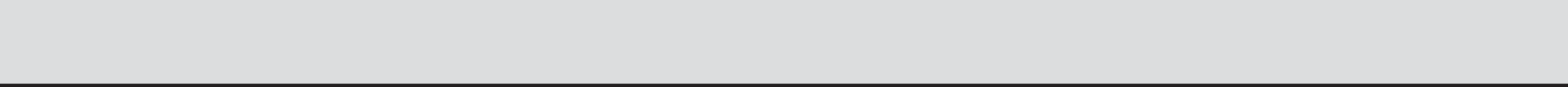


**Verne Chapman Memorial Lecture &
Plenary Talk & RIKEN Sympo
Abstracts VC1-PL10**



Verne Chapman Memorial Lecture Sunday October, 28**5.20 – 6.20pm**

VC1

BIOLOGICAL ROBUSTNESSHiroaki Kitano

The Systems Biology Institute

Robustness is a ubiquitously observed property of biological systems. It is considered to be a fundamental feature of complex evolvable systems. It is attained by several underlying principles that are universal to both biological organisms and sophisticated engineering systems. Robustness facilitates evolvability and robust traits are often selected by evolution. Such a mutually beneficial process is made possible by specific architectural features observed in robust systems. But there are trade-offs between robustness, fragility, performance and resource demands, which explain system behaviour, including the patterns of failure. Insights into inherent properties of robust systems will provide us with a better understanding of complex diseases and a guiding principle for therapy design.

Plenary Talk 1 Monday October, 29**8.30 – 9.00am****PL1****Stochasticity and Networks in Genomic Data**John Quackenbush

Dana-Farber Cancer Institute and the Harvard School of Public Health

Two trends are driving innovation and discovery in biological sciences: technologies that allow holistic surveys of genes, proteins, and metabolites and a realization that biological processes are driven by complex networks of interacting biological molecules. However, there is a gap between the gene lists emerging from genome sequencing projects and the network diagrams that are essential if we are to understand the link between genotype and phenotype. 'Omic technologies were once heralded as providing a window into those networks, but so far their success has been limited. To circumvent these limitations, we developed a method that combines 'omic data with other sources of information. Here we will present an approach that uses literature networks as constraints on a Bayesian Network analysis of microarray data, we show that we are able to recover evidence for a wide range of known networks and pathways, even in experiments not explicitly designed to probe them.

With a putative gene-interaction network, the problem of producing viable models of the cell remains. While systems biology approaches that attempt to develop quantitative, predictive models of cellular processes have received great attention, it is surprising to note that the starting point for all cellular gene expression, the transcription of RNA, has not been described and measured in a population of living cells. To address this problem, we propose a simple model for transcript levels based on Poisson statistics and provide supporting experimental evidence for genes known to be expressed at high, moderate, and low levels. Not only do these data confirm our model, but this general strategy opens up a potential new approach, Mesoscopic Biology, that can be used to assess the natural variability of processes occurring at the cellular level in biological systems.

Plenary Talk Monday October, 29**11.00 – 11.30am****PL2****RAT GENOMICS, GENETICS AND RESOURCES**Tadao Serikawa

Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University

The laboratory rat (*Rattus norvegicus*) is an indispensable tool in experimental medicine and drug development. The EU STAR project proposes to initiate complete genetic dissection of the ancestral segments of the most commonly used inbred strains. The proposed SNP-based haplotype map will be a useful tool for functional genomics, particularly for positional cloning of QTLs. The second term of the National Bio Resource Project for the Rat in Japan started in 2007, following completion of the first term (2002-2006). The major aims of NBRP-Rat are the collection, preservation and supply of rat strains. The repository includes spontaneous mutants, congenic and recombinant strains as well as transgenic and mutagenized rats. Furthermore, NBRP-Rat provides a unique database of various rat strain phenotypes accompanied by basic genetic information.

<http://www.anim.med.kyoto-u.ac.jp/NBR>

The following points will be emphasized. 1) Rat models not only complement but also expand and improve the knowledge obtained from experiments using mouse models. 2) Collaboration between NBRP-Rat and STAR/EURATools contributes to the promotion of biomedical sciences in the genome era. 3) The LEXF/FXLE RI strain set consists of 36 lines and is available for genetic analysis in a variety of research topics. 4) In addition to the completion of genome sequencing of the BN rat, genome sequences of additional rat strains are required, for instance F344/Stm, LE/Stm, SHR and WKY.

Plenary Talk Monday October, 29**2.00 – 2.30pm****PL3****HIGH-THROUGHPUT GENE TARGETING IN MOUSE EMBRYONIC STEM CELLS**William C. Skarnes

Wellcome Trust Sanger Institute

The European Conditional Mouse Mutagenesis program (EUCOMM) and Knockout Mouse Project (KOMP) aim to provide a public resource of thousands of lacZ-tagged, conditional mutations in ES cells over the next 5 years. This effort requires the design and construction of vectors and the production of targeted ES cell lines on an unprecedented scale, beyond the scope of conventional methodologies.

We have established a high-throughput pipeline at the Sanger Institute for the construction of plasmid-sized conditional gene targeting constructs through recombineering of an indexed BAC library. Our strategy combines automated vector design with a highly efficient recombineering process that involves serial liquid handling in a 96-well format. Importantly, our approach is modular, allowing us to match the specific requirements of the target locus with the optimal targeting cassette through the use of custom GatewayTM exchange elements. The inherent flexibility of the system also enables the re-use of the library of targeting vectors to keep pace with innovations in gene targeting technology and to generate other useful alleles in the mouse. Large-scale production of targeted ES cell lines is now underway and a summary of our progress will be presented.

Taking advantage of the library of EUCOMM/KOMP targeting vectors, we are currently developing high-efficiency strategies for the generation of homozygous mutant ES cells and for epitope-tagging of genes expressed in ES cells. These large collections of targeting vectors and targeted ES cells will thus provide investigators with essential reagents for the detailed analysis of gene function in the mouse.

Plenary Talk Monday October, 29**5.00 – 5.30pm****PL4****INDUCTION OF PLURIPOTENCY BY DEFINED FACTORS**Shinya Yamanaka

Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Japan & CREST, JST, Japan

Clinical application of human ES cells faces difficulties regarding use of human embryos, as well as tissue rejection following implantation. One way to circumvent these issues is to generate pluripotent cells directly from somatic cells.

We have previously shown that pluripotent stem cells can be induced from mouse fibroblasts by retroviral introduction of Oct3/4 (also called Pou5f1), Sox2, c-Myc and Klf4, and subsequent selection for Fbx15 (also called Fbxo15) expression. These induced pluripotent stem (iPS) cells (hereafter called Fbx15 iPS cells) are similar to embryonic stem (ES) cells in morphology, proliferation and teratoma formation; however, they are different with regards to gene expression and DNA methylation patterns, and fail to produce adult chimaeras. Here we show that selection for Nanog expression results in germline-competent iPS cells with increased ES-cell-like gene expression and DNA methylation patterns compared with Fbx15 iPS cells. The four transgenes (Oct3/4, Sox2, c-myc and Klf4) were strongly silenced in Nanog iPS cells. We obtained adult chimaeras from seven Nanog iPS cell clones, with one clone being transmitted through the germ line to the next generation. Approximately 20% of the offspring developed tumors attributable to reactivation of the c-myc transgene. Thus, iPS cells competent for germline chimaeras can be obtained from fibroblasts, but retroviral introduction of c-Myc should be avoided for clinical application.

Plenary Talk Tuesday October, 30

8.30 – 9.00am

PL5

CONSTRUCTING THE GENOME NETWORK OF ADULT STEM CELLS

Christine A. Wells, George Mellick, Alan Mackay-sim

The National Centre for Adult Stem Cell Research, Eskitis Institute for Cell and Molecular Therapies, Griffith University

Adult stem cells offer exciting potential in the development of new models for human development and therapies for disease. The Australian National Centre for Adult Stem Cell Research generates adult stem cells from the olfactory epithelium of humans, mice and rats. The relative accessibility of this material facilitates the collection of stem cell lines from cohorts of patients with neurological disorders, including Parkinson's disease, Schizophrenia and motor neuron disease. Our approach is to generate large-scale genomic and transcriptomic stem cell datasets from donor populations, to investigate the genetic networks and cellular processes that are expressed in the olfactory stem cell niche, and to discover novel molecules involved in the olfactory stem-cell niche and neural differentiation. The application of this system to the study of neurological disorders offers several advantages over the study of other peripheral tissues, not least the ability to differentiate these cultures into relevant cell types differentiated into the cells of interest, including dopaminergic neurons to study Parkinson's disease.

Plenary Talk Tuesday October, 30**11.00 – 11.30am****PL6****THE SPATIO-TEMPORAL REGULATION OF SOMITOGENESIS**Yumiko Saga

National institute of genetics

The metameric structure of vertebrates is based on the periodic formation of somites from the unsegmented presomitic mesoderm (PSM). The periodicity is regulated by a segmentation clock and this temporal information is translated into the segmental units. We succeeded in visualization of the oscillation of Notch1-activity in mice, and found that the periodicity is generated by the negative-feedback function of Lunatic-fringe (L-fng), a glycosyltransferase in the posterior PSM. In the anterior PSM, a transcription factor *Mesp2* functions to translate information provided by segmentation clock into the segmental morphology. We previously showed that a T-box transcription factor, *Tbx6*, directly bound to the *Mesp2* enhancer and synergistically worked with Notch signaling to activate *Mesp2* transcription. To elucidate the spatio-temporal regulation of the periodic *Mesp2* expression by these factors, we used high-resolution in situ hybridization (ISH) and immunohistological techniques and successfully visualized these molecular relationships in individual cells. These experiments revealed that the Notch signal oscillation determines the timing of *Mesp2* transcription but not the place; conversely the *Tbx6* protein determines the anterior expression border of *Mesp2* transcription. I like to discuss the regulatory network centered by *Mesp2* function, implicated in the transition point from the PSM to the somite.

Plenary Talk Tuesday October, 30**2.00 – 2.30pm****PL7****Modeling Diabetes and Metabolic Syndrome**Takashi Kadowaki

Department of Metabolic Diseases, Graduate School of Medicine, University of Tokyo

Type 2 diabetes and metabolic syndrome are caused by interactions of genetic factors and environmental factors such as high-fat (HF) diet and sedentary lifestyle. Recent advances of genome research have revealed ~10 type 2 diabetes susceptibility genes such as SNPs in PPAR γ , adiponectin, HNF4 α , TCF7L2, and HHXE. We have been modeling diabetes and metabolic syndrome by generating genetically engineered mice models. Recent studies have revealed the following novel pathways in type 2 diabetes and metabolic syndrome: 1) Upregulation of IRS-2 is important in compensatory β cell hyperplasia in response to HF-diet induced insulin resistance. Failure of upregulation of IRS-2 may be causally involved in the development of type 2 diabetes. 2) Downregulation of adiponectin and adiponectin receptors (Adipo R1 and Adipo R2) are also causally involved in obesity-linked insulin resistance and type 2 diabetes. 3) Moreover, insulin signaling defect in endothelial cells may play a role in obesity-linked insulin resistance in the skeletal muscle. In this lecture, I will talk about recent advances in the understanding of molecular mechanism of type 2 diabetes and metabolic syndrome and also discuss about treatment strategies based upon susceptibility genes and molecular mechanisms of type 2 diabetes.

References

- 1) *Nature* 372: 182-186, 1994, 2) *J.Clin.Invest.* 99: 861-866, 1997, 3) *J.Clin.Invest.* 101: 1354-1361, 1998, 4) *J.Clin.Invest.* 106: 459-465, 2000, 5) *Nature Medicine* 7:941-946, 2001, 6) *Nature Medicine* 8: 1288-1295, 2002, 7) *Nature* 423: 762-769, 2003, 8) *J.Clin.Invest.* 114: 917-927, 2004, 9) *J.Clin.Invest.* 116: 1784-1792, 2006, 10) *Nature Medicine* 12:73-74, 2006, 11) *J.Clin.Invest.* 117: 246-257, 2007, 12) *Nature Medicine* 13: 332-339, 2007, 13) *Cell Metabolism* 6: 55-68, 2007

Plenary Talk Wednesday October, 31**8.30 – 9.00am****PL8****FUNCTION AND EVOLUTION OF MACROPHAGE-SPECIFIC PROMOTERS**David A. Hume

The Roslin Institute, University of Edinburgh

Macrophages are cells of the innate immune system. They have a remarkably diverse transcriptome, which has evolved rapidly between species in the face of the strong evolutionary pressure from potential pathogens. The systematic analysis of transcription start sites using CAGE and other approaches, combined with in-depth cDNA sequencing and microarray analysis, has revealed many aspects of the way that the macrophage transcriptome is controlled and enabled the construction of the first predictive transcriptional network models. Many genes have separate promoters used specifically by macrophages, and alternative promoter use, internal splicing and polyadenylation generates multiple protein isoforms from individual loci. A particular focus of my group has been on transcriptional control of macrophage-specific genes, exemplified by the gene encoding the receptor for macrophage colony-stimulating factor, the *csf1r* gene. The promoter of this gene is typical of a specific subclass of mammalian promoters that initiates transcription from a broad region, lacks a TATA box or GC-rich sequence, and instead has a purine-rich proximal promoter. CAGE analysis provided a definitive delineation of the transcription start sites of the *csf1r* gene in mouse and human, permitting an anchored functional alignment across multiple mammalian species. This alignment reveals that mouse and rat have distinctive architecture compared to other species; the same elements exist, sites for PU.1, AML1 and C/EBP, but they are in different relative positions. The alignment across species reveals a weakly conserved element immediately upstream of the transcription start site cluster. Despite the weak conservation, the mouse and human elements bind the same proteins, which we identified by purification and mass spectrometry peptide fingerprinting as the related FUS/TLS and EWS factors. These proteins are part of the basal transcription machinery, and likely substitute for TATA recognition by TBP in this class of promoters.

**RIKEN Symposium Wednesday October, 31
[The Transcriptom World]**

1.00 – 1.40pm

PL9

GENOME-WIDE MAPS OF THE HUMAN TRANSCRIPTOME REVEAL AN INTERLEAVED ORGANIZATION AND NOVEL SHORT AND LONG CLASSES OF RNAs

Thomas R. Gingeras
Affymetrix, inc

Genomic regions not coding for proteins nor involved in cis or trans-acting regulatory activities are at best viewed as sites for evolution-mediated experimentation of novel functional domains and at worst, “junk” However, recent unbiased empirical genomic wide have revealed that there are large portions of the non-protein coding are transcribed in a regulated fashion in several organisms including humans¹⁻³. A recurrent question derived from these recent findings centers upon the biological functions of the observed unannotated transcripts. Considerable portions of the unannotated transcription observed in these species serve as unreported parts of protein coding transcripts and as precursors to the generation of short RNAs. As part of the Encyclopedia of DNA Elements (ENCODE) project, studies reveal that more than half of the well characterized protein coding loci present in ENCODE designated human genome regions (~400) make use of tissue specific alternative, unannotated 5' transcriptional start sites (TSS) which for as much as 30% of the extended transcripts, are more than 200,000 nucleotides (nt) upstream of the annotated portions of the transcripts (108,000 nt on average). We have made similar observations in the organization and regulation of transcription during the first 24 hours of development of *Drosophila melanogaster*⁴. In addition, often sharing the same genome sequences as protein coding transcripts are distinct nuclear transcripts which serve as primary transcripts for the formation of small RNAs ranging in size from ~20-200 nt. Recently, two new classes of short RNAs have been identified from our analyses of the sites of transcription across the human genome. These data support a new model for genome organization which is not co-linear but rather lattice-like and in part focused on the production of short RNAs.

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**RIKEN Symposium Wednesday October, 31
[The Transcriptom World]**

1.40 – 2.20pm

PL10

THE RNA IMPACT ON THE CENTRAL DOGMA: THE ROAD TO KNOWLEDGE GOES THROUGH THE RNA CONTINENT

Yoshihide Hayashizaki

RIKEN Genomic Sciences Center

The first step on the road to knowledge was taken in 1995 when we first glimpsed the RNA complexity. We realized the need of new technologies to construct the full-length cDNA library (Cap trapper method, normalization, subtraction, new cDNA vector and thermoprotection technology of reverse transcriptase using trehalose), and high throughput sequencing (Riken integrated sequence analysis system; RISA) was essential to reach the goal of large-scale data collection. In order

to process the data we started to collect people, and the International FANTOM consortium was founded in 2000. The combination of talented people and data have given us millions of full-length cDNA sequences, CAGE tags and ditags, collected in the /de facto/ world standard database (5 visits/second)

The efforts of the FANTOM consortium have revealed non-coding RNA (ncRNA) as the major product of the genome (53%), and that the actual number of genes is diminished through the history of life science due to gene fusion, but increased by the number of ncRNA. We also learned that 72% of all genes have sense/antisense transcripts.

All the discoveries we have made regarding RNA have given us a new view of the central dogma, collapsing the old DNA to protein concept. The double stranded RNA (dsRNA) for RNAi cannot only be created by virus and miRNA and S/AS is a new source of dsRNA. RNA is flexible and regulates gene expression through RNAi and other mechanisms. Now we have found a group of transcription factors that act like a switch between RNAi and regular gene expression by interacting with the RNAi machinery directly. Altogether these new findings dissolve the central dogma into a new picture with new interaction cascade and the unexpected complexity of combined omics.

Key references:

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