



# The 2008 Kyoto Prize Workshop in Basic Sciences

## Symposium

### “Signal Network in Biological Functions”

Laureate: Dr. Anthony James Pawson

[Distinguished Investigator, Samuel Lunenfeld Research  
Institute of Mount Sinai Hospital]

[University Professor, University of Toronto]

13:00 - 17:00, November 12, 2008 (Wed.)  
Kyoto International Conference Center

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## **Program**

### **Coordinator**

Shigetada Nakanishi

(Chairman, Kyoto Prize Committee; Director, Osaka Bioscience Institute)

### **Coordinator/Moderator**

Kozo Kaibuchi

(Member, Kyoto Prize Selection Committee; Professor, Graduate School of Medicine, Nagoya University)

13:00 **Opening Address**  
Shigetada Nakanishi

**Introduction of Laureate**  
Kozo Kaibuchi

**Laureate Lecture**  
Anthony James Pawson (the Laureate in Basic Sciences)  
“SH2 domains, Adapters and Tyrosine Kinases: Back to the Future”

**Lecture**  
Ryuichi Sakai (Chief, Growth Factor Division, National Cancer Center  
Research Institute)  
“Roles of Phosphotyrosine-Containing Molecules in Tumor Progression”

### **Intermission**

**Lecture**  
Michiyuki Matsuda (Professor, Graduate School of Biostudies, Kyoto  
University)  
“Live Cell Imaging of the Growth Signaling Network”

**Lecture**  
Kozo Kaibuchi  
“Signalling for Cell Polarity”

**Lecture**  
Shizuo Akira (Member, Kyoto Prize Selection Committee; Director, WPI  
Immunology Frontier Research Center, Osaka University)  
“Pathogen Recognition: Receptors and Signaling”

17:00 **Closing**

## **Abstract of the Laureate Lecture**

Dr. Anthony James Pawson

Distinguished Investigator, Samuel Lunenfeld Research Institute of Mount Sinai Hospital

University Professor, University of Toronto

### SH2 domains, Adapters and Tyrosine Kinases: Back to the Future

The majority of human proteins have a modular organization, in the sense that they possess one or more conserved domains, that either control specific molecular interactions or catalyze biochemical reactions. Interaction domains, in particular, are important in signal transduction, through their ability to link receptors to their intracellular targets and to selectively recognize sites of post-translational modification, such as phosphorylation. Individual domains can gain new properties through their covalent linkage to other domains, during the course of evolution. From this point of view, protein domains can be viewed as fundamental units of biological information, that can gain new properties either by intrinsic alterations to their biochemical functions, or by association with other domain types.

The Src homology 2 (SH2) domain is the prototypic interaction module, which functions in tyrosine kinase signaling through the direct and specific recognition of phosphotyrosine-containing peptide motifs sites on receptors and docking proteins. In addition, SH2 domains can undergo intramolecular interactions with linked domains, to regulate catalytic activity and protein-protein interactions. We originally identified the SH2 domain as an element that plays an essential positive role in stimulating the catalytic activity, substrate recognition and transforming properties of an oncogenic variant of the Fps/Fes tyrosine kinase. We have now identified the structural mechanism through which the Fes SH2 domain enhances kinase activity and selective phosphorylation of primed substrates. A related mechanism, involving a distinct SH2-kinase interface, appears important for the active Abl tyrosine kinase.

SH2 domains are frequently found in proteins that exclusively contain other types of interaction domains, such as SH3. We have termed such proteins adapters, since they serve to couple activated receptors to specific downstream targets. Such adapters can have broad and varied effects on cellular function. As an example, the Nck SH2/SH3 adapters link phosphotyrosine sites to regulation of the actin cytoskeleton. Data from mice containing mutant alleles of Nck1 and Nck2 have implicated these adapters in the morphology and function of podocytes, specialized cells in the glomeruli that form the kidney filtration barrier, and in the regulated projection of spinal cord neurons important for limb coordination.

## **Abstracts**

Ryuichi Sakai

Chief, Growth Factor Division, National Cancer Center Research Institute

### **Roles of Phosphotyrosine-Containing Molecules in Tumor Progression**

Phosphorylation of proteins at tyrosine residues is involved in the rapid and reversible regulation of various cell functions by modulating protein-protein interactions, protein conformation, localization and stability. On the other hand, dysregulation of protein tyrosine phosphorylation during the cancer development can be causative of malignant characteristics of cancer cells which leads to abnormal proliferation, metastasis and invasion. In addition to the activation of several receptor type tyrosine kinases, activation of non-receptor type tyrosine kinases such as Src family kinases is found to be responsible for the constitutive tyrosine phosphorylation of proteins during cancer progression. We have been working on the identification and functional analysis of proteins which are aberrantly phosphorylated by Src family kinases in association with malignant phenotypes of cancer. The biological role of such substrates of Src tyrosine kinases including p130Cas and CDCP1 during the progression of cancers will be discussed.

Michiyuki Matsuda

Professor, Graduate School of Biostudies, Kyoto University

### **Live Cell Imaging of the Growth Signaling Network**

After the discovery of the phosphotyrosine recognition by the SH2 domain, the elaborate map of growth signaling network has emerged primarily based on the information of protein-protein interactions. To animate this static map of the growth signaling network into a dynamic organism in the virtual space, we need to input spatio-temporal information on the signaling molecules. Unfortunately, however, the current techniques of molecular biology and biochemistry fall short to this demand. One answer to this task is the live cell imaging with fluorescence probes. In particular, probes based on the principle of fluorescence resonance energy transfer (FRET) enable us to visualize protein-protein interaction or conformational change of a protein in living cells, allowing us to extract parameters of the spatio-temporal information of the signaling cascades. Thus, the FRET probes enable us to study 'Real-time Spatio-temporal Biology'.

## **Abstracts**

Kozo Kaibuchi

Professor, Graduate School of Medicine, Nagoya University

### **Signalling for Cell Polarity**

In response to extracellular and intracellular signals, cell exhibits a polarized morphology with adhering neighboring cells and extracellular matrix. Cell polarization is a fundamental process that makes cells enable to exert specific physiological roles in tissues. A migrating cell has front-rear polarity for directional and persistent migration, and a neuron is highly polarized and comprised of two structurally and functionally distinct parts, an axon and dendrites. The adapter molecules such as Par3 and Par6 play critical roles in establishment of polarity of certain types of cells including epithelial cells, neurons and migrating cells. We have been studying the roles of the Rho family GTPases and revealing that the Rho family play important roles in cell polarization through the regulation of cytoskeleton and cell adhesion. Recent studies suggest that the interaction of the Par proteins with the Rho family is essential for cell polarization. I will talk about the interplay between the Par proteins and Rho family that regulate the front-rear polarity of migrating cells.

Shizuo Akira

Director, WPI Immunology Frontier Research Center, Osaka University

### **Pathogen Recognition: Receptors and Signaling**

The mammalian immune response can be broadly categorized into adaptive immunity and innate immunity. Innate immunity is mediated by the action of phagocytes such as macrophages and dendritic cells, and was formerly considered as non-specific. However, recent findings have shown that the innate immunity is not necessarily non-specific, but is specific enough to discriminate pathogens and self. Furthermore, accumulating evidence indicates that activation of innate immunity is essential to development of acquired immunity. Toll-like receptors (TLRs) play a critical role in such innate immunity. Individual TLRs recognize different microbial components and sense invasion of all pathogens from bacteria to viruses. Similarly, the signaling pathways among TLRs are different each other, resulting in induction of different patterns of gene expression. Recently, besides TLRs, cytoplasmic proteins involved in pathogen recognition have been identified. Thus, mammals can sense pathogen invasion by utilizing both membrane and cytoplasmic receptors.