The XX Ottorino Rossi Award

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Ottorino Rossi was born on 17th January, 1877, in Solbiate Comasco, a tiny Italian village near Como. In 1895 he enrolled at the medical faculty of the University of Pavia as a student of the Ghislieri College and during his undergraduate years he was an intern pupil of the Institute of General Pathology and Histology, which was headed by Camillo Golgi. In 1901 Rossi obtained his medical doctor degree with the highest grades and a distinction. In October 1902 he went on to the Clinica Neuropatologica *(Hospital for Nervous and Mental Diseases) directed by Casimiro Mondino to learn clinical neurology. In his spare time Rossi continued to frequent the Golgi Institute which was the leading Italian centre for biological research. Having completed his clinical preparation in Florence with Eugenio Tanzi, and in Munich at the Institute directed by Emil Kraepelin, he taught at the Universities of Siena, Sassari and Pavia. In Pavia he was made Rector of the University and was instrumental in getting the buildings of the new San Matteo Polyclinic completed.*
Ottorino Rossi made important contributions to many fields of clinical neurology, neurophysiopathology and neuroanatomy. Among these are: the identification of glucose as the reducing agent of cerebrospinal fluid, the demonstration that fibres from the spinal ganglia pass into the dorsal branch of the spinal roots, and the description of the cerebellar symptom which he termed "the primary asymmetries of positions". Moreover, he conducted important studies on the immunopathology of the nervous system, the serodiagnosis of neurosyphilis and the regeneration of the nervous system. He was the author of major scientific works including an extensive investigation of arteriosclerosis in the brain, giving a new interpretation of the development of lesions of vascular origin. He died in 1936 at the age of 59, having named the Ghislieri College as his heir. Ottorino Rossi was one of Camillo Golgi's most illustrious pupils as well as one of the most eminent descendants of Pavia's medico-biological tradition. Since 1990, the IRCCS "C. Mondino Institute of Neurology" Foundation has held an annual Ottorino Rossi Award Conference at which the award is presented to a scientist who has made an important contribution to research in the field of the neurosciences.

Past winners

In previous years the Ottorino Rossi Award has been conferred upon: Vittorio Erspamer, Rome, Italy (1990); Paolo Pinelli, Milan, Italy (1991); Giovanni Di Chiro, Bethesda, USA (1992); Clarence J. Gibbs Jr, Bethesda, USA (1993); David S. Zee, Baltimore, USA (1994); Elio Lugaresi, Bologna, Italy (1995); Michel Fardeau, Paris, France (1996); Salvador Moncada, London, UK (1997); Alain Berthoz, Paris, France (1998); Ottar Sjaastad, Trondheim, Norway (1999); J. Timothy Greenamyre, Atlanta, USA (2000); Salvatore DiMauro, New York, USA (2001); Elio Raviola, Boston, USA (2002); Kenneth Michael A. Welch, Chicago, USA (2003); François Boller, Paris, France (2004); Jes Olesen, Copenhagen, Denmark (2005); Stanley Finger, St Louis, USA (2006); Michael A. Moskowitz, Charlestown, MA, USA (2007), Patricia Smith Churchland, University of California, San Diego, USA (2008).

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This year, the IRCCS "C. Mondino Institute of Neurology" Foundation has conferred the Award on Stephen P. Hunt of the Department of Anatomy and Developmental Biology, University College London, London (UK). The awarding committee was composed of: Giacinto Bagetta (Cosenza), Umberto Balottin (Pavia), Francesco Barale (Pavia), Giorgio Bernardi (Rome), Giorgio Bono (Varese), Nereo Bresolin (Milan), Alberto Calligaro (Pavia), Vincenzo Guidetti (Rome), Andrea Lenzi (Rome), Arrigo Moglia (Pavia), Corrado Messina (Messina), Massimo Moscarini (Rome), Giuseppe Nappi (Pavia/Rome), Giorgio Sandrini (Pavia) - secretary, Angiolino Stella (Pavia).

The XX Ottorino Rossi Award was presented at the meeting "Neurological Sciences and the Gendered Brain", Pavia 23 April, 2009.

Academic profile and scientific achievements of the XX Ottorino Rossi Award winner

Stephen P. Hunt is Professor of Molecular Neuroscience at University College London (UCL), and a fellow of the Academy of Medical Sciences. Having completed his PhD in Neurobiology at the Department of Anatomy and Developmental Biology, UCL, Professor Hunt spent almost ten years as a post-doctoral fellow, first at the Institute for Brain Research in Zurich, and then, as a Senior Research Associate, at the Department of Psychiatry of the State University of New York at Stony Brook (USA). At the end of the 1970s, he joined the prestigious MRC Institute in Cambridge where he was soon to become a Senior Scientific Staff member, first of the Neurochemical Pharmacology Unit and subsequently of the Molecular Neurobiology Unit and the Laboratory of Molecular Biology, Division of Neurobiology. In the late nineties he took up his current academic position in London, where he is also a Principal Investigator in the London Pain Consortium funded by the Wellcome Trust. He has been Graduate Tutor in the Department of Cell and Developmental Biology since joining UCL in 1998, and he currently runs a third year BSc module on Pain Mechanisms.
Professor Hunt is on the editorial board of prestigious journals, an editor of books, a member of the MRC Panel of Experts, a frequent lecturer internationally and one of the most highly cited neuroscientists in the UK (according to ISI). Indeed, his work is published at the highest level and he is author of more than twenty seminal papers that have appeared in journals such as Nature*,* Science*,* Nature Neuroscience *and* Neuron*.*

At the MRC, from 1979, and now at UCL, Professor Hunt has pursued a number of lines of research, largely concerned with correlating molecular biology and behaviour. His work in the areas of regeneration, hippocampal plasticity and degenerative diseases and pain has been particularly successful. Professor Hunt's research on a molecular understanding of long-term potentiation (LTP), in the context of long-term collaborations with outstanding scientists like the highly knowledgeable Tim Bliss, a neuroscientist at NIMR, established the importance of the transcription factor zif268 as well as the regulation of signalling pathways after in vivo *induction of LTP. More recently this has extended to looking for expressed genes using differential display, and has produced a number of interesting gene candidates, particularly in the area of neuronal regeneration. When Professor Hunt first joined the MRC, the field of pain research was dominated by the search for novel neurotransmitters and little was known about long-term molecular changes in the spinal cord. He was able to show that transcription factors such as c-fos are activated in the dorsal horn following noxious stimulation and could be used to analyse the patterns of neuronal activation that follow injury as well as many other events within the nervous system. This contribution to our understanding of mechanisms underlying neuronal activation has proved fundamental. Indeed, the* Nature *paper in which this work was published has, so far, been cited over a thousand times. Professor Hunt also contributed substantially to the advancement of basic science by developing a number of techniques, such as* in situ *hybridisation, and he was able to show that opiate-like peptide containing neurons did not directly contact primary afferents. He then went on to develop a series of gene knockout mice. The most relevant here is the substance P (SP) receptor knockout mouse which was shown to be insensitive to the rewarding effects of morphine, although analgesia was intact, and also helped to demonstrate the crucial role of this receptor in the animal's own defence in the wild. This work, and other research, some conducted in collaboration with others, led to the idea that NK1R was a target for antidepressant drugs.*

Recently, Professor Hunt has made an important contribution to understanding of the descending control of pain. *In particular, he has identified a key circuit whereby incoming sensory information is transferred from spinal networks to the brainstem and also established what mediates return conversations from these supraspinal sites. This work has uncovered a role for spinal neurons at the origin of a serotonergic excitatory pathway from the brainstem that determines spinal excitability via action on ionotropic 5HT3 receptors. Intrathecal injection of SP conjugated to the cytotoxin saporin (SP-SAP) produces site-specific ablation of superficial dorsal horn neurons expressing the receptor for SP (NK1 receptor). This treatment results in attenuated pain behaviours following injury, accompanied by reduced central sensitisation (e.g. reduced receptive field size, attenuated formalin response and wind-up), and a failure of deep dorsal horn neurons to faithfully encode polymodal inputs. The majority of lamina I NK1 expressing neurons are projection neurons that ascend to the parabrachial area, a key supraspinal target implicated in the emotional and autonomic aspects of nociceptive processing as verified by recent human imaging studies. The role of supraspinal modulatory pathways in chronic pain states is further supported by findings of enhanced 5HT3 receptor mediated control on deep dorsal horn neurons following peripheral nerve injury. A randomised double-blind clinical study showed that a single intravenous bolus of ondansetron alleviates pain in neuropathic pain patients. However, results showed unaltered descending 5HT3 receptor mediated control in carrageenan-induced inflammation. Professor Hunt and coworkers speculate that a certain intensity of peripheral input is required to drive this excitatory pathway, and that the maintenance of central sensitisation is likely to involve distinct mechanisms in peripheral neuropathy and inflammation. They also showed that this pathway determined the actions of the widely used drug for neuropathic pain, gabapentin, and that wind-up and LTP depend on the spinal neurons but not the brainstem excitations. This information was then used to study the role of a gene, zif268, in persistent pain using microarrays based on cord tissue from animals after LTP. Thus, in addition to intrinsic spinal mechanisms and peripheral inputs, spinal excitability is influenced by activity from supraspinal sources, whether excitatory or inhibitory, and an overall balance of these events eventually governs the behavioural outcome.*

A second recent and fruitful line of research is that investigating the molecular mechanisms underlying sensitisation of superficial dorsal horn neurons*. Activity-dependent changes in superficial neurons of the rat dorsal horn are crucial for the induction and maintenance of neuropathic and inflammatory pain states. To identify the molecular mechanisms underlying the sensitisation of superficial dorsal horn neurons, Professor Hunt undertook a genome-wide microarray profiling of dorsal horn transcripts at various times after induction of peripheral inflammation of the rat ankle joint. At early time points, up-regulation of gene expression prevailed, but by 7 days down-regulation was predominant. Two to 24h post-inflammation, a small number of highly up-regulated transcripts previously shown to be repressed by the methyl-CpG-binding protein 2 (MeCP2), including serum- and glucocorticoid-inducible kinase (SGK1), a gene known to be important in experience-dependent plasticity and to be mutated in Rett's disease, was identified. Previous research had indeed shown that in a mouse model of Rett's disease, which demonstrates the primary features associated with mental retardation in humans, the highly regulated genes are the same as those found following induction of central sensitisation after inflammation. MeCP2 is regulated by phosphorylation in an activity dependent manner and is also thought to play an essential but as yet unidentified role in neuronal plasticity. Crucially, Professor Hunt found that MeCP2 was phosphorylated in lamina I projection neurons, which have been shown to be essential for the development of pain states. Following joint inflammation, SGK1 protein expression increased and, in part, localised to lamina I projection neurons. Furthermore, antisense knockdown of SGK1 delayed the onset of inflammatory hyperalgesia by 24 hours. These results have uncovered an unexpected complexity in the regulation of gene expression that accompanies the development and maintenance of an inflammatory pain state and a role for modulation of transcriptional repression in modulating pain sensitivity.*

Finally, local regulation of mRNA translation in primary afferent neurons is beginning to yield basic information on neuronal plasticity. *Local regulation of mRNA translation in axons has been implicated in neuronal plasticity, the axonal response to damage and growth cone navigation during development. Through his research work, Professor Hunt has identified in the rat a subpopulation of myelinated primary afferent fibres that contain constitutively active forms of the mammalian target for rapamycin (mTOR) and downstream targets of the kinase, p70S6kinase and eukaryotic initiation factor 4E binding protein 1 as well as ribosomal protein S6 and other components of the local translational machinery. Confocal analysis revealed that the translational machinery was restricted to a subset of myelinated primary afferents some of which co-stained for calcitonin gene-related peptide (CGRP) suggesting local protein synthesis in small diameter A delta fibres. Unmyelinated C-fibres were not positively stained for markers of local translation of mRNA. Local injection of rapamycin, an inhibitor of mTOR signalling, into the hind paw resulted in a decrease in phospho-p70S6kinase, phospho-EBP1 and phospho-S6. Electrophysiologically, an increase in A delta heat thresholds developed at 3-6h following rapamycin injection without affecting C-fibre thresholds. Secondary mechanical hyperalgesia but not primary thermal hyperalgesia established by capsaicin injection into the paw was substantially attenuated by pre-treatment with rapamycin while in a rat model of neuropathic pain mechanical thresholds were also reduced by prior treatment with rapamycin. Professor Hunt's results suggest that the sensitivity of subpopulations of A sensory fibres innervating skin, including high threshold A delta axons, is maintained by active local protein synthesis and suggests a new route for the control of chronic and acute pain.*

Since joining UCL as Professor of Molecular Neuroscience, Stephen Hunt has been awarded several important programme grants mostly on pain research and his research is now focused largely on the molecular biology of pain and related topics. Professor Hunt's research work and his natural ability to transfer his scientific knowledge to undergraduate and postgraduate students has been a key factor in the professional development of several established researchers worldwide.

G. Bagetta, G. Sandrini