The University of Bologna was probably the first University in the western world. Its history is one of great thinkers in science and the humanities, making it an indispensable point of reference in the panorama of European culture. Therefore it is only appropriate that Bologna play host to this meeting "Molecular Approaches to Neuronal Regeneration: Opportunities in Neurodegenerative Diseases".

Neurodegenerative diseases represent some of today's most devastating diseases afflicting man. With an aging population, thanks to improved medicine and healthcare, the incidence of diseases such as Alzheimer's disease, multiple sclerosis, Parkinson's disease and other neurodegenerative disorders is increasing, and is taking a significant toll on patients, their families and caregivers, healthcare providers and worldwide economies.

Multiple Sclerosis (MS) alone affects about 2.5 million people worldwide, with approximately 200 people diagnosed weekly in the US alone. The typical age for the onset of the disease is between 20 and 50. MS is not considered a fatal disease, since the vast majority of patients live to a normal life span. However, MS does result is a significant impact to the quality of life to patients as they experience increasing physical and mental limitations. Few therapies exist which modify the progression of the disease. While these drugs lessen the severity and frequency of MS attacks and reduce the accumulation of lesions, none significantly address the underlying disease pathology, are able to prevent further attacks, or are capable of reversing the damage to myelin.

This meeting brings together key thought leaders from the field of neurodegeneration research to share their latest findings and to highlight therapeutic opportunities that may reduce or even reverse the devastating effects of neurodegenerative diseases.

We hope you find this a stimulating and enjoyable meeting.

Regards,

The Organizing Committee

Dr. Kelly Charles
Prof. Pat Doherty
Prof. Gino Toffano
Prof. Frank Walsh

Agenda

09:00 - 09:30 **Welcoming Address**
Pier Ugo Calzolari (Chancellor, Alma Mater Studiorum-University of Bologna)
Giorgio Cantelli Forti (Alma Mater Studiorum-University of Bologna)
Sergio Dompé (President Farmindustria Italy)

Session 1: **Molecular Correlates of Neuronal Regeneration**
Chairpersons: Ciaran Regan (Dublin, Ireland) and Tullio Pozzan (Padova, Italy)

09:30 - 10:00 Neurofascins are Required to Establish Axonal Domains for Saltatory Conduction in the PNS
Peter Brophy (Edinburgh, Scotland)

10:00 - 10:30 Early Neuronal and Glial Fate Restriction of Embryonic Neural Stem Cells
Boris Zalc (Paris, France)

10:30-11:00 Coffee Break

11:00 - 11:30 Small Molecules Promoting Neuronal Survival and Axonal Growth
Menelas Pangalos (Princeton, USA)

11:30 - 12:00 Novel Agonists for Promoting Repair Mechanisms
Patrick Doherty (London, UK)

12:00 - 12:30 New Bioactive Molecules From Natural Sources in Neuroprotection
Patrizia Hrelia (Bologna, Italy)

12:30 - 14:00 Working Lunch

Session 2: **Clinical and Therapeutic Approaches**
Chairpersons: Giancarlo Comi (Milano, Italy) and Lynn Rutkowski (Collegeville, USA)

14:00 - 14:30 Progression in Multiple Sclerosis
Alastair Compston (Cambridge, UK)

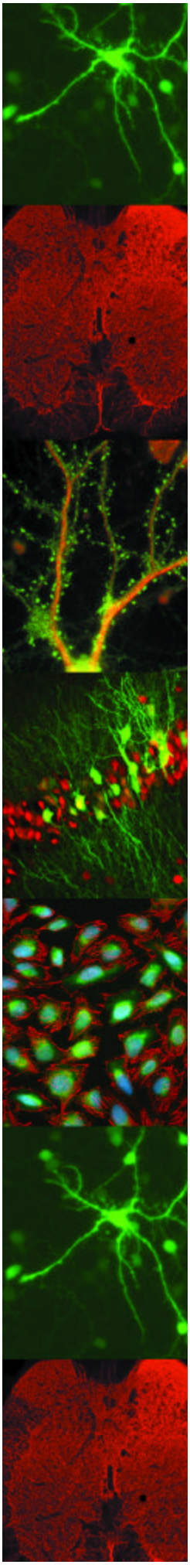
14:30 - 15:00 Neural Stem Cell Systems for Studying Signalling Mechanisms and Modelling Neurological Diseases In Vitro
Luciano Conti (Cambridge, USA)

15:00 - 15:30 Coffee Break

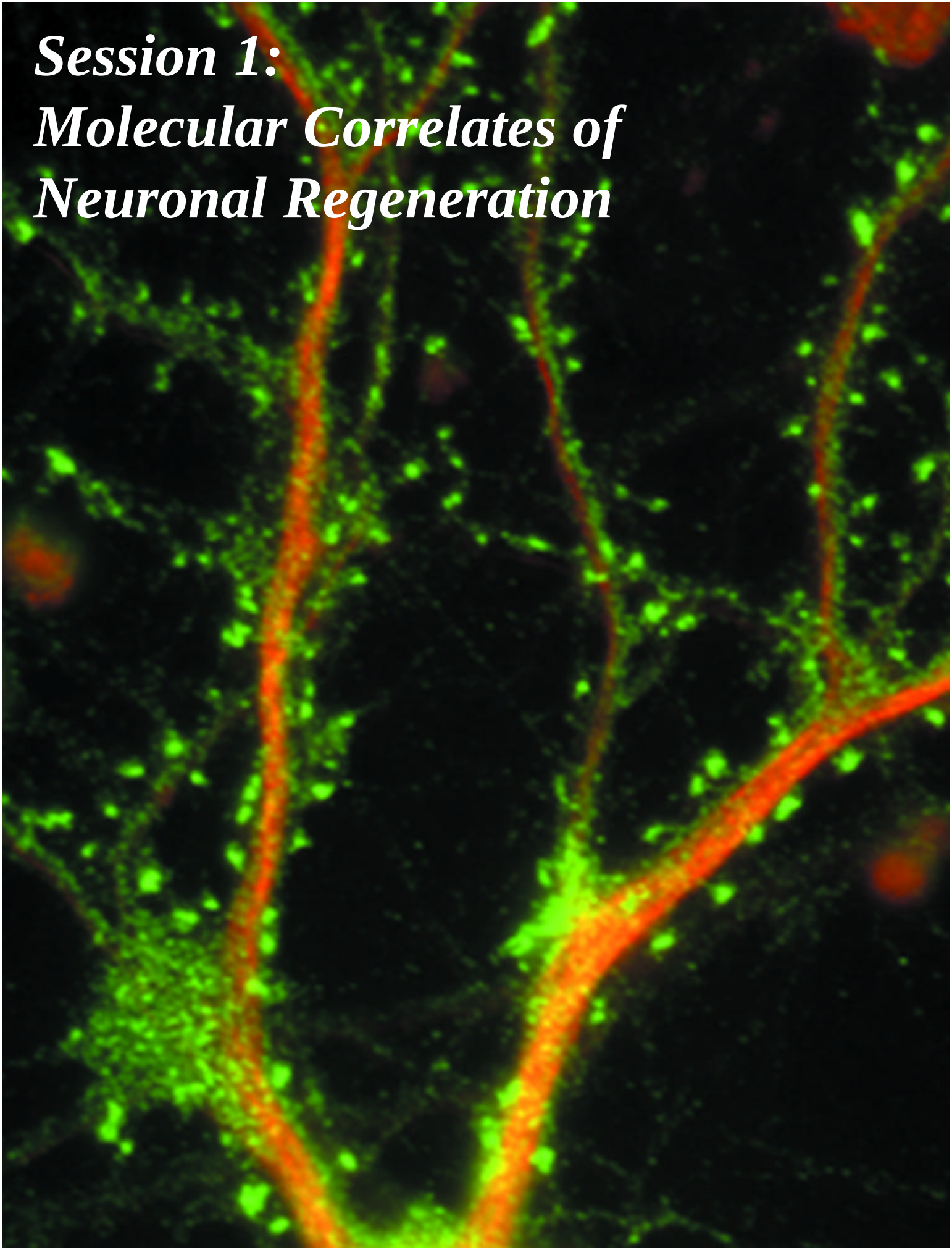
15:30 - 16:00 Studying Neural Stem Cells in the Embryonic and Adult CNS by Cre-Lox Transgenesis
Bill Richardson (Milan, Italy)

16:00 - 16:30 New Therapeutic Perspectives in Multiple Sclerosis
Giancarlo Comi (Milano, Italy)

16:30 - 17:00 Concluding Remarks
Giancarlo Comi (Milano, Italy)
Frank Walsh (Collegeville, USA)



Session 1: Molecular Correlates of Neuronal Regeneration

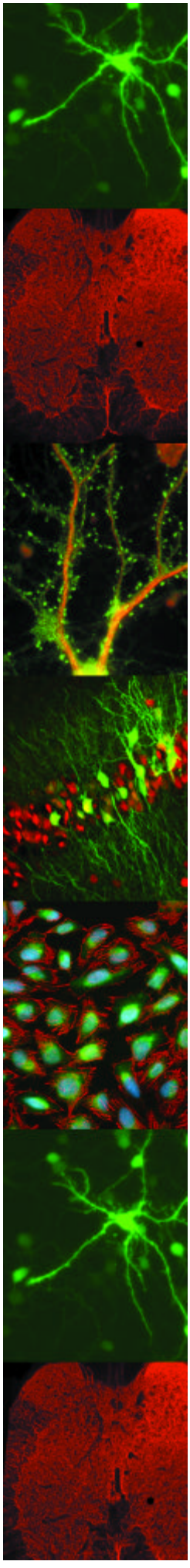


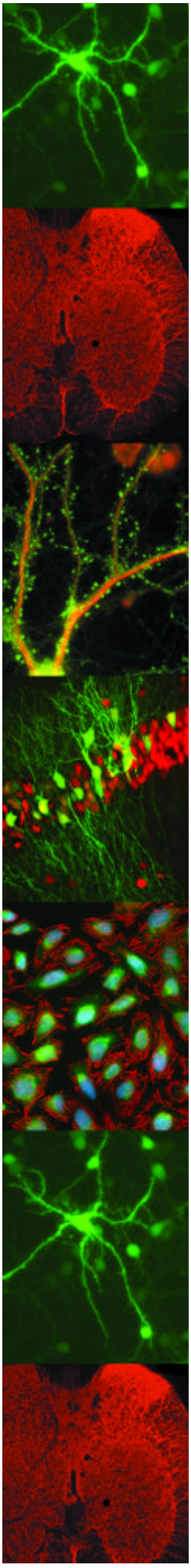
Neurofascins are Required to Establish Axonal Domains for Saltatory Conduction in the PNS

Peter Brophy (Edinburgh, Scotland)

Abstract:
Voltage-gated sodium channels are concentrated in myelinated nerves at the nodes of Ranvier flanked by paranodal axoglial junctions. Establishment of these essential nodal and paranodal domains is determined by myelin-forming glia but the mechanisms are not clear. Here we show that two isoforms of Neurofascin, Nfasc155 in glia and Nfasc186 in neurons, are required for the assembly of these specialized domains. In Neurofascin-null mice neither paranodal adhesion junctions nor nodal complexes are formed. Transgenic expression of Nfasc155 in the myelinating glia of Nfasc-/- nerves rescues the axoglial adhesion complex by recruiting the axonal proteins Caspr and Contactin to the paranodes. However, in the absence of Nfasc186, sodium channels remain diffusely distributed along the axon. Our study shows that the two major Neurofascins play essential roles in assembling the nodal and paranodal domains of myelinated axons; therefore they are essential for the transition to saltatory conduction in developing vertebrate nerves.

Biography:
Peter Brophy received his BSc from London University and PhD from Guy's Hospital Medical School. He has been at Edinburgh since 1995 and Director of the Centre for Neuroscience Research since 2002. Peter has served on the research panels of a variety of bodies, including Action Research, the MS Society and the Medical Research Council, and he is currently a member of the Neurosciences and Mental Health Panel at the Wellcome Trust. This work is currently supported by programme grants from the Wellcome Trust and the Medical Research Council, together with a project grant from the MS Society. Peter was recently elected to Chair of the international Gordon Conference on Myelin for 2008.





Early Neuronal and Glial Fate Restriction of Embryonic Neural Stem Cells

Boris Zalc (Paris, France)

Abstract:
Since the pioneer work by Wilhem His published in 1889, there has been a debate regarding the question of how neurons and glial cells are generated during the development of the central nervous system. Over time, two alternate models have been proposed: (1) neuroepithelial cells are capable of giving rise to neurons first and to glial cells at a later stage ("switching model") or (2) they are committed to generate either neurons or glia ("segregating model"). Using the developing diencephalon as a model and by selecting a subpopulation of ventricular cells, we show both in vitro and in vivo that ventricular cells generated at different time points fall into two distinct categories. Early, while at the neuroepithelial cell stage, ventricular cells give rise to neurons. Later in development, when ventricular cells have acquired radial glia characteristics, they give rise to glia. Combining in vitro clonal analysis and in vivo inducible Cre/loxP fate mapping, we demonstrate that the latter are not the progeny of the former. This work provides therefore for the first time clear evidence in favor of the segregating model and offers a solution to this biological conundrum.

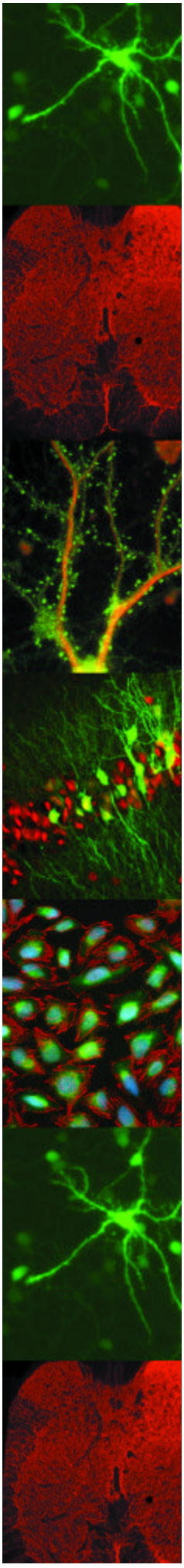
Biography:
Dr. Bernard Zalc obtained his MD from Pitié-Salpêtrière Medical School in Paris, and his PhD from University Pierre et Marie Curie, Paris. After graduating, Dr. Zalc was a post-doc with Prof. Norman Radin at University of Michigan, USA and then with Dr. P. Dupouey at the Institute Pasteur in Paris. Then Dr. Zalc received a position in Dr. Nicole Baumann's lab at INSERM. Since 1998, Dr. Zalc has been Director of the INSERM Unit "Biologie des Interactions Neurones/Glie", which is located in Paris at the Hôpital de la Salpêtrière. Since 2006, Dr. Zalc has also been Director of the Institut Fédératif de Recherche en Neurosciences de la Salpêtrière. Dr. Zalc's scientific interest is in the biology of myelin forming cells and related diseases such as Multiple Sclerosis. For the past few years, he has concentrated his effort on the understanding of the origin during development of the oligodendrocyte, the myelin-forming cell in the central nervous system. Major findings from Dr. Zalc have been to establish the map of the restricted site of emergence of oligodendrocytes along the neural tube and to demonstrate that oligodendrocytes are generated by different sources of progenitors. His present work is devoted to the phylogenic and ontogenetic origin of myelin forming cells. Dr. Zalc's ongoing research with Dr Jean Leon Thomas is aimed at deciphering the molecular mechanisms that underlies the specification of a multipotent stem cell into an oligodendrocyte and on the molecules that control the migration of oligodendrocyte precursors. Another project, in collaboration with Dr. Catherine Lubetzki, is related to the undertanding of the processes controling myelin deposition, with a special focus for remyelination.

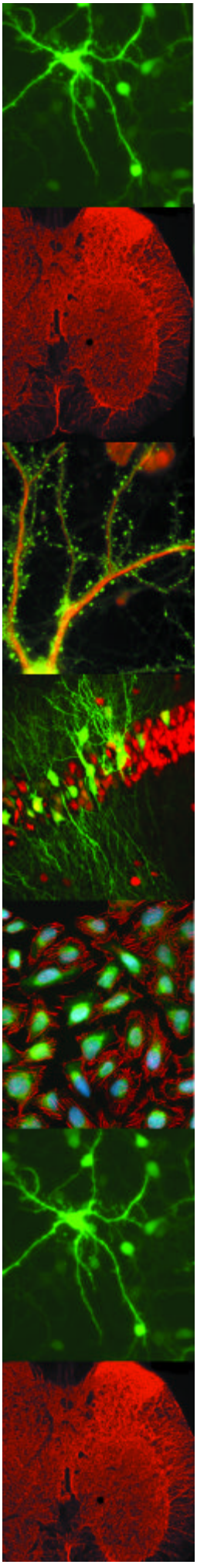
Small Molecules Promoting Neuronal Survival and Axonal Growth

Menelas Pangalos (Princeton, USA)

Abstract:
Diseases of the central nervous system (CNS) make up some of the most devastating and poorly treated illnesses in the world. The development of new and improved therapies for these illnesses has the potential to provide patients and their families with great improvements in overall quality of life as well as impact the future economic viability of healthcare systems in the Western world. Given these issues, the successful discovery and development of novel therapeutics for the treatment of CNS disorders is critically important from both a patient and health payer perspective. Current strategies for the treatment of neurological disorders such as Alzheimer's disease, Parkinson's disease, stroke and multiple sclerosis are generally sparse or non-existent. The handful of existing therapies for these diseases are founded on replenishment of diminishing neurotransmitter systems such as acetylcholine or dopamine and are poorly effective at best, losing their beneficial effects with time. This presentation will highlight a number of innovative 'first-in-class' approaches being pursued within the Wyeth Neuroscience group with the aim of stimulating neuronal regeneration in the damaged CNS. We are pursuing small molecule-based, as well as peptide and protein- based therapeutics. Our ultimate goal is to develop an array of innovative medicines that will modify disease pathophysiology by slowing, halting or perhaps even reversing the neurodegenerative disease process. Such approaches will hopefully result in a paradigm shift in treatment options for patients suffering from these devastating and deadly diseases.

Biography:
Menelas Pangalos is Vice President of Neuroscience Research and co-chair of the Neuroscience Leadership team at Wyeth. He previously served as Group Director and Head of Neurodegenerative Research at GlaxoSmithKline in Harlow, UK. Dr. Pangalos oversees the neuroscience pre-clinical portfolio focusing on psychiatric and neurological diseases of high unmet medical need. In particular his group is working on developing novel therapies to treat Depression, Anxiety, Schizophrenia, Bipolar Disorder, Alzheimer's disease, Stroke, Parkinson's disease and chronic inflammatory and neuropathic pain. Dr. Pangalos is an Adjunct Professor of Neuroscience at the University of Pennsylvania and a Visiting Professor at King's College London. He is on the editorial boards of Molecular and Cellular Neuroscience, Neuropharmacology and The Scientific World and on scientific advisory boards for the Wolfson Centre for Age Related Diseases (King's College London University), Rider University and the New Jersey Association for Mental Illness. He has previously served on the BBSRC Molecular and Cell Biology council and is a member of the American Society for Neuroscience, British Pharmacological Society and an Associate of the Royal College of Science. Dr. Pangalos has edited the book "Understanding G-protein coupled receptors in the CNS", as well as a number of journal issues focused on drug discovery in the CNS. He has published over 75 peer-reviewed articles in journals such as PNAS, Journal of Neuroscience, Nature Neuroscience, The Lancet, British Journal of Psychiatry and Journal of Biological Chemistry.





Novel Agonists for Promoting Repair Mechanisms

Patrick Doherty (London, UK)

Abstract:
The past decade or so has been marked by a clearer understanding of why repair mechanisms might fail in the damaged CNS; in brief, a combination of a lack of growth promoting factors and the presence of inhibitory molecules seems to conspire to create a non-permissive environment for regeneration. Yet, little is known concerning if, and how, growth promoting and inhibitory molecules interact. In a permissive environment BDNF promotes growth by activating the TrkB receptor. However, in the presence of myelin, the ability of BDNF to promote growth is compromised. This is due, at least in culture, to the ability of myelin inhibitors (MAG, Nogo-66, Omgp) to activate an inhibitory receptor complex in neurons that contains the NgR1, LINGO-1, GT1b and the low affinity p75 neurotrophin receptor (p75NTR). The p75NTR appears to be the signalling component for the inhibitory receptor complex, and this is intriguing given that this is also a receptor for BDNF. On the basis of this observation, we postulated that the binding of BDNF to the p75NTR might compromise the ability of BDNF to stimulate neurite outgrowth in an inhibitory environment. To test this we have designed a "mini-neurotrophin" called BAG to activate TrkB in the absence of p75NTR binding. We find that BAG is as effective as the natural TrkB ligands (BDNF and NT-4) at promoting neurite outgrowth from cerebellar neurons. Furthermore, the neurite outgrowth responses stimulated by BDNF and BAG are inhibited by a common set of reagents, including the Trk receptor inhibitor K252a, as well as protein kinase A and phosphoinositide 3-kinase inhibitors. However, in contrast to BDNF, BAG promotes growth in the presence of a myelin inhibitor, or when antibodies directly activate the p75NTR inhibitory pathway. As cerebellar neurons do not express TrkA, NGF can be used to compete out the BDNF/ p75NTR interaction in the absence of NGF/Trk signalling. Interestingly, BDNF acquires the ability to promote neurite out-growth in the presence of a myelin inhibitor when NGF is present at a ten-fold molar excess. The data suggest that in an inhibitory environment, the BDNF/ p75NTR interaction compromises regeneration. Agents that activate Trk receptors in the absence of p75NTR binding, or agents that inhibit the BDNF/p75NTR interaction, might therefore be useful therapeutic candidates.

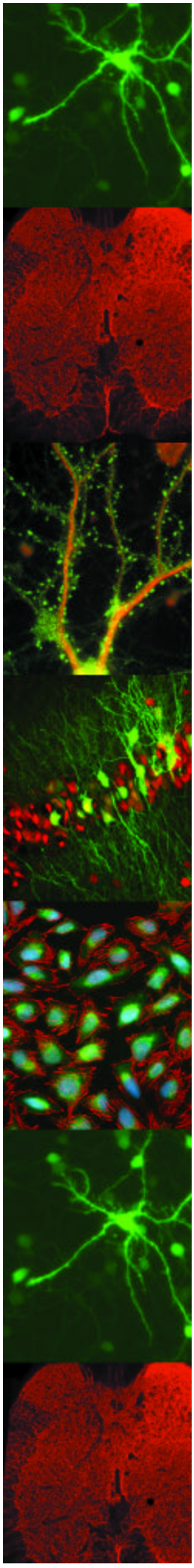
Biography:
Pat Doherty works on the signalling pathways that control axonal growth and guidance. Recent achievements include the identification of cross talk between receptor tyrosine kinases and the endocannabinoid system, and cloning of the sn-1 specific diacyglycerol lipases, the enzymes that are responsible for the synthesis of the major endocannabinoid in the brain. Doherty is also working on the design of small molecule agonists for the TrkB receptor and utilising these to overcome the inhibitory activity of myelin. Doherty is currently the Director of the Wolfson Centre for Age-Related Diseases at KCL.

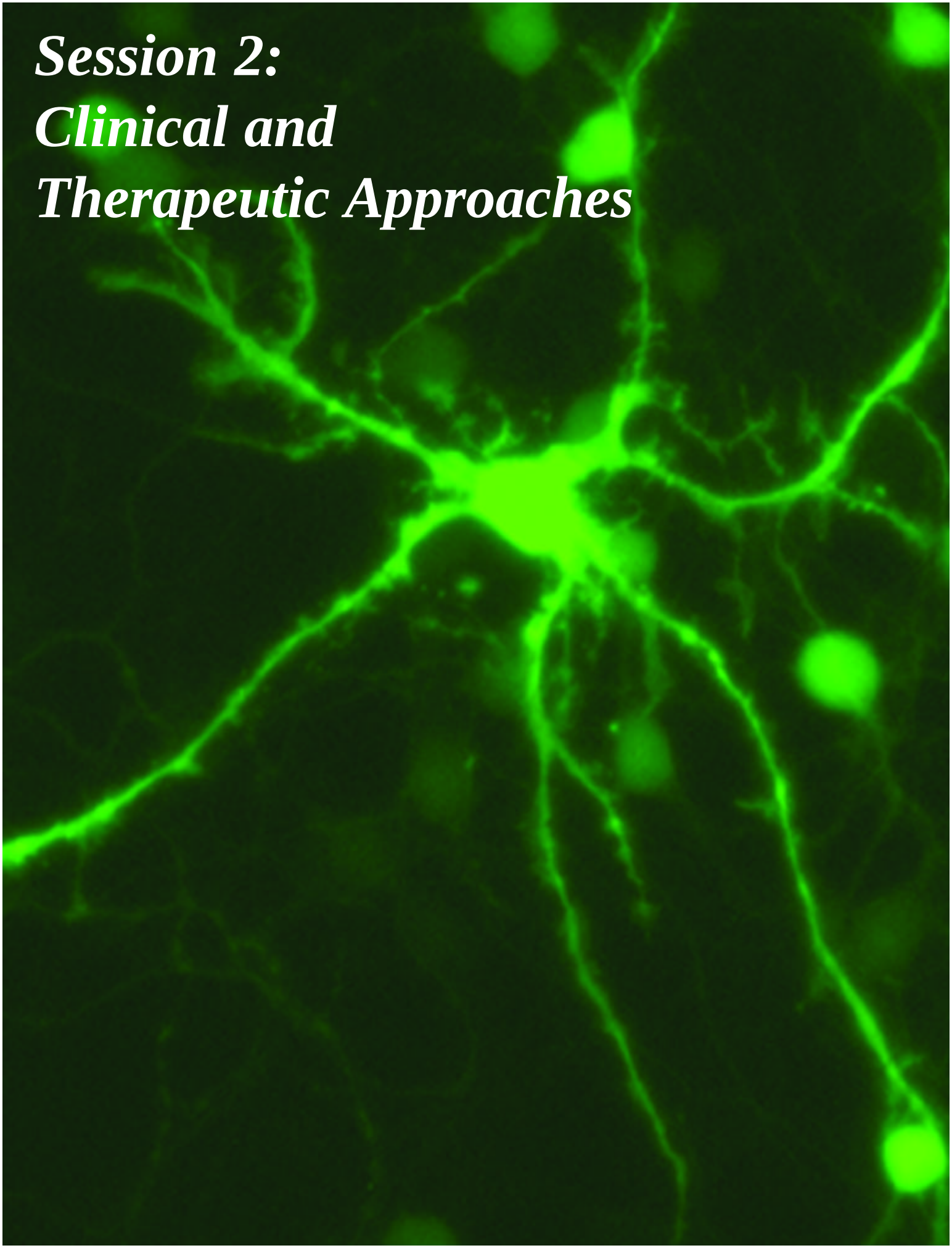
New Bioactive Molecules from Natural Sources in Neuroprotection

Patrizia Hrelia (Bologna, Italy)

Abstract:
The increasingly refined identification of molecular targets in pathophysiological cascades of Parkinson's (PD), Alzheimer's (AD) and other neurodegenerative diseases is rapidly leading to the definition of pharmacologically tractable therapeutic targets, the manipulation of which promises to interfere in basic disease processes or produce substantial neuroprotection. From the studies of drug discovery, natural sources can provide candidate compounds with potential therapeutic effects in neurodegenerative diseases. Isothiocyanates (ITCs), present in abundance in cruciferous vegetables, are known as cancer chemopreventive agents and strong inducers of phase II detoxification enzymes. Among the various ITCs, sulforaphane (SUL) shows interesting ability to decrease aging-related CNS inflammation in rats. In this context, we investigated the mechanistic basis of the neuroprotective potential of SUL in a neuronal cell model of PD. In particular, we demonstrated that SUL decreases the oxidative damage and neuronal death induced by 6-hydroxydopamine (6-OHDA), a specific neurotoxin. In parallel, we found a potent indirect antioxidant activity of SUL on neuronal cells that could be ascribed to increased GSH levels and phase II enzyme activities, such as glutathione-S-transferase, glutathione reductase and NADPH-quinone. However, our results also indicated that in addition to the indirect antioxidant activity, other mechanisms such as modulation of mitochondrial function, caspase activity, and neuronal survival pathways, contribute significantly to SUL neuroprotective effects. These preliminary results should encourage further research in animal models to explore the profile of SUL and other isothiocyanates as novel neuroprotective compounds.

Biography:
Dr. Hrelia received her BS in Medicinal Chemistry and Ph.D. in Cell Biology (1986) from the University of Bologna. She was a visiting Assistant Professor and Adjunct Faculty (until present) at the University of Texas Medical Branch,Galveston (TX) USA. Dr. Hrelia began her current position as a Adjunct Faculty (1988-1990) and then as Assistant Professor (1990-1997) at the University of Bologna. From 1997-2001 she was Associate Professor of Pharmacolgy and Toxicology. She is currently Professor of Toxicology in the Faculty of Pharmacy (since 2001) and Director of the Postgraduate School of Toxicology (since 2003). Her contribution to the understanding of the mechanism of damage at different end-points provided new insight into the potential hazard from exposure to mutagenic/carcinogenic drugs and environmental pollutants. A current research interest is exploring the molecular interactions of natural phytochemicals with human cells to identify new chemopreventive agents for cancer therapy and neurodegenerative diseases. International collaborative studies were launched in 1996 to determine association with cancer, ageing and selected genetic syndromes. She has authored more than 120 articles in peer-reviewed journals and book chapters. She has served on several Scientific Advisory Boards. At the national level, she served as councillor of the Italian Society of Toxicology and is the editor of the society newsletters. She is a registered Italian and European Toxicologist.





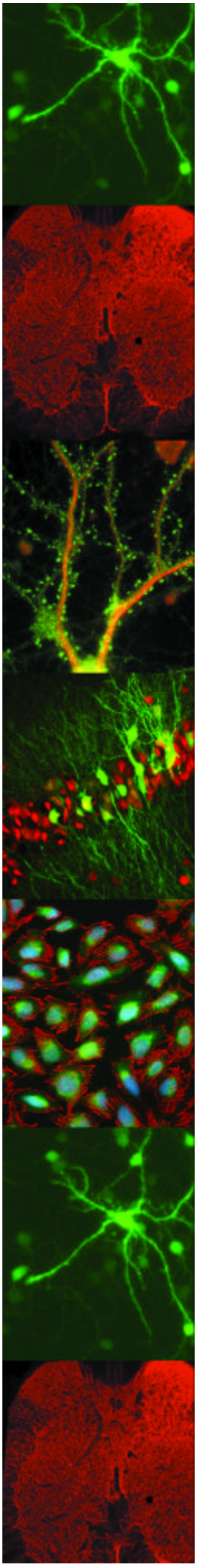
Session 2: Clinical and Therapeutic Approaches

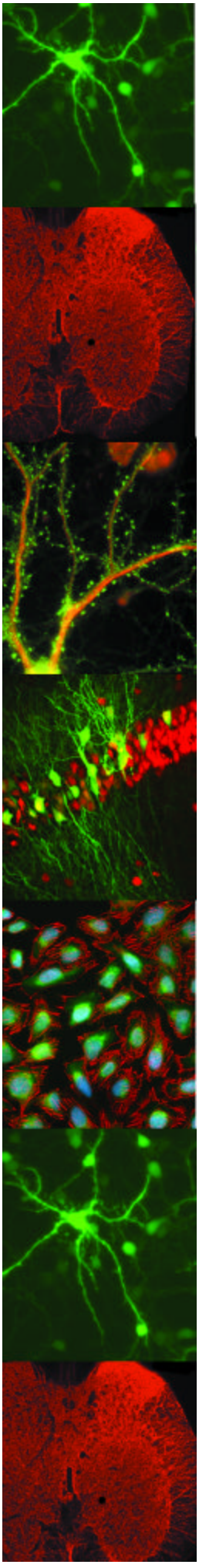
Progression in Multiple Sclerosis

Alastair Compston (Cambridge, UK)

Abstract:
Understanding and preventing disease progression in multiple sclerosis is the major unmet clinical need in this difficult disease. Progression is due to cumulative axonal loss, initiated and maintained by a complex inflammatory response acting in individuals who are inherently susceptible to the disease process, and changing as tissue damage increases over time. Genetic studies of multiplex families with 2 first degree affected relatives show concordance of the clinical course, attributable to a primary effect on disease progression, either from onset or after a period of relapsing-remitting disease. One interpretation of the epidemiological studies suggesting independence of the natural history of relapses and progression is that the complex and evolving interaction between inflammation and vulnerability to injury gives the progressive phase an apparently stable trajectory. Successful suppression of inflammation in the relapsing-remitting phase with prolonged protection from relapses and new lesion formation does not alter the gradual accumulation of disability in secondary progressive multiple sclerosis; but the rate of progression and accumulation of cerebral atrophy are greatest in patients with the highest inflammatory lesion burden before treatment. Nitric oxide causes direct axonal injury that initially is reversible, whereas calcium dependent excitotoxic events follows more prolonged exposure. Cells of the oligodendrocyte lineage normally support neuronal survival by both contact mediated and soluble mechanisms: insulin-like growth factor-1 (IGF-1) contributes to this effect through the PI3 kinase / Akt signalling pathway; conversely, differentiated oligodendrocytes increase neurofilament phosphorylation and axonal length due to an effect of glial cell derived nerve growth factor (GDNF) acting through the MAP kinase / Erk pathways. Furthermore, IGF-1 and GDNF have been shown to modulate the direct effects of nitric oxide on survival of neurones and axonal injury mediated by exposure to nitric oxide in vitro, suggesting that, at any one time, the amount of tissue injury reflects the interplay of active inflammation, the extent of existing neurodegeneration, and the dynamic vulnerability of intact axons. Therefore, loss of trophic support normally provided by oligodendrocytes and myelin may be responsible for chronic axonal loss. But although the absolute amount of inflammation may reduce with time, its impact is not necessarily reduced given the increasing susceptibility of injured axons to residual inflammatory insult.

Biography:
Alastair Compston is Professor of Neurology and head of the Department of Clinical Neurosciences in the University of Cambridge. He trained in medicine at the Middlesex Hospital Medical School (now UCL) and in neurology at the Institute of Neurology, Queen Square. He received his PhD in 1979 for work on the immunogenetics of multiple sclerosis and his subsequent research has focused on the genetic epidemiology, applied neurobiology and clinical neuroscience of human demyelinating disease. He is a past-president of the European Neurological Society (2002-3), and is currently Editor of Brain.





Neural Stem Cell Systems for Studying Signalling Mechanisms and Modelling Neurological Diseases In Vitro

Luciano Conti (Milan, Italy)

Abstract:
Classically, neural stem and progenitor cells are derived from neural tissue and cultured in aggregates known as neurospheres. However, the proportion of stem cells is low and their identity, stability, and physiological relevance uncertain. Furthermore, the cellular complexity of the neurospheres confounds direct experimental interrogation of neural stem cells. Outside of the brain, an homogeneous source of neural stem cells is represented by pluripotent mouse embryonic stem (ES) cells that expand by symmetrical divisions in adherent monoculture.Differently from ES cells, homogenous expansion of somatic tissue-restricted stem cells has proven elusive. Here we describe derivation and homogenous propagation of adherent neural stem(NS) cells both from ES cells via neural lineage commitment of ES cells followed by growth factor addition in basal culture conditions. NS cells proliferate continuously in the presence of growth factors, are diploid, and clonogenic. After prolonged expansion, they remain able to differentiate efficiently into neurons and astrocytes in vitro and upon transplantation into the adult brain. NS cells uniformly express morphological and molecular features of radial glia, developmental precursors of neurons and astrocytes. Consistent with this profile, equivalent adherent NS cell lines can readily be established from fetal mouse brain. Similar NS cells can be generated from human ES cells and human fetal brain. NS cells represent the first tissue-specific stem cells that can be propagated without accompanying differentiation. As homogenous cultures they can thus be contrasted directly with pluripotent ES cells in the investigation of fundamental properties and biomedical potentials of stem cells. They can also provide a novel system for the pharmacological exploitation and drug screening strategies.

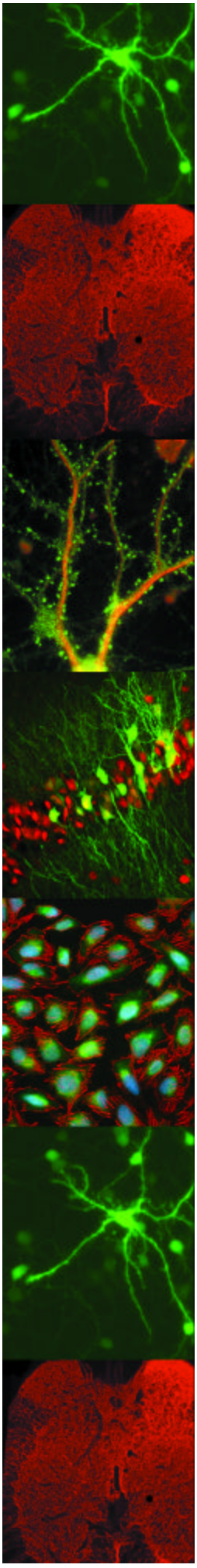
Biography:
Prof. Conti attended the School of Biology ,University of Milan, Italy, where he obtained his degree in Biology in 1995 with a work on "Janus Kinases' and their involvement in the proliferation of CNS progenitor cells". From 1994 to 2001 he was a post doctoral research fellow in the laboratory headed by Prof. Elena Cattaneo, Department of Pharmacological Sciences and Centre of Excellence on Neurodegenerative Diseases, University of Milano. In 2001 Luciano Conti got his PhD (Research Doctorate) in Cellular and Molecular Biotechnology applied to the Biomedical sciences at the University of Brescia, Italy. From 2001 to 2004 Dr. Conti was a Postdoctoral fellow in Prof. Austin Smith's laboratory at the Institute for Stem Cell Research, Edinburgh University,Scotland.
In 2004 Dr. Conti became a Senior Research Fellow in the Department of Pharmacological Sciences, University of Milano, Italy and in 2005 he was appointed Associate Professor of Pharmacology with tenure track in the Dept of Pharmacological Sciences, University of Milan. He is the author of 30 articles in extenso on international journals (26 indexed by the Index Medicus) and 3 Book chapters.

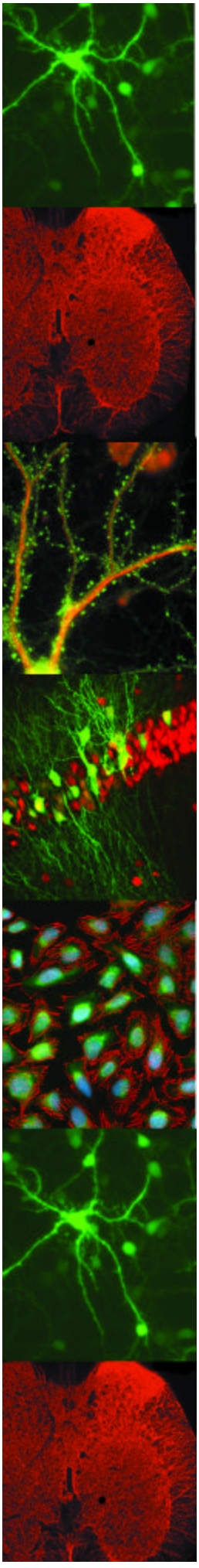
Studying Neural Stem Cells in the Embryonic and Adult CNS by Cre-Lox Transgenesis

Bill Richardson (London, UK)

Abstract:
Neurons and glia in the mature central nervous system (CNS) are derived from neuroepithelial progenitor (stem) cells in the ventricular zone (VZ) of the embryonic spinal cord and brain. Different parts of the VZ generate different subtypes of neurons and glia. We have been marking different spatially distinct sub-populations of neural stem cells in the embryo by Cre-lox transgenesis in mice, in order to follow the subsequent fates and dispersal patterns of their differentiated progeny. In the adult mouse brain, new neurons and glia are formed continuously throughout life from stem cells in the so-called subventricular zone (SVZ) that persists at the lateral edges of the lateral ventricles of the forebrain. We have found that the SVZ stem cells themselves are a heterogeneous population with different embryonic sites of origin in the ganglionic eminences (MGE and LGE) and cerebral cortex. We are currently investigating whether these different stem cells with different embryonic histories have different cell fate potential, using Nkx2.1-Cre, Gsh2-Cre and Emx1-Cre mice to follow adult stem cells derived from the embryonic MGE, LGE and cortex, respectively. As well as the localized SVZ stem cells, there are dispersed populations of mitogenically competent precursor cells in the adult brain and spinal cord. One such population consists of PDGFRa/NG2-positive adult oligodendrocyte precursors (OLPs), which are spread uniformly throughout the white and grey matter. These cells can generate new oligodendrocytes during adult life and in response to demyelinating disease or injury. In culture, they can also generate neurons and astrocytes but it is not known if they are equally pluripotent in vivo. We are using tamoxifen-inducible Pdgfra-CreER(T2) mice to investigate the potential stem cell-like properties of OLPs in the adult CNS.

Biography:
Bill studied at Manchester University (BSc Physics) and King's College London (PhD Biophysics) between 1970-78. He spent postdoctoral periods at the National institutes of Health, USA (1978-82) and the National Institute for Medical Research, London (1982-85), where he was involved in ground-breaking work on the mechanism of protein translocation into the cell nucleus. Since 1985 he has been at University College London (UCL) where he is now Professor of Biology and Head of the Department of Biology. His work during that time has focussed on the biology of glial cells in the developing CNS. For example, he has shown that the number and distribution of oligodendrocyte progenitors (OLPs) is tightly controlled by the distribution and availability of Pdgf-AA secreted from neurons. He also showed that most OLPs in the spinal cord are derived from a specialized region of the VZ dedicated to producing motor neurons followed by OLPs. This has had a major influence on the way the field has subsequently developed. More recently, he and his collaborators have been investigating the origins of OLPs and other glia in the embryonic and adult brain. Bills research is supported by the UK Medical Research Council, the Wellcome Trust and the Royal Society.





New Therapeutic Perspectives in Multiple Sclerosis

Giancarlo Comi (Milano, Italy)

Abstract:
Immunomodulating and immunosuppressive treatments for multiple sclerosis patients are directed against the inflammatory process and are only partially effective. This partial failure could be explained by mechanisms of axonal damage at least partially independent from acute or chronic inflammation. This suggests that there is a need for better use of available treatments and the necessity of alternative new therapeutic options to halt disease progression and enhance recovery mechanisms. Concerning actual treatments, two strategies are quite interesting: early treatment and combination therapy. The former approach is based on converging epidemiological, immunological and pathological studies and is proved by some recent clinical trials. The second one is under evaluation in ongoing clinical trials. Progress in understanding the mechanisms of T cell activation, inactivation and modulation has been translated into new therapeutic strategies aiming at inducing selective immunosuppression. Such an approach is now being tested in phase II-III clinical trials.

Biography:
Professor Giancarlo Comi is the Director of the Department of Neurology-Neurorehabilitation and Clinical Neurophysiology at the Scientific Institute H San Raffaele in Milan. He is a professor of Neurology at the University Vita-Salute San Raffaele and is the chairman of its graduate school in neurology. Prof. Comi is also the Scientific Director of the Multiple Sclerosis Centres of San Raffaele Hospital, as well as the hospital 'S. Antonio Abate' in Gallarate and since December 2004, Scientific Director of INSPE (Institute of Experimental Neurology).
Prof. Giancarlo Comi is an active member of various neurological societies, and is involved in Steering Committees and Advisory Boards of numerous international trials. He is currently Vice President of the European Charcot Foundation, member of the Executive Committee of the European Committee for Treatment and Research in Multiple Sclerosis and President of the European Neurological Society and the Italian Society of Clinical Neurophysiology. In addition, he is the Managing Editor for 'Topics in Neuroscience', and a member of the editorial boards of European Neurology, Trends in Medicine, Neurological Sciences, Clinical Neurophysiology and the Lancet (Italy). Prof. Comi has published more than 600 peer-reviewed papers, mostly in the area of multiple sclerosis and clinical neurology.

Closing Remarks

Giancarlo Comi (Milano, Italy)
Frank Walsh (Collegeville, USA)