PLENARY LECTURES

PLE-SUN-01

ANS OVERSEAS LECTURE

ELUCIDATING RECEPTOR TYROSINE KINASE-DEPENDENT SIGNALING IN NEURAL CIRCUIT ASSEMBLY AND PLASTICITY

Ip N.Y.
Division of Life Science, Molecular Neuroscience Center and State Key Laboratory of Molecular Neuroscience,The Hong Kong University of Science and Technology.

Proper neural function depends on the intricate interplay of well co-ordinated signaling pathways. My laboratory is interested in deciphering how receptor tyrosine kinases (RTKs) and their downstream effectors relay extracellular signals during neural development and functioning. In the first part of my talk, I will discuss how the Rho GTPase regulator α2-chimaerin, a signaling protein activated by the RTK EphA4, and the scaffold protein Axin direct neuronal polarity and regulate development of cerebral cortex through modulating microtubule dynamics. Our studies revealed that activation of the RTK TrkB by its cognate ligand brain-derived neurotrophic factor (BDNF) results in phosphorylation of Axin that is mediated by the serine/threonine kinase Cdk5, and this phosphorylation event is critical for axon formation in the developing cerebral cortex *in vivo*. On the other hand, knockdown of α2-chimaerin expression in embryos by *in utero* electroporation results in impaired neuronal migration. Remarkably, mice with depleted α2-chimaerin at embryonic stages show greater susceptibility to convulsant-induced seizures during adulthood. Our findings therefore provide *in vivo* evidence that neuronal migration regulated by α2-chimaerin is essential for normal functioning of the cerebral cortex in mature animals. My laboratory also investigates how synaptic function is regulated in the adult brain under normal and diseased conditions. Experience-dependent changes in synaptic transmission form the cellular basis of neural plasticity that underlies cognitive functions such as learning and memory. One major mechanism by which synaptic transmission is regulated involves the growth and elimination of dendritic spines. Loss of dendritic spines and impaired synaptic plasticity has been observed at early stages of Alzheimer's disease before extensive neuronal death. Elucidating the molecular mechanisms underlying spine morphogenesis is therefore pivotal in our understanding of brain functions and the identification of new molecular targets for drug development. In the second part of my talk, I will describe signaling pathways activated by two distinct RTKs that differentially regulate spine growth and elimination. We found that TrkB can be phosphorylated at neuronal synapses by Cdk5, which promotes dendritic spine growth in response to synaptic activity. Mice lacking this phosphorylation display impaired spatial memory, therefore revealing a novel neuronal signaling pathway during memory formation. On the other hand, we have identified EphA4 as a major negative regulator of excitatory neurotransmission through elimination of dendritic spines in a Cdk5-dependent manner. These observations illustrate how Cdk5 differentially regulates spine remodeling through coupling to different RTKs. Given the association of impaired synaptic functions and aberrant Cdk5 activity with Alzheimer's disease (AD), our findings suggest that EphA4 is a promising target for developing novel treatments. Towards this end, we have identified small molecule inhibitors of EphA4 based on a knowledge-based drug discovery program to search for novel drug leads from traditional Chinese medicine. I will discuss the ability of these inhibitors to counteract the synaptic loss and impaired synaptic plasticity induced by amyloid-β peptide oligomer, which is believed to be a causative agent of synaptic loss in AD.

PLE-MON-02

LAWRIE AUSTIN LECTURE

COLOUR VISION, COLOUR BLINDNESS, AND IMPORTANCE OF AN EYE FOR DETAIL

Martin P.R.[1, 2, 3]
[1]ARC Centre of Excellence in Vision Science. [2]Save Sight Institute, University of Sydney. [3]School of Medical Sciences, University of Sydney.

The world is full of colourful things, and most of us take colour vision for granted. We use colour to navigate a busy street or a busy web page; to select our clothing, cars, and foods; to recognise a lover's blush or a road-rager's anger. And today we have added colour to much of what we see: just take the multi-billion dollar cosmetic industry for a nice example. Here, then, are are some obvious questions for neuroscience: how do the eye and brain work together to enable us to see in colour? And how can it be that some people might say two things have the same colour, but other people say that these colours are completely different? In my lecture I will show how we study the visual system to answer these questions. We use anatomical, physiological, and genetic methods to identify and trace the visual pathways, beginning with cone photoreceptor cells in the eye and passing through the visual thalamus. These experiments have shown that an evolutionary ancient nerve pathway supplies the blue-yellow axis of colour vision, whereas the red-green axis of colour vision has taken a "free ride" on nerve pathways designed to see fine detail in the visual world. In addition to describing these discoveries, I hope to show more generally how our research has applied Lawrie Austin's principle of using multiple methods to attack complex problems.

PLE-MON-03

ECCLES LECTURE

DECIPHERING THE EPILEPSY GENOME AND ITS IMPACT ON CLINICAL PRACTICE

Scheffer I.E.
Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Austin Health and Royal Children's Hospital, Melbourne, Australia.

Personalized medicine is on our doorstep with the promise that deciphering our genetic code will change clinical practice. New techniques allow for our entire DNA code to be deciphered yet interpretation of the myriad of variants in each individual's genome remains challenging. The epilepsies are a complex group of disorders in which these new molecular technologies are shedding light on the underlying genetic components, allowing insights into the neurobiology of many epilepsy syndromes. Whole exome approaches in the severe epileptic encephalopathies of infancy and childhood have highlighted an excess of de novo mutations in genes that do not tolerate variation. While many genes are implicated in this group as a whole, genotype-phenotype correlations are emerging and allow the development of animal models with a view to targeted therapies. These studies are complemented by multigene panels that allow translation of genetic findings to larger groups of patients and herald the advent of clinical panels. Genetic findings are impacting more broadly as well to the common focal epilepsies, which were previously regarded as largely acquired disorders. Finding the gene is but the beginning as, for some genes, elucidating their role requires considerable thought and collaborative science. Looking to the future, how will our approaches change in the next five years? Will the clinical researcher still have a role and how will these molecular discoveries facilitate translational research approaches? Exciting times indeed and the future looks bright for improving clinical outcomes.

PLE-TUE-04

ANS LECTURE

FOOD ON THE BRAIN

Morris M.
Pharmacology, School of Medical Sciences, UNSW, Sydney, Australia.

The World Health Organisation predicts that by 2015, 75% of the adult population will be overweight, and 41% obese. The dramatic increase in obesity over the past 20 - 30 years cannot be due to changes in the human genome. Rather, this increase is due to a range of environmental factors, among them dietary intake, which has steadily increased in industrialised societies during the past 50 years. Food composition and availability have also changed remarkably in just one generation. The brain plays a critical role in regulating energy homeostasis. Circuits in the hypothalamus assess and integrate peripheral metabolic, endocrine and neuronal signals that reflect current energy status, influencing appetite. Our laboratory has developed rodent models to investigate brain changes during the development of obesity, and the mechanisms underlying the intergenerational transmission of obesity. Questions currently under investigation include: how does provision of a varied, energy rich diet override the regulatory control mechanisms evolved to regulate body weight? What is the impact of maternal and paternal obesity on offspring and how might this contribute to the growing obesity epidemic? What is the role of stress in obesity, and the role of a palatable high fat diet in the alleviation of effects produced by early life stress? We have demonstrated that chronic consumption of palatable high fat, high sugar diet leads to changes in the hypothalamic expression of key appetite regulators. Exposure to an obesogenic diet in early life appears to be a major contributor to obesity in childhood. Maternal obesity leads to “programming” of the neural circuitry involved in appetite regulation. We have observed that maternal obesity alters hypothalamic mRNA expression of key appetite regulators such as neuropeptide Y, pro-opiomelanocortin (POMC), and the leptin receptor, as early as one day after birth. We have now shown for the first time, using our model of maternal obesity in rats, that voluntary exercise in the offspring of obese mothers, regardless of postnatal diet, improves their metabolic profile. Feeding behaviour is altered by the palatable diet, with increased ‘snacking’ seen early in diet exposure, relative to lean rats. Obese rats also showed less locomotor activity but greater energy expenditure. Finally, impairments in overall cognitive function have been associated with obesity. We have recently found that as little as one week of exposure to a high fat, high sugar diet selectively impaired hippocampal dependent object place recognition memory while completely sparing perirhinal cortex-dependent object recognition memory. Exposure just to a high sugar diet had similar effects, and the impairments from both diets were associated with increased expression of TNFα in the hippocampus. These diet-induced cognitive deficits are worrying, particularly in light of the current community debate regarding sugar intake.