1st DNAFORM seminar

Novel cellular functions revealed by Cap Analysis of Gene Expression (CAGE)

2023. 3.15 (Wed) 14:00-16:45 (Zoom webinar)

Host: Dr. Yoshihide Hayashizaki

Representative Director, Kabushiki Kaisha DNAFORM

A Cell Model to Study Embryonic Genome Activation

Dr. Juha Kere

Professor Biosciences and Nutrition, Karolinska Instituted (Sweden)

Development of new genomics tools to functionally annotate the human genome

Dr. Yasuhiro Murakawa

Professor, Human Genomics, Medical Science and Systems Biology, Kyoto University

Muscles-specific Transcribed Regulatory Elements in the Human Genome

Dr. Oleg Gusev

Senior Associate Professor at Graduate School of Medicine, Juntendo University

Development of Super High-speed Genomic analyzer, AAS-G1

Dr. Toshikazu Ebisuzaki

Chief Scientist, Computational Astrophysics Laboratory, RIKEN

Session 1 14:00-14:50 (Presentation: 40min, Q&A: 10min)

A Cell Model to Study Embryonic Genome Activation

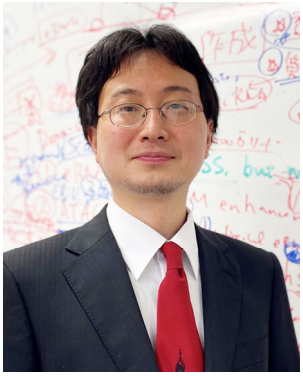
Dr. Juha Kere

Professor Biosciences and Nutrition, Karolinska Instituted

Juha Kere, MD, PhD, Professor of Molecular Genetics at Karolinska Institutet, Stockholm, Sweden, has broad experience in the molecular analysis of single-gene and complex disorders, and most recently, in embryo research and cellular reprogramming approaches. His laboratory recently reported the reprogramming of embryonic stem cells to the early 8-cell stage blastomere phenotype. Dr. Kere lived in Japan in 2017-2018 as a JSPS Senior Fellow and has served in Advisory Council tasks at RIKEN.

In human, Embryonic Genome Activation (EGA) occurs during days 2-3 after fertilization, at 4-8 cell stages, when the combined genes from the egg and sperm cells first start to be transcribed. EGA coincides with the reprogramming of the oocyte transcriptome to the totipotent cell phenotype of the 4-8 cell stage cells. We have earlier studied human EGA by single-cell RNA sequencing of oocytes, zygotes, and single cells from 4- and 8-cell stage embryos, altogether 348 cells (Töhönen & al. 2015). This study allowed us to list 32 genes activated at 4-cell stage compared to oocytes (minor EGA), 129 genes activated at 8-cell stage compared to 4-cell stage (major EGA), and thousands of specifically degraded mRNAs until the 4-cell stage, corresponding to ≈75% of oocyte mRNA content. We cloned new paired-like (PRDL) homeobox family genes not detected earlier active in any human tissues (Töhönen & al. 2015; Madissoon & al. 2016). Among the new genes, we found especially one, LEUTX, with a strong transcription activating function (Jouhilahti & al. 2016;). Recently, we have continued to characterize the roles of key genes, such as DUX4, the first transcript upregulated in the human zygote and rapidly degraded (Vuoristo & al. 2022). Our results implicated DUX4 functions to include chromatin modification, enhancer activation, transcriptional activation, and regulation of oocyte mRNA degradation. We also characterized the protein-protein interaction network of DUX4. However, work to understand human EGA in detail has been hampered not only by technical aspects, such as the requirement of highly sensitive methods to work with single cells, also by the rule that work destroying human embryos is not allowed by, e.g., the European Union funding schemes. Therefore, cell models to study human EGA and the genes involved in it are badly needed. Toward this aim, we succeeded in reprogramming human embryonic stem cells (hESCs) to 8-cell-like cells (8CLC, called by us as induced blastomeres, iBM) by a brief pulse of DUX4 expression (Yoshihara & al. 2022). Human 8CLCs had recently been derived also by chemical induction (Mazid & al. 2022). These two models will now allow the characterization of the differences resulting from chemical induction or reprogramming by gene activation.

The cell models now also open up new routes to study human EGA without harming human embryos, allowing manipulations such as inactivation of selected genes, studying effects of chemical compounds and biochemical changes, and drawing the complete landscape of human EGA.



Session 2 14:50-15:40 (Presentation: 40min, Q&A: 10min)

Development of new genomics tools to functionally annotate the human genome

Dr. Yasuhiro Murakawa

Professor, Human Genomics, Medical Science and Systems Biology, Kyoto University

Yasuhiro Murakawa graduated from Kyoto University School of Medicine (2008). After completing his residency at Kyoto University Hospital, he moved to the Max Delbrück Center for Molecular Medicine in Berlin, Germany. He obtained his PhD from Free University of Berlin (2014). He has been leading a laboratory at RIKEN since 2016 (Unit Leader at RIKEN Innovation Center since 2016, Team Leader at RIKEN Center for Integrative Medical Sciences since 2018, Group leader at IFOM in Milan since 2018). In 2020, he became a professor at the Kyoto University Institute for Advanced Study (KUIAS).

It has been about 20 years since the first draft of the human genome, the basic blueprint of the human species, was published. The deciphering of the human genome and the elucidation of its working principles have continuously required the development of new methodologies and innovative technologies. The human genome still contains a large number of regions of unknown function, and the majority of the human genome is still poorly understood. To understand the function of the human genome, it is useful to comprehensively analyze RNA molecules transcribed from the genome.

This lecture will introduce the human genome structure that has been clarified through the development of new genome technologies and recent efforts for medical applications.

Session 3 15:40-16:30 (Presentation: 40min, Q&A: 10min)

Muscles-specific Transcribed Regulatory Elements in the Human Genome

Dr. Oleg Gusev

Senior Associate Professor at Graduate School of Medicine, Juntendo University

Oleg Gusev got his PhD in 2007 at Okayama University Graduate School of Science and then in 2008-2012 served as JSPS Posdoctoral Fellow and then Researcher at the National Institute of Agrobiological Sciences, Tsukuba, focusing on adaptational biology of extremophile organisms. In 2012 he was invited to JAXA, where he managed several international projects in gene expression analysis in space biology. From 2014 to 2020 Dr. Gusev acted as a Translational Genomics Unit Leader at RIKEN. Since 2021 Dr. Gusev is a Senior Associate Professor at the Intractable Disease Research Center, Juntendo University School of Medicine, leading research in complex gene expression analysis of cardiovascular and skeletal muscle systems.

A deeper knowledge of the dynamic transcriptional activity of promoters and enhancers is needed to improve mechanistic understanding of the pathogenesis of muscle and cardiovascular diseases. In my talk, I will give an introduction and the first milestone of the international research initiative MUSLE FANTOM which uses cap analysis of gene expression (CAGE) to identify and quantify the activity of transcribed regulatory elements (TREs) in skeletal muscle and hearts. Our ultimate goal is to elucidate the genetic and transcriptional background of heterogeneity of resistance of different muscles to age-associated changes, dystrophy, and disuse-induced atrophy. As a first milestone of the project, we recently showed that there are thousands of heart-specific TRE and that these regulatory elements are alternatively transcribed in different heart regions, in healthy versus failing hearts, and in ischemic versus non-ischemic heart failure samples. Cardiac-disease-related single-nucleotide polymorphisms (SNP) appeared to be enriched in TREs, potentially affecting the allele-specific transcription factor binding. An open-source CAGE atlas will serve the cardiovascular community in improving the understanding of the role of the cardiac gene regulatory networks in cardiovascular disease and therapy.

Session 4 16:30-16:45 (Presentation: 10min, Q&A: 5min)

Development of Super High-speed Genomic analyzer, AAS-G1

Dr. Toshikazu Ebisuzaki

Chief Scientist, Computational Astrophysics Laboratory, RIKEN

Toshikazu Ebisuzaki was born in Yamaguchi Prefecture in 1958. After graduating from the Department of Physics, Osaka University, he entered the Graduate School of Science at the University of Tokyo, where he worked as a NASA researcher, an assistant at Kobe University, an assistant at the University of Tokyo, and an assistant professor there before becoming a senior scientist at RIKEN in 1995, where he remains today. He specializes in astrophysics and computational science.

In recent years, with the advent of next-generation sequencers, the cost of sequencing genomes which are the design information of life, has dropped dramatically, resulting in an explosion of genomic information, and it has become increasingly important to shorten the time required for its analysis.

Professor Junichiro Makino of Kobe University, together with Advanced Acceleration Systems, Inc. (President: Dr. Ryutaro Himeno), has developed the AAS-G1 ultra-fast genome analysis system. It consists of a desktop PC without expensive hardware such as GPUs or FPGAs.

The AAS-G1 performs a whole human genome analysis (x30) in about 25 minutes, achieving more than three times cost/performance ratio comparing with that of conventional systems. Conventionally, the reconstruction of whole genome sequence from the trace sequence data output from next-generation sequencers has conventionally used BWA-MEM, a computational method based on the Burrows-Wheeler transformation. Professor Makino has invented an index data structure (patent pending) that enables much faster searches than BWA-MEM, achieving the dramatical acceleration of several dozens of times or more comparing with BWA-MEM. Accuracy has also been confirmed to surpass BWA-MEM results.

In addition, the updated version of AAS-G1, which designed to detect structural variants, is scheduled to be completed soon. It will detect not only germline mutations, but also structural variants and accelerate the whole-genome analysis of cancers to identify appropriate molecular targets for cancer chemotherapy. The AAS-G series will have a great potential to promote personalized medicine. Advanced Acceleration Systems Co., Ltd. will start selling AAS-G1 to give a great impact on the price of genome analysis.

Registration URL

https://us06web.zoom.us/webinar/register/WN_8S-3_SZMRAe9SuZPWpHNvA

- This webinar is free for participating.
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