Plenary Lectures

Special Lectures

Memorial Lectures

Plenary Lecture 1

March 28 (Tue), 14:20 – 15:20, Hall A

PL1

Restoring harmony with Bumetanide in autism

Yehezkel Ben-Ari[1,2]

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Developmental disorders including autism are triggered by intrauterine or delivery related insults. I have suggested that intrauterine genetic or environmental insults deviate developmental sequences of ionic currents leading to neurons with immature currents in adult brains. The presence in pathologies of neurons with excitatory GABA due to high $[Cl^-]_i$ levels normally observed in immature neurons is an illustration of this Neuroarcheology concept (Ben-Ari, TINS, 2008). Also during delivery, oxytocin produces a powerful neuro-protective reduction of $[Cl^-]_i$ levels (Tyzio et al., Science, 2006). This shift is abolished in 2 animal models of autism and its restoration by the diuretic NKCC1 chloride importer antagonist bumetanide attenuates the severity of autism in off springs (Tyzio et al., Science, 2014). We tested the effects of bumetanide first in pilot studies, then double blind randomized single and multiple sites trials with positive results and are proceeding now to a final phase 3 (Lemonnier et al., Transl Psychiat, 2012). We also showed that visual communication is ameliorated with the diuretic (Hadjikhani et al., Autism, 2016). Therefore, by restoring an efficient GABAergic inhibition, Bumetanide might provide a novel therapeutic perspective to treat developmental disorders. We suggest that the diuretic that exerts its actions only on neurons endowed high $[Cl^-]_i$ levels, attenuates perturbing behaviorally relevant oscillations thereby restoring "harmony" in electrical activity. This approach is relevant to many other disorders as many ionic currents are also most likely affected by early insults. (COI:Properly Declared)

Plenary Lecture 2

March 28 (Tue), 15:30 – 16:30, Hall A

PL2

KCC2: a multifunctional protein in brain development, plasticity and disease

Kai Kaila

Dept Biosci Neurosci Center, Univ Helsinki, Helsinki, Finland

In recent years, the mechanisms regulating the intracellular Cl^- concentration in neurons have attracted an increasing amount of attention. The key molecules involved, the cation-chloride cotransporters (CCCs), have turned out to be multifunctional proteins with fundamental roles in shaping the properties of neurons and neuronal networks. In my talk I will highlight the diverse functions of CCCs, with a particular focus on the main neuronal Cl^- extruder, KCC2, and its roles in neuronal signaling and plasticity during brain development and disorders. (COI:No)

Plenary Lecture 3

March 30 (Thu), 11:00 – 12:00, Hall A

PL3

Angiogenesis revisited: role and (therapeutic) implications of endothelial metabolism

Peter Carmeliet

Lab Angiogenesis Vascular Metabolism, VRC, Dept Oncol, KU Leuven, Belgium

The past 40 years of research in the angiogenesis field have focused on identifying genetic signals such as VEGF and Notch, which determine vessel sprouting. However, the role and therapeutic potential of targeting endothelial cell (EC) metabolism have been largely overlooked. We have recently reported that ECs are glycolysis addicted and that glycolysis importantly co-determine vessel sprouting downstream of VEGF and other pro-angiogenic signals. In addition, we documented that ECs are rather unique in utilizing fatty acid-derived carbons for the de novo synthesis of deoxyribonucleotides for DNA synthesis during EC proliferation when vessels sprout. Moreover, targeting (blocking) glycolysis and fatty acid oxidation inhibit pathological angiogenesis and induce tumor vessel normalization (thereby reducing metastasis and improving chemotherapy), suggesting that these metabolic pathways are new targets for anti-angiogenic drug development without evoking systemic side effects. Furthermore, lymphatic ECs differ from other EC subtypes in their metabolic requirements for lymphangiogenesis. Since many of these metabolic targets are pharmacologically druggable, these metabolic pathways represent a new promising target for therapeutic anti-angiogenesis. (COI:No)

Special Lecture 1

March 28 (Tue), 12:00 – 13:00, Hall A

SL1

Molecular mechanisms of heart failure: a central role of the Hippo pathway

Junichi Sadoshima

Rutgers New Jersey Medical School, USA

The Hippo pathway is a conserved signaling mechanism that controls organ size through regulation of apoptosis and proliferation. Serine threonine kinases, including mammalian sterile 20-like 1 (Mst1) and large tumor suppressor 1/2 (Lats1/2), and transcription co-factors, including Yes-associated protein (YAP) and Taz, are the key components of the Hippo pathway. Mst1 and Lats2 are activated by stress and mediate myocardial injury and the progression of heart failure. Mst1 activates Lats2, which in turn phosphorylates YAP and suppresses its function. YAP promotes survival and either cardiac hypertrophy or proliferation through regulation of TEAD and FoxO, and miRNAs, including miR-206. Stress-induced activation of the Hippo pathway inhibits YAP, thereby inducing apoptosis, suppressing compensatory hypertrophy, and facilitating cardiac dysfunction. Excessive downregulation of the upstream Hippo pathway and/or persistent activation of YAP, however, induce dedifferentiation of cardiomyocytes (CMs) and contractile dysfunction through stimulation of TEAD. Thus, CMs under stress risk their own death by apoptosis by activating the Hippo pathway in order to maintain the differentiation status and contraction against hemodynamic overload. These results suggest that it would be important to keep the activity of the Hippo pathway within an appropriate range, in order to suppress cell death and, at the same time, to maintain the differentiation status of CMs. In this presentation, I will discuss both physiological and pathological roles of the Hippo pathway during myocardial injury and heart failure, with an emphasis on the role of YAP in the heart. (COI:No)

Special Lecture 2

March 29 (Wed), 13:30 – 14:30, Hall A

SL2

Brain science using iPS cell technologies and genetically modified non-human primates

Hideyuki Okano

Dept Physiol, Keio Univ Sch Med, Tokyo, Japan

For effective modelling of human psychiatric/psychiatric disorders, we took advantage of iPS cell technologies and transgenic non-human primates. So far, we have established iPS cells from the patients of about 40 human psychiatric/psychiatric disorders, including Alzheimer disease (Yagi et al., Human Mol Genet, 2011; Imaizumi et al., Stem Cell Reports, 2015), Parkinson disease (Imaizumi et al., Mol Brain, 2012; Ohta et al., Human Mol Genet, 2015; Matsumoto et al., Stem Cell Reports, 2016), ALS (Ichiyanagi et al., Stem Cell Reports, 2016), Rett syndrome (Andoh-Noda et al., Mol Brain, 2015) and Pelizaues-Merzbacher disease (Kuroiwa-Numasawa et all., Stem Cell Reports, 2014) . Furthermore, for faithfully modeling the human disorders in vivo, we developed transgenic non-human primates (common marmosets) with germline transmission (Sasaki et al., Nature, 2009). In the present talk, we also wish to mention our recent data of generation of common marmoset transgenic models of neurodegenrerative diseases, including Parkinson disease, Alzheimer disease and ALS. Furthermore, we could generate knock-out technologies of common marmoset using genome editing technologies (Sato et al., Cell Stem Cell, 2016), which can be applied for generation of models of autism and psychiatric disorders. At the end, I will mention about Brain Mapping Projects in Japan, in which investigation of common marmoset brains plays key roles (Okano et al. Philos Trans R Soc Lond B Biol Sci. 2015; Okano and Yamamori, Nat Rev Neurosci, 2016; Okano et al., Neuron, 2016).COI disclosure: HO is a paid SAB of SanBio CoLtd. (COI:Properly Declared)

Special Lecture 3

March 29 (Wed), 16:50 – 17:50, Hall A

SL3

Molecular identification of two types of volume-activated anion channels involved in multiple functions controlling cell life

Yasunobu Okada[1], Ravshan Z Sabirov[2,4], Toshiaki Okada[2,3], Petr G Merzlyak[2,4], Md Rafiqul Islam[2], Kaori Sato-Numata[5], Hiromi Uramoto[6], Yuhko Ando-Akatsuka[7], Hiroshi Matsuura[8]

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The volume-sensitive outwardly rectifying anion channel (VSOR, also called VRAC) and the maxi-conductance anion channel (Maxi-Cl) represent two types of volume-activated anion channels which are directly activated by cell swelling. Their molecular entities have long been elusive. In 2014, LRRC8A and its paralogs were shown to be essentially involved in VSOR activity. Our recent gene-silencing studies demonstrated that VSOR activity requires an additional essential core molecule. Also, we have attempted to identify the Maxi-Cl molecule by genome-wide approaches, since we dismissed the VDAC hypothesis as the Maxi-Cl candidate in 2005. By subjecting proteins from bleb membranes rich in Maxi-Cl activity to proteomics combined with siRNA-screening, we recently succeeded in identification of the Maxi-Cl core protein, MAC-1. Our studies showed that VSOR and Maxi-Cl play wide-ranging physiological roles especially in control of cell life/death by regulating the cell volume and in paracrine/autocrine signaling by releasing intracellular organic anions such as ATP and glutamate. (COI:No)

Special Lecture 4

March 29 (Wed), 17:50 – 18:50, Hall A

SL4

Depolarising GABA triggers glutamatergic sprouting in epilepsy

Claudio Rivera[1,2,3], Christophe Pellegrino[1,2], Nazim Kourdougli[1,2]

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Plastic remodelling of glutamatergic neuronal network is one of the major pathophysiological processes observed in epileptic tissue and post-traumatic brain injuries. The understanding of the molecular mechanisms involved is of particular importance since this plastic remodelling creates a powerful hyperexcitable cerebral focus that drives recurrent disabling seizures. Besides the rewiring of excitatory circuit, an abnormal depolarizing GABAergic drive has been hypothesized to participate in epileptogenic processes. This includes the deregulation of functional expression of the neuronal specific K^+-Cl^- co-transporter KCC2 and the Na^+-K^+-$2Cl^-$ co-transporter NKCC1. We have also previously shown that depolarizing GABAergic transmission triggers the up-regulation of the pan-neurotrophin receptor, p75NTR. We have now tested the hypothesis that the early alteration of Cl^- homeostasis following status epilepticus (SE) is a precipitating event that triggers recurrent mossy fibre sprouting via the activation of p75NTR. We also examined a novel therapeutic strategy based on the transient blockade of Na^+-K^+-$2Cl^-$ co-transporter NKCC1 early after SE to reduce ectopic sprouting and recurrent seizures in the chronic phase (i.e. several months after SE). The findings from this study define promising and novel targets to constrain reactive glutamatergic network rewiring in adult epilepsy. (COI:Properly Declared)

Special Lecture 5

March 30 (Thu), 15:30 – 16:30, Hall A

SL5

Role of reactive astrocytes in neurodegenerative diseases

Changjoon Justin Lee

Cent Neurosci Functional Connectomics, Brain Sci Inst, KIST, Seoul, Korea

Brain is composed of not only neurons but also glia. It has been recently established that in addition to neurons, glial cells can release various transmitters (termed gliotransmitters), such as GABA, glutamate, and d-serine. The functional significance of these gliotransmitters is beginning to unravel as the detailed mechanisms of release have become available. We have recently demonstrated the role of GABA, synthesized via MAO-B and released through GABA-permeable Best1 channel from reactive astrocytes, in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. During the course of these studies, we have developed various molecular tools, mouse and rat models, and neural probes to address specific questions in animal models of neurodegenerative diseases. These newly developed targets and tools will prove useful in developing novel therapeutics for various neurodegenerative diseases that currently have no cure for. (COI:No)

The Susumu Hagiwara Memorial Lecture

March 29 (Wed), 14:30 – 15:30, Hall A

ML1

Looking for next-generation physiology

Keiji Imoto

Natl Inst Physiol Sci, Okazaki, Japan

Physiology is a field of science to elucidate the functional mechanism of living organisms. Classical physiology tried to understand the macroscopic functions of respiration, circulation and so on. Technical advances of biochemical and molecular biological methods have allowed us to recognize molecules involved biological phenomenon and their functions as well as disorders related to those molecules. Based on the enormous amount of knowledge of molecules, however, we are still struggling to understand how the regulatory mechanism operates as a whole body or how the homeostasis is so well maintained in our body. The role of physiology is more important than ever before. I would like to discuss directions of next-generation physiology. (COI:No)

The Sunao Tawara Memorial Lecture

March 30 (Thu), 14:30 – 15:30, Hall A

ML2

Regulation of body environments by epithelial ion transport

Yoshinori Marunaka

Dept Mol Cell Physiol, Grad Sch Med Sci, Kyoto Pref Univ Med, Kyoto, Japan

Body environments such as body fluid amounts, blood pressure, amounts of surface fluid covering the epithelial cells, etc. are essentially regulated by epithelial ion transport, which is mediated by ion movements across the apical and basolateral membrane requiring energy consumption. Various factors including hormones, osmolarity, etc. regulate the epithelial ion transport by controlling ion channels and transporters located at the apical and basolateral membranes. Disorders of regulation of epithelial ion transport cause diseases such as hypertension, respiratory tract infection, etc. In this lecture, I will introduce some new regulatory pathways of epithelial ion transport via changes in cell volume, intracellular chloride ion concentration, and membrane tension, and provide further information on regulation of intracellular trafficking and activity of ion channels/ transporters. (COI:No)