WORKSHOP REPORT

UNDER THE U.S.-JAPAN COOPERATIVE CANCER RESEARCH PROGRAM

AREA	(1). Basic Science 2. Clinical Science 3. Epidemiology & Behavioral Science

Date: Nov. 25, 2011

1. Title of Workshop: Cancer Genomics and Epigenomics: Towards personalized cancer medicine

2. Period of Workshop: from October 24 to October 26, 2011, 3 days

3. Place of Seminar: City / country Kyoto/Japan

4. Total Budget

a. Financial Support by JSPS: Total amount: 8,993 thousand yen

b. Financial Support by NCI : Total amount: U.S. dollar

c. Other Financial Support : Total amount: 2,155 thousand yen (Tanaka FIRST program)

5. Organizers

a. Japanese Organizer	
Name	**Hiroyuki Aburatani**
Institution / Department Position	**University of Tokyo /Research Center for Advanced Science and Technology** **Professor**
b. U.S. Organizer	
Name	**Matthew Meyerson**
Institution / Department Position	**Dana-Farber Cancer Institute, Harvard Medical School** **Professor of Pathology**

6. Participants

Number of Participants: Japanese: 15 U.S.: 15 Others: 13

a. List of Japanese-side Participants（Except for Organizer）

Name	Institution/Department	Position
Daigo, Yataro	1Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, The University of Tokyo / 2Department of Medical Oncology, Shiga University of Medical Science	Professor
Inoue, Satoshi	Departments of Anti-Aging Medicine and Geriatric Medicine, Graduate School of Medicine, The University of Tokyo / Research Center for Genomic Medicine, Saitama Medical University	Professor
Ishikawa, Fuyuki	Kyoto University, Graduate School of Biostudies	Professor
Ishikawa, Shumpei	Department of Pathology, Graduate School of Medicine, The University of Tokyo	Associate Professor
Ito, Takashi	Department of Biophysics and Biochemistry, Graduate School of Science, University of Tokyo	Professor
Kondo, Yutaka	Division of Molecular Oncology, Aichi Cancer Center Research Institute	Section Head
Mano, Hiroyuki	Division of Functional Genomics, Jichi Medical University / Department of Medical Genomics, Graduate School of Medicine, TheUniversity of Tokyo	Professor
Mori, Seiichi	The Cancer Institute of Japanese Foundation of Cancer Research Division of Cancer Genomics	Senior Research Fellow
Nakagawa, Hidewaki	Laboratory for Biomarker Development, RIKEN Center for Genomic Medicine	Team Leader
Ogawa, Seishi	Cancer Genomics Project, The University of Tokyo	Associate Professor
Saya, Hideyuki	Division of Gene Regulation, Institute for Advanced Medical Research Keio University School of Medicine	Professor
Shibata, Tatsuhiro	Division of Cancer Genomics, National Cancer Center Research Institute	Chief
Takahashi, Takashi	Division of Molecular Carcinogenesis, Center for Neurological Diseases and Cancer, Nagoya University	Professor
Tsunoda, Tatsuhiko	Research Group for Medical Informatics, RIKEN Center for Genomic Medicine	Group Director
Nakagama,Hitoshi Yoshida,Teruhiko Totoki,Yasushi	National Cancer Center Research Institute National Cancer Center Research Institute National Cancer Center Research Institute	Other participants Other participants Other participants

b. List of US-side Participants（Except for Organizer）

Name	Institution/Department	Position
Matthew Ellis	Washington University School of Medicine	Professor
Robert Gentleman	Bioinformatics and Computational Biology, Genentech Inc.	Senior Director
Neil Hayes	Lineberger Comprehensive Cancer Center Division of Medical Oncology Department of Internal Medicine University of North Carolina, Chapel Hill	Associate Professor
Hanlee Ji	Department of Medicine / Division of Oncology Stanford University School of Medicine And Stanford Genome Technology Center	Senior Associate Director
Raju Kucherlapati	Paul C. Cabot Professor of Genetics and Professor of Medicine, Harvard Medical School	Professor
Thomas LaFramboise	Department of Genetics, Case Western Reserve University School of Medicine	Assistant Professor
Bradley Ozenberger	The Cancer Genome Atlas (TCGA), National HumanGenome Research Institute	Program Director
Donald Parsons	Texas Children's Cancer Center and Depts. of Pediatrics and Molecular and Human Genetics, Baylor College of Medicine / Ludwig Center for Cancer Genetics and Therapeutics, Johns Hopkins Kimmel Cancer Center	Assistant Professor
Scott Powers	Cold Spring Harbor Laboratory	Associate Professor
Joshua Stuart	The University of California Santa Cruz	Associate Professor
Angela Ting	Cleveland Clinic Lerner Research Institute	Associate Professor
David Wheeler	The TCGA Research Network Human Genome Sequencing Center, Baylor College of Medicine	Associate Professor
Catherine Wu	Division of Hematologic Neoplasia, Dana-Farber Cancer Institute, Harvard Institutes of Medicine	Assistant Professor
Zemin Zhang	Department of Bioinformatics and Computational Biology, Genentech Inc.	Principal Scientist

c. List of Other Country Participants

Name	Institution/Department /Position	Country

7. Agenda and Topics of Workshop

Day 1 - October 24
key note
Raju Kucherlapati: Genetics and Genomics of Colorectal Cancer
Hiroyuki Mano: ALK Fusions, Novel Targets in Lung Cancer
genomic technology
Hanlee Ji: From Whole Cancer Genome Sequencing to Clinical Diagnosis - Bridging the Translational Gap towards with Novel Diagnostic Technologies
Tatsuhiko Tsunoda: Comprehensive Whole-Genome Sequence Analysis of Cancer
Thomas LaFramboise: Statistical Analysis of Allelic Imbalance in Tumors for Cancer Gene Identification
Robert Gentleman: A Comparison of 454 and Illumina for RNA-sequencing
TCGA/ICGC
Bradley Ozenberger: The Cancer Genome Atlas: A Status Report
Hidewaki Nakagawa: Whole Genome Sequencing for Somatic Mutation Detection of Virus-related Hepatocellular Carcinoma
somatic mutation 1
David Wheeler: Mutational Analysis of Primary and Recurrent Tumors in Ovarian Cancer
Hiroyuki Aburatani: Genomic Instability Caused by MLH1 Haploinsufficiency in Pancreatic Cancer
Donald Parsons: The Genetic Landscape of the Childhood Cancer Medulloblastoma
somatic mutation 2
Scott Powers: Oncogenomic Screening in Hepatocellular Carcinoma
Tatsuhiro Shibata: Whole Genome Sequencing of Virus- Associated Hepatocellular Carcinoma
Catherine Wu: SF3B1 and Other Novel Cacner Genes in Chronic Lymphocytic Leukemia
Seishi Ogawa: Genetic Analysis of Myelodysplastic Syndromes and Related Disorders

Day 2 - October 25
somatic mutation 3: lung cancer
Seiichi Mori: Exploration of Molecular Targets for Ovarian Serous Adenocarcinomas with Poor Prognoses
Yataro Daigo: Variation in TP63 Gene Confers the Risk of Lung Adenocarcinoma in the East Asian Population
Matthew Meyerson: Genomic Analysis of Human Lung Cancer
Takashi Takahashi: Metastasis-Suppressing MYBPH as a Novel Transcriptional Target of TTF-1 Lineage-Survival Oncogene in Lung Adenocarcinoma
Neil Hayes: Genomic Classification of Tumors of The Lung
Zemin Zhang: Combined Whole Genome and Transcriptome Analysis of Lung and Liver Cancers

Day 3 – October 26
epigenetics
Takashi Ito: Whole-Genome Bisulfite Sequencing from Subnanogram Quantities of DNA
Angela Ting: Genome-Wide DNA Methylation Profiling in Colon Cancer
Yutaka Kondo: Epigenetic Regulatory Network in Plastic Interconvertibility between Tumor-Initiating Cells and Non-Tumor- Initiating Cells
Fuyuki Ishikawa: Highly Conserved Molecular Architectures of Telomeres in Eukaryotes
data analysis
Shumpei Ishikawa: Systematic Profiling of Cancer- Microenvironment Interactome in Cancer Tissue
Joshua Stuart: Predicting the Impact of Mutations in Cancer Using an Integrated Pathway Approach
Satoshi Inoue: Genome-wide Androgen Receptor Signaling in Prostate Cancer
beyond sequencing: translational medicine
Hideyuki Saya: Role of CD44v in Cancer Stem Cells
Matthew Ellis: Analysis of Luminal-Type Breast Cancer by Massively Parallel Sequencing

8. Scientific Achievements

The all speakers presented evocative wide range of research progresses including the leading-edge topics, and we had very active discussions about these subjects. The followings are the abstracts of each speaker.

key note

Raju Kucherlapati: Genetics and Genomics of Colorectal Cancer

The Cancer Genome Atlas (TCGA) network has examined a set of 224 tumor/normal pairs of colorectal cancer for changes in somatic copy number, chromosomal structural aberrations, expression profiling, promoter DNA methylation, miRNA expression and somatic mutations in all 23,000 genes. Our integrative analyses show that besides the well known genes such as APC, KRAS, PIK3CA and TP53 and pathways such as WNT, MAP Kinase, PI3 Kinase and TGFB involved in these tumor types there are several additional features that are important for tumor development. Integrative analysis of the data obtained through the different platforms also enabled us to identify several critical pathways that are altered in specific subsets of the tumors.

Hiroyuki Mano: ALK Fusions, Novel Targets in Lung Cancer

We have discovered, from a specimen of non-small cell lung cancer (NSCLC), a novel oncogenic fusion-type tyrosine kinase EML4-ALK. Transgenic mice expressing EML4-ALK in lung epithelial cells developed hundreds of adenocarcinoma nodules in both lungs only at a few weeks after birth, and oral administration of a specific inhibitor to ALK successfully cleared such nodules from the mice. We started from early 2009 “ALK Lung Cancer Study group (ALCAS)”, a nation-wide diagnostic network for such tumors. Through this activity, we discovered another fusion of ALK in NSCLC, KIF5B-ALK. Currently, crizotinib, one of the ALK inhibitor, has been just made public.
Through the ALCAS initiative, we also noticed a patient who was once effectively treated with crizotinib, but later underwent abrupt relapse. Molecular analyses of these specimens led to the discovery of secondary mutations within EML4-ALK accounting for the observed drug tolerance.
Our data thus demonstrate that a subset of lung cancer express previously unidentified fusion kinases that are promising candidates for a therapeutic target as well as for a diagnostic molecular marker for this intractable disorder.

genomic technology

Hanlee Ji: From Whole Cancer Genome Sequencing to Clinical Diagnosis - Bridging the Translational Gap towards with Novel Diagnostic Technologies

Whole genome sequencing IWGS) has limited effectiveness at specific types of mutations and genomic aberrations. To overcome limitations of detection with either current diagnostic methods or WGS, we have developed technologies that enable us to rapidly target nearly any non-repetitive region-of-interest in a genome and employ robust deep resequencing methods to determine the presence of minor allele mutations and sequences of complex genomic structure. We are applying these methods towards gastric cancer with potential for combined personal therapeutic target identification and metastatic recurrence risk assessment.

Tatsuhiko Tsunoda: Comprehensive Whole-Genome Sequence Analysis of Cancer

We are now participating in the International Cancer Genome Consortium (ICGC), and making precise catalogues of somatic alterations in 500 virus-associated hepatocellular carcinomas (HCCs). That work allowed us to establish methodologies for detecting multiple types of variations: single nucleotide variations (SNVs), structural variations including copy number variations (CNVs), and novel sequences. We confirmed that our methods could detect these multiple types of variation with high accuracy.

Thomas LaFramboise: Statistical Analysis of Allelic Imbalance in Tumors for Cancer Gene Identification
Allelic imbalance (AI) occurs in a tumor cell. Our laboratory applies statistical techniques from population genetics to high-dimensional allelic data with the goal of identifying genes with important roles in tumorigenesis. We have developed a technique to localize focal regions of LOH by adapting classical Hardy-Weinberg disequilibrium measures, and statistical tests - termed the amplification disequilibrium test (ADT) and the deletion disequilibrium test (DDT) - to detect allelic selection in cancer cells.

Robert Gentleman: A Comparison of 454 and Illumina for RNA-sequencing
We recently carried out deep sequencing of two cell lines using both 454 and Illumina sequencing. The former were single long sequences (about 430nt each) while the latter were 75nt paired end sequences. The sequences were aligned to the genome using gMAP (Wu and Watanabe, 2005) and gSNAP (Wu and Nacu, 2010). We then performed a detailed comparison of the two methodologies.

TCGA/ICGC
Bradley Ozenberger: The Cancer Genome Atlas: A Status Report
The Cancer Genome Atlas (TCGA) is a large-scale effort to obtain a complete description of the genetic basis of human cancers by developing a comprehensive catalog of the significant genomic alterations in all major types of cancer. TCGA will analyze over 3,000 tumor cases representing as many as 20 types of cancer by the end of 2011. Achieving this goal has required substantial efforts in three areas: sample accrual, technological innovation, and data management/analysis innovation. Progress in each of these areas and the current status of active tumor projects within the TCGA program were described.

Hidewaki Nakagawa: Whole Genome Sequencing for Somatic Mutation Detection of Virus-related Hepatocellular Carcinoma
Hepatitis B or C virus infection is the critical risk factor for HCC development. Here we have sequenced and analyzed whole genomes of multiple HCCs, including two sets of multi-centric occurrences, and their corresponding lymphocytes. A combination of statistical and functional analyses, together with validation cohorts, yielded a long-tailed list of recurrently mutated genes and found some driver gene candidates among them.

omatic mutation 1
David Wheeler: Mutational Analysis of Primary and Recurrent Tumors in Ovarian Cancer
Late stage ovarian cancer recurs in approximately 25% of patients after standard surgical and chemotherapy treatments. The TCGA network secured normal, primary and recurrent tumors from 17 patients, the largest set of primary and recurrent tumors ever analyzed. We performed whole exome and whole genome shotgun sequencing on these patients and characterized the mutations and mutation rates from each patient. We observed that the number of mutations present in these ovarian tumors is higher than originally suspected.

Hiroyuki Aburatani: Genomic Instability Caused by MLH1 Haploinsufficiency in Pancreatic Cancer
We here performed Exome sequencing of 15 pancreatic cancer cell line-normal pairs. We captured 162,073 exons of 16,954 genes and sequenced the targeted regions to a mean coverage of 56 folds by Illumina GAIIx. We identified a total of 1,517 somatic mutations and validated 934 of them by transcriptome sequencing. We detected recurrent mutations in 56 genes, among which 41 have not been reported to be mutated in cancer. The mutation rates varied widely among tumors and were significantly correlated with the MLH1 copy-number status. With the additional analysis, our data suggest that MLH1 hemizygous deletion, through increasing the mutation rate of somatic indels, could drive the development and progression of sporadic cancers.

Donald Parsons: The Genetic Landscape of the Childhood Cancer Medulloblastoma
Medulloblastoma (MB) is the most common malignant brain tumor of children. Although aggressive multimodal therapy has improved the prognosis for children with these tumors, a significant proportion of patients are currently incurable. Moreover, survivors often suffer significant treatment-related morbidities, including neurocognitive deficits related to radiation therapy. New insights into the pathogenesis of these tumors are therefore sorely needed. Gene-based research has identified two subgroups of MBs, one associated with mutated genes within the Hedgehog pathway and the other associated with altered Wnt pathway genes. Our results highlight the important connection between genetic alterations in the cancer genome and epigenetic pathways and provide potentially new avenues for research and disease management in MB patients.

somatic mutation 2
Scott Powers: Oncogenomic Screening in Hepatocellular Carcinoma
Hepatocellular carcinoma (HCC) afflicts more than 560,000 people worldwide each year and has one of the worst one-year survival rates of any cancer type. Currently, there aren't any molecular therapies that target specific mutations or other genetic alterations in HCC. We screened 124 genes that are amplified in human HCC using a mouse hepatoblast model. Our study underscores the potential for clinical translation of results obtained from genetic screens guided by cancer genome analysis.

Tatsuhiro Shibata: Whole Genome Sequencing of Virus- Associated Hepatocellular Carcinoma
More than 15% of human cancers are estimated to be virus-associated. Despite recent successes with anti-viral therapies and vaccination for cancer prevention, the development of effective therapies based on a molecular understanding of pathogenesis is required to control the established cancers. Our group and RIKEN have taken the initiative in Japan's ICGC project that attempts to elucidate whole genetic changes in virus-associated HCC genome. A wide-ranging and detailed analysis of HCV and HBV-associated liver cancer genome would facilitate our understanding of the pathogenesis as well as novel therapeutic targets of HCC.

Catherine Wu: SF3B1 and Other Novel Cacner Genes in Chronic Lymphocytic Leukemia
The somatic genetic basis of chronic lymphocytic leukemia (CLL), a common and clinically heterogenous adult leukemia, remains poorly understood. Through massively parallel DNA sequencing of 91 CLL samples (with matched germline), collected from patients displaying a wide range of characteristics representing the broad clinical spectrum of CLL, we detected tumor-derived point mutations and indels. Understanding the mutational landscape of CLL provides a starting point for systematic analyses to address fundamental questions in CLL, including how mutated genes alter cellular networks and phenotypes, and thereby contribute to disease heterogeneity.

Seishi Ogawa: Genetic Analysis of Myelodysplastic Syndromes and Related Disorders
Myelodysplastic syndromes (MDS) are heterogeneous groups of myeloid neoplasms characterized by multi-lineage cytopenias of varying degrees and transition to acute myeloid leukemia (AML). At present, no curative therapeutics for MDS has been established except for allogeneic hematopoietic stem-cell transplantation, which is not applicable to the majority of the MDS patients due to their higher ages. Thus, to improve the outcome of MDS, it is essential to develop novel therapeutic agents with both high efficacy and low toxicity, and to this goal, the discovery of the key molecules for MDS pathogenesis is of particular importance. To date, a number of gene mutations have been identified and implicated in the pathogenesis of MDS, including NRAS, TP53 , RUNX1, c-CBL, TET2, ASXL1, and more recently, IDH1, IDH2 and EZH2. However, in view of therapeutic targets, our current knowledge of disease causing mutations in MDS is still incomplete. Our results suggested that target-capture resequencing technology is a powerful method to identify new gene mutations that are implicated in the pathogenesis of MDS.

somatic mutation 3: lung cancer

Seiichi Mori: Exploration of Molecular Targets for Ovarian Serous Adenocarcinomas with Poor Prognoses

The hallmark of human cancer is heterogeneity, mirroring the complexity of genetic and epigenetic alterations acquired during oncogenesis. To address this heterogeneity in the context of ovarian serous adenocarcinoma, it is critical to identify tumor subgroups exhibiting more homogeneity. We developed a classification scheme based on patterns of gene expression by microarray analysis of 1,538 samples derived from a combination of 16 independent datasets. The scheme creates a useful framework for developing novel diagnostic and personalized therapeutic strategies.

Yataro Daigo: Variation in TP63 Gene Confers the Risk of Lung Adenocarcinoma in the East Asian Population

Lung cancer comprises various types of histology that are often divided into two main types, non-small cell lung cancer and small cell lung cancer. Each type has different pathophysiological and clinical features, suggesting that their mechanisms of carcinogenesis differ. We conducted a genome-wide association study in a Japanese cohort, with replication in two independent studies in Japanese and Korean individuals, in a total of 2,098 lung adenocarcinoma cases and 11,048 controls. The combined analyses identified two susceptibility loci for lung adenocarcinoma: TERT and TP63. Additional studies on other ethnic populations will also provide detailed information on the genetic etiology and heterogeneity of lung cancer.

Matthew Meyerson: Genomic Analysis of Human Lung Cancer

Our approaches include next-generation sequencing of cancer genomes, exomes, and transcriptomes as well as single nucleotide polymorphisms (SNP) array analysis of copy number. As part of TCGA project, we are performing genomic analysis of lung carcinomas. New results regarding mutations, genomic structure, and classification were presented.

Takashi Takahashi: Metastasis-Suppressing MYBPH as a Novel Transcriptional Target of TTF-1 Lineage-Survival Oncogene in Lung Adenocarcinoma

The vast majority of lung cancerrelated deaths is caused by invasion and metastasis, thus it is crucially important to elucidate the underlying mechanisms. We have proposed that TTF-1 (also known as NKX2-1 and TITF1), a lineage-specific transcription factor required for branching morphogenesis and physiological lung functions. We have recently found that myosin binding protein H (MYBPH) is a transcriptional target of TTF-1, a lineage-survival oncogene in lung adenocarcinoma. Our findings and analysis results strongly suggest that TTF-1 plays multiple roles in the molecular pathogenesis of lung adenocarcinomas, conferring distinct clinicopathologic features in the TTF-1-positive, TRU-type lung adenocarcinomas.

Neil Hayes: Genomic Classification of Tumors of The Lung

At the molecular level, a number of key mutations have been described including mutations of the oncogenes EGFR and KRAS. Despite these and other observations made about the set of tumors of the lung, most patients treated with the disease are not managed in the context of any specific morphologic, clinical, or genomic category, but rather treated for a disease called “non-small cell lung cancer.” The challenges for clinicians include the fact that accurate morphologic classification is challenging in many cases either due to heterogeneity of the tumor or limitations in the amount of tissue provided.

Zemin Zhang: Combined Whole Genome and Transcriptome Analysis of Lung and Liver Cancers

Next-generation sequencing technologies have greatly reduced the barrier for whole genome and transcriptome analyses of human cancer samples. We have analyzed multiple lung and liver tumor samples and cell lines and observed a diverse collection of genomic and transcriptional perturbations near viral integration sites, suggesting that widespread viral integration substantially expands carcinogenic opportunities in HBV-infected individuals.

epigenetics

Takashi Ito: Whole-Genome Bisulfite Sequencing from Subnanogram Quantities of DNA

Whole-genome bisulfite sequencing (WGBS) has enabled methylome analysis at single-base resolution. It is increasingly becoming the method of choice, as the cost of next-generation sequencing steadily decreases. To circumvent bisulfite-induced degradation of sequencing templates, we conceived a novel strategy by simply reversing the order of adaptor-tagging and bisulfite treatment, reasoning that, if adaptor-tagging follows bisulfite treatment, adaptortagged templates would escape destructive conditions and could then be fully used for sequencing. Therefore, this "post-bisulfite adaptor tagging (PBAT)" strategy should, in principle, achieve a wider coverage than current protocols that include bisulfite treatment of adaptor-tagged templates. We expect that the PBAT method will enable various novel applications that would not otherwise be possible, thereby contributing to the rapidly growing field of epigenomics.

Angela Ting: Genome-Wide DNA Methylation Profiling in Colon Cancer

DNA methylation is essential for normal development and is frequently altered in cancers. Our lab developed the MBD-isolated Genome Sequencing, which combines precipitation of methylated DNA by recombinant methyl-CpG binding domain of MBD2 protein and sequencing of the isolated DNA by a massively parallel sequencer, for our studies of DNA methylomes in human cancer. We have recently applied this method to studying a subset of colorectal cancers postulated to have the CpG Island Methylator Phenotype (CIMP), a higher propensity for CpG island DNA methylation. Our observations suggest defects in controlling DNA methylation seeding and spreading in CIMP and serve as an important first step in delineating such molecular mechanisms, which can form the basis of novel cancer therapies.

Yutaka Kondo: Epigenetic Regulatory Network in Plastic Interconvertibility between Tumor-Initiating Cells and Non-Tumor- Initiating Cells

Recent studies have revealed that tumors contain a minor population of tumor-initiating cells, called cancer stem cells (CSCs). These CSCs are considered able to aberrantly differentiate into diverse cell types. Aberrant epigenetic alterations have emerged as common hallmarks of many cancers including glioblastoma. Epigenetic silencing in cancer cells is mediated by at least two mechanisms, namely polycomb repressive complex (PRC)-mediated histone H3 lysine 27 trimethylation (H3K27me3) and DNA methylation-mediated gene silencing. Using glioblastoma-initiating cells (GICs) as a model, we found that biological interconversion between the GICs and differentiated non-GICs is accompanied by the gain or loss of PRC-H3K27me3 marks at the promoters of developmental genes, together with alterations in the subcellular localization of EZH2, a PRC component. Our data provide important new insights into molecular mechanisms for brain tumorigenesis that may be relevant to other neoplasms.

Fuyuki Ishikawa: Highly Conserved Molecular Architectures of Telomeres in Eukaryotes

The end of linear DNA and specific proteins form a specialized chromatin called telomeres. The nucleotide at the DNA end is highly reactive with other DNA ends to undergo reactions such as end-to-end fusion and homologous recombination. When such reactions happen illegitimately, the genome becomes highly unstable, leading to the occurrence of mutations and cancers. Telomeres protect DNA ends from biologically hazardous reaction. It is known that the end of DNA is not completely replicated especially during the lagging strand synthesis. Thus, the two major biological functions of telomeres are the protection and replication of DNA ends.

data analysis

Shumpei Ishikawa: Systematic Profiling of Cancer- Microenvironment Interactome in Cancer Tissue

Cancer-microenvironment interaction is suggested to be of potential significance in cancer progression. Although there are many reports about molecules responsible for these interactions, lack of methods for systematic and quantitative profiling of the whole interactome makes it difficult to compare many different types of interactions and prioritize them for target discovery. Through transcriptome sequencing analysis of cancer xenograft tissue, we differentially assigned

human/cancer- and mouse/environment- derived transcripts and constructed cancer-microenvironment interactome maps integrating several public databases. This approach provides quantitative information about how a particular interaction contributes to the whole cancermicroenvironment interactome. This approach further discovered several molecular targets with extracellular and cell-surface localization, which are relatively easily accessible by bio-molecular drugs.

Joshua Stuart: Predicting the Impact of Mutations in Cancer Using an Integrated Pathway Approach
We have developed a method called MuPPET (for Mutation's Predicted Pathway Effects Tool) that predicts the impact of a mutation based on the inferred differences in upstream and downstream influences. The method is an extension of our previously published PARADIGM tool that infers gene activities from multiple sources of genomics data using the pathway context within which each gene resides. We applied MuPPET to characterize mutations in several of the Cancer Genome Atlas cohorts including glioblastoma multiform, serous ovarian carcinoma, colorectal adenocarcinoma, squamous lung carcinoma, and breast adenocarcinoma. It should augment the analysis of complementary approaches to predict not only drivers from passengers but to further refine the kind of effect the mutations have on tumors.

Satoshi Inoue: Genome-wide Androgen Receptor Signaling in Prostate Cancer
In prostate cancer, androgen receptor (AR) is a critical transcriptional factor. To understand a comprehensives view of AR-mediated gene network in prostate cancer, we utilized chromatin immunoprecipitation (ChIP) on array (ChIP-chip) analysis. We identified AR binding sites (ARBSs) and histone H3 acetylated (AcH3) sites as well as AR-target genes such as UGT1A1, CDH2 and APP using ENCODE array and human chromosome 21 and 22 array. Then we performed genome-wide ChIP-chip/ChIP-seq analyses combined with 5'-cap analysis of gene expression (CAGE) and RNA-seq transcriptome analyses. The integrated highthroughput genome analyses of CAGE and ChIP-chip/ChIP-seq provide useful information for elucidating the AR-mediated transcriptional network that contributes to the development and progression of prostate cancer.

beyond sequencing: translational medicine
Hideyuki Saya: Role of CD44v in Cancer Stem Cells
CD44, a major adhesion molecule for the extracellular matrix, has been implicated in a wide variety of physiological processes, including leukocyte homing and activation, wound healing, and cell migration, as well as in tumor cell invasion and metastasis. It exists in numerous isoforms generated through alternative mRNA splicing. Our findings reveal a novel function for CD44v in protection of cancer stem cells from high levels of ROS in the tumor microenvironment.

Matthew Ellis: Analysis of Luminal-Type Breast Cancer by Massively Parallel Sequencing
Endocrine-therapy resistant HER2 negative luminal-type breast cancer is the commonest cause of breast cancer death but the molecular basis for aggressive clinical behavior is poorly understood. Massively parallel DNA sequencing was applied to samples from two neoadjuvant endocrine trials to define the whole genome sequence of 50 luminal-type breast cancers with an average 30 fold coverage. The mean number of single nucleotide non-silent variants (SNV) and small deletions (indels) was greater in the resistant group (49 per case) than sensitive cases (23) ($p=0.02$). The significantly mutated gene list included PIK3CA, TP53, ATR, RUNX1, MYST3, PRSS8, ZNHIT2 and MAP3K1. These analyses suggest a classification of the disease that is not based on individual gene abnormalities but common cancer pathway activation events that ultimately determine outcome for patients with luminaltype disease.

9. Other Workshop Activities (Reception, Excursion, other Meetings)

Reception and Dinner
The reception was held in the evening of October 24 at Kyokusui banquet room on the third floor of Kyoto Hotel Okura. We deepened exchanges with each other, and both the organizers of US and Japan gave the closing remarks at the end of the reception.
On October 25, we had a garden dinner at the restaurant Ganko Takasegawa Nijyo-en near the Kyoto Hotel Okura.

Excursion
In the afternoon of October 25, we had the excursion to Saiho-ji, sometimes called koke-dera, and the museum of sake breweries. Saiho-ji has the beautiful garden and we extended the time to enjoy walking around the garden. After that, we visited the sake breweries of the old Japanese company Gekkeikan. We learned the detail about sake brewing through the presentation video and the lecture by an expert. During the excursion and the garden party, especially in the bus, the guide named Tomoko intensively explained wide-ranging topics about the history of Kyoto and Japan. The guide got a favorable response by the US participants and also Japanese people.

Other meetings
After closing the workshop session, in the afternoon of October 26, three US participants, Matthew Meyerson, Matthew J. Ellis, and Raju Kucherlapati, were invited to the Tanaka project open symposium for US-Japan cancer research workshop, and gave the presentations. The seminar was supported by the FIRST Program (Funding Program for World-Leading Innovative R&D Science and Technology) run by Nobel laureate Koichi Tanaka.

In October 27, the 164 genome technology committee of JSPS had the 4th kick off meeting at Tokyo Ginza, and the four US and two Japanese participants were invited to the meeting. The details of the meeting and the photo gallery are available at the web site (http://gt164.jpn.org/seminar/20111027_kickoff.html).

10. Comments and Opinions

This meeting was originally scheduled in March 2011, but postponed to October because of the Tohoku earthquake on March 11. The organizers were so grateful that this meeting was finally held under the support of JSPS and NCI. Many of US participants kindly provided continuous support for this meeting and even sent some donation to the victims in the disaster.
As a scientific topic for the workshop, we chose ‘cancer genomics and epigenomics’ because cancer genomics have advanced so rapidly and would require international alliance.
The meeting went very well. All the sessions had active discussions on each presentation. Besides 15 Japanese scientists who gave presentations, we additionally invited 13 scientists as discussants. I believe it must have been a good opportunity for young scientists to experience the top level genomic research.

Here are comments from participants:
“It was a real honor to speak among a group of distinguished researchers. Also, the setting and events were absolutely wonderful. I think it's the best cancer genome meeting I've attended!”
“It was a great privilege to attend to US-Japan Cancer Genomics workshop last week. I immensely enjoyed the talks, food, the city, and the hospitality from the hosts.”
“thank you for being such fantastic hosts. It has truly been one of the most stimulating meetings I've ever attended,”

Finally, Dr. Meyerson, the organizer of US, commented,
“I wanted to thank you again for the incredible scientific meeting and the truly extraordinary

hospitality that you showed all of us in Kyoto. I am only hearing non-stop praise from the American participants, and I think this credit goes entirely to you and your colleagues including of course your colleagues from Shimadzu (Tanaka FIRST project). It was one extraordinary experience after another, and truly a great time both to learn about one another's science and to build friendships.
I appreciate the chance to partner with you in leading this meeting and I hope we will be able to return the favor in the United States in two or three years."

Hopefully, I would like to have another meeting in a few years in US to follow up the progress in this rapidly advancing field.