Plenary Lectures

Named Lectures

Special Lectures

Plenary Lecture

March 22 (Tue), 11:00 – 12:00, Room A

1SL1A1

HUMAN ORGANS ON CHIPS

Donald E. Ingber, M.D.,Ph.D.

(Founding Director, Wyss Institute for Biologically Inspired Engineering at Harvard University;
Judah Folkman Professor of Vascular Biology, Harvard Medical School & Boston Children's Hospital; Professor of Bioengineering, Harvard School of Engineering & Applied Sciences)

At the Wyss Institute for Biologically Inspired Engineering at Harvard University that I lead, we seek to develop innovative technologies that will transform medicine and the environment by emulating the way nature builds. One of the biggest problems in medicine today is that the drug development model is broken. Even though financial investment in research and drug discovery has increased dramatically over the past few decades, the number of medicines approved per dollar investment has steadily decreased over the past 50 years. A major limiting factor is that animal models remain at the core of drug testing and development even though they are costly, time-consuming, lead to loss of innumerable animal lives, and often fail to predict results in humans. In this presentation, I will describe work we have been carrying out in the Biomimetic Microsystems platform at the Wyss Institute, which is focused specifically on developing a solution to this problem. The goal of the platform is to engineer human 'Organs-on-Chips': microdevices lined by living human cells created with computer microchip manufacturing techniques that recapitulate organ-level functions as a way to replace animal testing. We started by defining the biological design principles that govern the structure and physiological function of a key functional unit of a living human lung: the air sac or alveolus that is the site of gas exchange, aerosol-based drug delivery, inhalation of airborne particulates, pneumonia, etc. The air sac is composed of a single layer of epithelial cells that line the air sac, which form an interface with underlying layer of blood vessel endothelial cells, separated by a planar porous extracellular matrix adhesion scaffold. The function of the lung also requires mechanical breathing motions and fluid flow in the vascular system. Inspired by these design principles, we used computer chip manufacturing methods to microfabricate a synthetic human lung air sac. The engineered human lung-on-a-chip is a crystal clear, flexible rubber device about the size of a memory stick that contains three, tiny hollow channels oriented in parallel. The top and bottom parts of the central channel are separated by a thin, flexible, porous membrane that is coated with extracellular matrix and lined on one side with human lung air sac cells and exposed to air; human lung capillary blood cells are placed on the other side with medium containing human immune cells flowing over their surface to mimic blood. A vacuum applied to the two outer side channels deforms this tissue-tissue interface to recreate the way lung tissues physically expand and retract when breathing in the whole human lung (see video at: http://wyss.harvard.edu/viewpage/240/lungonachip). Studies carried out with this device have provided the proof-of-principle that an organ-on-a-chip can be used to identify drug toxicities, discover new potential therapeutic agents, and model complex human diseases such as pulmonary edema ('fluid-on-the-lungs') in vitro. I will review our work on the lung chip as well as recent advances we have made in the development of many other human organ chips, including small airway, gut, kidney, liver and bone marrow chips, as well as novel human disease and infection models. I will also describe our ongoing efforts to develop a 'human body on chips' composed of more than 10 different human organ chips linked together by fluid flowing through their vascular channels, and to engineer an automated instrument for real-time analysis of cellular responses to pharmaceuticals, toxins, cosmetics and other chemicals using these bioinspired devices. (COI:Properly Declared)

Plenary Lecture

March 22 (Tue), 15:00 – 16:00, Room A

1SL2A2

Synaptic dysfunction in Alzheimer's disease

Christophe Mulle

(CNRS, University of Bordeaux, Bordeaux, France.)

Alzheimer's disease (AD) is the first cause of dementia that leads to progressive loss of memory and cognitive functions. Synaptic dysfunction has been identified as a possible cause of AD. Synaptic plasticity in the autoassociative network of recurrent connections among hippocampal CA3 pyramidal cells is thought to enable episodic memories storage. Our lab has been interested in unravelling the mechanisms for synapse-specific dysfunction in CA3 in models of AD. We will provide evidence that at the early onset of cognitive deficits in a mouse model of AD, associative long-term synaptic potentiation (LTP) is abolished in CA3 pyramidal cells. This is caused by activation of up-regulated neuronal adenosine A_{2A} receptors ($A_{2A}R$) and can be rapidly reverted by pharmacological or genetic manipulation of these receptors. We have also started to unravel the role of presenilins (PS) and APP at a distinct glutamatergic input to CA3 pyramidal cells, the mossy fiber synapses. Mutations of presenilins (PS1 or PS2), catalytic subunits of γ-secretase, represent are most commonly found in the early onset or familial form of Alzheimer disease (FAD). We have generated a ready-to-use optogenetic tool kit to study the presynaptic function of PS at mossy fiber to CA3 synapses. We will show how the γ-secretase activity of PS and accumulated ß-C-terminal fragment of APP (ß-CTF) exert a powerful control on synaptic release mechanisms and short-term plasticity at Mf-CA3 synapses. Overall, functional dysregulation of synapses in models of AD involves a complex combination of pathways, where Aβ and Tau are only part of the explanation, and which are dependent on synapse identity. (COI: No)

The Memorial Lecture for Dr. Tawara

March 23 (Wed), 10:30 – 11:30, Room A

2SL1A3

Intracellular factors that regulate activity of Cav1.2 channels

Kameyama Masaki

(Department of Physiology, Graduate School of Medical and Dental Sciences, Kagoshima University)

The Cav1.2 voltage-dependent Ca^{2+} channels are widely expressed in tissues, including neurons, cardiac myocytes and smooth muscle cells, and play an important role in Ca^{2+} signaling. We have explored intracellular factors that regulate activity of Cav1.2 channels in cardiac myocytes.

1. Ca^{2+} and calmodulin (CaM): Activity of the channels is abolished in the inside-out (IO) mode with a simple salt solution (rundown). This rundown can be reversed by adding CaM (~1 μM) and ATP (3-5 mM) in the solution. In IO mode, the concentration-response curve of CaM is bell-shaped, indicating that CaM has dual effects, facilitation and inactivation. We propose a simple model for the effects of CaM that the channel has two CaM-binding sites, either for facilitation or inactivation (two-CaM sites model).

2. Protein kinases: PKA is known to facilitate channel activity, but the underlying molecular mechanism is still unknown. We found Ser1574 (guinea pig) of Cav1.2 as a phosphorylation site. CaMKII is also known to enhance channel activity. We have found one of the phosphorylation sites is Thr1603, which is within a CaM-binding region (preIQ) of Cav1.2. Thus, CaMKII's effect might be mediated by a change in CaM-binding properties of the channel.

3. ATP: In addition to a substrate of phosphorylation, ATP binds directly to the Cav1.2 channel and maintain its activity. Photo-active ATP labeled both N- and/or proximal C-terminal tail of Cav1.2.

In conclusion, multiple intracellular factors, Ca^{2+}, CaM, kinases and ATP interact with Cav1.2 channels and finely tune its activity.(COI:No)

The Memorial Lecture for Dr. Hagiwara

March 23 (Wed), 14:00 – 15:00, Room A

2SL2A4

Unveiling functions of the central circadian clock by imaging "clock time"

Honma Sato

(Dept. Chronomedicine, Hokkaido Univ. Grad Sch. Med, Sapporo, Japan)

Dr. Susumu Hagiwara is well known as a pioneer in understanding the mechanisms of excitability in nerve and muscle cells, but he started his scientific carrier studying mechanisms of rhythmic phenomena. His first paper demonstrated that cicadas begin to sing at a certain level of light in the morning and his thesis topic was the fluctuation of intervals in rhythmic excitation in frog stretch receptors. These facts could be the excuse to give Hagiwara lecture on the theme of circadian clock in the brain.

The mammalian circadian system consists of the master clock in the hypothalamic suprachiasmatic nucleus (SCN) and peripheral clocks throughout the body. Intracellularly, a molecular feedback loop involving clock genes and their protein products is regarded as the molecular machinery for circadian rhythm generation. The SCN entrains to an environmental light-dark cycle and resets the peripheral clocks to accomplish temporal coordination of physiological functions in a day. The mechanisms how the SCN works as the master clock out of numerous bodily clocks have not been clarified, but the networks of heterogeneous oscillator neurons in the SCN seem to play an important role. Bioluminescence and fluorescence reporters enabled us to monitor gene expression and cellular functions for days and weeks from single cells as well as tissues. Ex vivo and in vivo imaging of "clock time" gradually unveils the network properties of the circadian clock. Not only neuronal interactions but also diffusible signals differentially involve in the oscillatory networks depending on postnatal development. (COI:No)

Special Lecture

March 24 (Thu), 10:30 – 11:30, Room A

3SL1A5

Cl^- and H^+ as mediators of biofunction and biodysfunction in health and disease

Marunaka Yoshinori[1,2]

(*[1]Dept Mol Cell Physiol, Grd Sch Med Sci, Kyoto Pref Univ Med, Kyoto, Japan*、*[2]Dept Bio-Ionomics, Grd Sch Med Sci, Kyoto Pref Univ Med, Kyoto, Japan*)

It is well known that one of the most important key factors for homeostasis of our body function is the ion environment, which is regulated by various ion channels/transporters. In this special lecture, I provide ideas how ion environments such as cytosolic Cl^- concentration and pH are regulated and participate in retaining homeostasis of our body function. 1) Cl^- is the major anion existing in our body fluid, however little information is available on function of Cl^- as the second messenger of hormones. I introduce evidence that cytosolic Cl^- plays key roles in regulation of various cell functions including cell growth, neurite elongation, cytoskeleton formation, gating kinetics and gene expression of ion channels, and activity of enzymes. 2) H^+ is well known to regulate various enzymes. Blood pH is finely regulated to be within 7.35-7.45 under the physiological condition, however little information is available on pH of interstitial fluid. I provide evidences on low pH of interstitial fluid in diabetes mellitus (DM) even if blood pH is within the physiological range (7.35-7.45), and low pH of interstitial fluid produces insulin resistance. I also propose an idea that low pH of interstitial fluid in DM is one of the most important key factors developing Alzheimer-type dementia: at the present time an epidemiological study has indicated that DM patients have a higher risk developing Alzheimer-type dementia than non-DM with little explanation on the mechanism easily developing Alzheimer-type dementia in DM compared with non-DM. (COI:No)

Special Lecture

March 24 (Thu), 14:00 – 15:00, Room A

3SL2A6

We need the brain to cure the spinal cord injury.

Isa Tadashi

(*Dept Neurosci, Grad Sch Med, Kyoto Univ, Kyoto, Japan*)

After spinal cord injury (SCI), patients experience severe paralysis but considerable recovery can occur through rehabilitative training, however, the underlying neuronal mechanism is still elusive. We are studying the mechanism of recovery after partial SCI using non-human primate model combining multidisciplinary approaches. It is generally accepted that direct connection from the motor cortex to spinal motoneurons is first established in higher primates through evolution and this direct pathway has been regarded as the basis of dexterous hand movements in these species. However, in addition to the direct pathways, there exist indirect pathways mediated by propriospinal neurons (Alstermark and Isa, Ann Rev Neurosci, 2012). Recently, we clarified that after lesion of the direct pathway, such indirect pathway can compensate for the hand movements, first by classical lesion experiments, and more recently by a novel viral vector system that enabled pathway-selective and reversible transmission blockade in macaque monkeys (Kinoshita et al. Nature, 2012). Moreover, we showed that various cortical areas including ipsilateral M1 and ventral premotor cortex are causally involved in the functional recovery (Nishimura et al. Science, 2007). In addition, we found that the nucleus accumbens (NAc) increases the activation during the recovery in association with the motor cortex, and causally contributes to the recovery by local inactivation technique (Sawada et al. Science 2015). This may underlie the mechanism of how the motivation facilitates the functional recovery. Such knowledge will contribute to development of novel therapeutic strategies against the SCI. (COI:No)