Cancer Drug Resistance: Mechanisms and Strategies for Its Circumvention

March 14, 2015
International Conference Hall
Aichi Cancer Center
Nagoya, Japan
Aichi Cancer Center 50th Anniversary
International Symposium

Cancer Drug Resistance:
Mechanisms and Strategies for Its Circumvention

Organizing Committee

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March 14, 2015
International Conference Hall
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WELCOME REMARKS

Taira Kinoshita
President, Aichi Cancer Center

On behalf of the organizing committee, it is my honor and pleasure to have the welcome remarks on the Aichi Cancer Center 50th International Symposium. Aichi Cancer Center was established in 1964, when the Tokyo Olympic Games and the New Tokaido Line (Shinkansen) were also opened in the same year. Aichi Cancer Center was the third oldest institution with a cancer hospital and a research institute (the oldest one is the Cancer Institute, and the second is National Cancer Center) in Japan. These three institutions have been acting as representative cancer centers in Japan. In these 50 years, Aichi Cancer Center has worked hard as a top runner of the cancer clinics and research. Its achievements are not only the treasures of Aichi prefecture but what we are proud of.

Last October, the 50th Anniversary Ceremony was held. This symposium is also a part of the 50th Anniversary Events for the next 50 years progress of Aichi Cancer Center. The theme of this Symposium is “Cancer Drug Resistance: Mechanisms and Strategies for Its Circumvention”. This theme was selected because of the considerable progress in the research field of drug resistance, especially of the molecular target drugs. As the molecular target drugs become popular, drug resistance becomes a serious problem recently. In this meaning this theme is really a leading edge topic.

We sincerely hope that this meeting will be an excellent opportunity to learn the current status and future perspectives of molecular target therapy and the fruitful discussion will contribute to overcome a cancer drug resistance.

We also wish that this Symposium will contribute to improve cancer drug therapy itself.

At last, I would like to extend a warmest welcome for all participants, and please enjoy this Symposium and Nagoya!
**INFORMATION FOR PARTICIPANTS**

**On-Site Registration is available at Registration Desk**
The Registration Desk will be opened at the venue.
Location: International Conference Hall, Aichi Cancer Center.
Open hours: 8:30-17:00
Service: On-site registration and general information

Those who have made Advance Registration do not need to register on-site.

**Name Tags**
Please wear your name badge all the times during the symposium for identification and security purposes.

**No Photos, No Audio Recording**
Photos and audio recording are prohibited.

**No Smoking**
Smoking is prohibited in all areas of the campus.

**Cloakroom**
Cloakroom is available for your luggage. Please note that valuables and computers cannot be accepted. We are not responsible for any damage or loss at the cloakroom.
Open hours: 8:30-18:00
**Program**

9:00-9:10  **Opening Remarks:** Taira Kinoshita (Aichi Cancer Center)

**Opening Keynote Lecture**

Chairperson: Masahiro Aoki (Aichi Cancer Center)

9:10-10:10  **Targeting KRAS-induced stemness**

Frank McCormick (University of California, San Francisco, USA)

10:10-10:20  **Coffee Break**

**Session 1. Cancer Heterogeneity and Drug Resistance**

Chairpersons: Hiroji Iwata (Aichi Cancer Center)

Takashi Takahashi (Nagoya University)

10:20-11:00  **Genome-directed therapeutics for endocrine therapy resistant ER+ breast cancer**

Matthew Ellis (Baylor College of Medicine, USA)

11:00-11:35  **Trans-ethnic landscape of hepatocellular carcinoma genomes**

Tatsuhiro Shibata (National Cancer Center, Tokyo, Japan)

11:35-12:00  **Acquired resistance in targeted therapy against driver gene mutation in lung cancer**

Tetsuya Mitsudomi (Kinki University)

12:00-13:00  **Lunch Break**
Session 2. Cancer Stem Cells, Tumor Dormancy, and Drug Resistance

Chairpersons: Yoshitaka Sekido (Aichi Cancer Center)  
Shinsuke Iida (Nagoya City University)

13:00-13:40  Lgr5+ stem cells in epithelial self-renewal and cancer of the stomach and ovary  
Nick Barker (A*STAR Institute of Medical Biology, Singapore)

13:40-14:15  Regulation of cell differentiation by actin dynamics and its application in cancer treatment  
Hideyuki Saya (Keio University)

14:15-14:40  Cancer research on the two noteworthy issues: tetraploidy and primary cilia  
Masaki Inagaki (Aichi Cancer Center)

14:40-15:00  Coffee Break

Session 3. Strategies for Circumvention of Cancer Drug Resistance

Chairpersons:  Toyoaki Hida (Aichi Cancer Center)  
Yutaka Kondo (Nagoya City University)

15:00-15:40  T-cell therapy for cancer using gene modified T-cells and strategies to overcome tumor escape or immunosuppression  
Gianpietro Dotti (Baylor College of Medicine, USA)

15:40-16:15  Loss of autophagy causes metabolic changes through a transcription-factor pathway  
Masaaki Komatsu (Niigata University)

16:15-16:40  Interventional radiology in oncology  
Yasuaki Arai (National Cancer Center, Tokyo, Japan)
Closing Keynote Lecture

Chairperson: Tomohiro Kinoshita (Aichi Cancer Center)

16:40-17:40 Apoptosis and exposure of phosphatidylserine
Shigekazu Nagata (Kyoto University)

17:40-17:50 Closing Remarks: Masahiro Aoki (Aichi Cancer Center)
ABSTRACT
Frank McCormick, Ph.D., F.R.S., D.Sc.

University of California, San Francisco (UCSF), USA

Frank McCormick, Ph.D., F.R.S., D.Sc. (Hon) is the Professor Emeritus of the University of California, San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center. A native of Cambridge, England, Dr. McCormick received his B.Sc. in biochemistry from the University of Birmingham (1972) and his Ph.D. in biochemistry from the University of Cambridge (1975). Postdoctoral fellowships were held at the State University of New York at Stony Brook and in London at the Imperial Cancer Research Fund. He has been a Fellow of the Royal Society since 1996 and a Member of the National Academy of Sciences since 2014. Prior to joining the UCSF faculty, Dr. McCormick pursued cancer-related work at Cetus Corporation (Director of Molecular Biology, 1981-90; Vice President of Research, 1990-91) and Chiron Corporation (Vice President of Research from 1991-92), and in 1992 he founded Onyx Pharmaceuticals and served as its Chief Scientific Officer until 1996. His group discovered and developed sorafenib and palbociclib, and pioneered cancer therapy using oncolytic viruses. His laboratory at UCSF focuses on functions of Ras proteins. More recently, he has taken a leadership role at the Frederick National Laboratory for Cancer Research, overseeing an NCI supported national effort to develop therapies against Ras-driven cancers.
Targeting KRAS-induced stemness

Frank McCormick & Man-Tzu Wang

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Of the three Ras genes, KRAS, NRAS and HRAS, KRAS is by far the major contributor to human cancer, whereas HRAS is rarely activated. In spite of this dramatic difference, KRAS and HRAS interact with the same effectors and are equally potent at transforming cells in culture. However, cells transformed by KRAS have unique properties relative to HRAS: they cause a stem-like phenotype that enables them to grow as spheres in culture, to establish tumors in mice at high efficiency and to resist the effects of multiple chemotherapy and targeted drugs. These effects are due to KRAS’ ability to bind calmodulin, and to inhibit calmodulin-dependent kinase. Low CaM kinase promotes Wnt signaling and initiates a set of programs that confer stemness. Binding of K-Ras to calmodulin is prevented by phosphorylation of K-Ras on serine-181, by protein kinase C. Treatment of mice with a natural product, prostratin, that activates PKC and K-Ras phosphorylation prevents initiation of pancreatic tumors in xenograft models. Part of the “stemness” program initiated by K-Ras involves secretion of the cytokine LIF, an IL-6 family member with a unique role in maintaining stemness. Neutralization of LIF with a monoclonal antibody reduces stemness and sensitizes established pancreas tumors to gemcitabine. We propose that attacking targets in these stem-like pathways offers new opportunities for therapeutic intervention in KRAS-driven cancers.

Key words: K-Ras, Stem cells, calmodulin, PKC
Matthew J. Ellis, Ph.D., M.D.

Baylor College of Medicine, USA

Dr. Matthew James Ellis is a native of the United Kingdom. He completed his medical degree at Queens’ College & School of Clinical Medicine at the University of Cambridge in England, postgraduate clinical training at the Royal College of Physicians in London and gained a Ph.D. at the Royal Postgraduate Medical School and Imperial Cancer Research Fund at the University of London. After a medical oncology fellowship at the Lombardi Cancer Center, Georgetown University, Washington DC, he was an Assistant Professor there until moving to Duke University in 2000 and subsequently to Washington University in St Louis where he served as professor of medicine and section head of breast oncology until 2014. Ellis was recently recruited to Baylor College of Medicine to serve as the Director of the Lester and Sue Smith Breast Center and to hold the C. Kent Osborne Chair of Breast Oncology. Both the McNair Foundation and the Cancer Prevention Research Institute of Texas recently awarded him scholarships. He has been instrumental in developing a Genome Atlas and Therapeutic Road Map for estrogen receptor positive breast cancer by applying genomic techniques to samples accrued through a series of neoadjuvant endocrine therapy trials. Most recently, he has found that metastatic breast tumors harbor mutations and translocations in the estrogen receptor gene that render the tumor resistant to therapies used to block estrogen receptor function. He also pioneered research into the clinical relevance of activating mutations in HER2 and in the deployment of patient-derived xenografts for the pharmacological annotation of breast cancer genomes. He is currently Co-Chair of the translational medicine committee for the NRG cooperative group, co-leader for The Cancer Genome Atlas (TCGA) Breast Project and also serves as a Co-PI for the Clinical Proteomic Tumor Analysis Consortium that endeavors to translate TCGA genomic discoveries into protein-based biomarkers with clinical utility. Dr. Ellis has a successful track record in international clinical and translational research, with recent trainees from Brazil, Chile, Poland and Turkey.

Specialty & Research Field of Interest

Translational Breast Cancer Genomics and Proteomics

Selected Publications


Genome-directed therapeutics for endocrine therapy resistant ER+ breast cancer

Matthew J. Ellis
McNair and CPRIT Scholar, Director and Professor, Lester and Sue Smith Breast Center, Baylor College of Medicine, Houston, TX, USA

As a result of improvements in DNA and RNA sequencing techniques the genomic structure of estrogen receptor positive breast cancer is increasingly well documented, but extracting clinically actionable information from these complex data sets has proved fraught with difficulties. Barriers to progress include the lack of pharmacological hypotheses for novel luminal breast cancer tumor suppressor genes (e.g. MAP3K1, MLL3, SF3B1); 2) a lack of a full understanding of interactions between mutation status, the prognosis of ER+ breast cancer, and the effectiveness of endocrine therapy; 3) an inadequate collection of patient-derived xenograft (PDX) models for luminal breast cancer that fully encompass the heterogeneity of the disease; 4) the logistical barriers of developing adjuvant strategies to exploit rare drivers present in less than 5% of tumor samples; 5) insufficient genomic discovery efforts directed towards samples accrued from patients suffering from endocrine therapy resistant disease progression and 6) an incomplete understanding of how complex somatic genotypes drive the biochemical events responsible for the “hallmarks” of luminal cancer.

To better address these issues, five areas of investigation will be discussed: 1) somatic mutation diagnosis in DNA from primary breast cancer samples from patients treated with adjuvant tamoxifen and followed for over 20 years; 2) DNA and RNA sequencing of samples accrued from patients treated with neoadjuvant endocrine therapy to define the molecular origins of intrinsic aromatase inhibitor resistance and to identify pharmacological hypothesis; 3) efforts to expand and catalog patient-derived xenografts from ER+ breast cancers, including the use of mass spectrometry-based analysis of their proteomes and phosphoproteomes to expand our knowledge of the biochemistry of individual tumors; 4) a functional and pharmacological investigation of mutations in ESR1, including resistance-activating chromosomal translocations, and 5) the development of a neoadjuvant endocrine therapy strategy that identifies patients with intrinsic endocrine therapy resistance within a month of starting treatment so that they can be triaged to mutation-matched investigational treatment.

Tatsuhiro Shibata, M.D., Ph.D.
National Cancer Center, Tokyo, Japan

1984 M.D., University of Tokyo, School of Medicine, Japan
1990 Ph.D., University of Tokyo, School of Medicine, Graduating School (Pathology), Japan
1995 Postdoctoral fellow, University of California, Irvine, Developmental Biology Center, USA
2005 Project Leader, Cancer Genomics Project, National Cancer Center Research Institute, Tokyo, Japan
2010-present Chief, Division of Cancer Genomics, National Cancer Center Research Institute, Tokyo, Japan
2014 Professor, Laboratory of Molecular Medicine, Human Genome Center, The Institute of Medical Science, University of Tokyo, Japan

Specialty & Research Field of Interest
Cancer Genomics, Tumor Pathology, Informatics

Selected Publications
Trans-ethnic landscape of hepatocellular carcinoma genomics

Tatsuhiro Shibata1, 2, David A. Wheeler3, Hiroyuki Aburatani4

1Division of Cancer Genomics, National Cancer Center, Tokyo, Japan; 2Laboratory of Molecular Medicine, The Institute of Medical Science, 4Genome Science Division, Research Center for Advanced Science and Technology, The University of Tokyo, Tokyo, Japan; 3Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX, USA

Multiple etiological factors (hepatitis virus infection, alcohol, obesity etc) are associated with the occurrence of hepatocellular carcinoma (HCC) and their contributions diverse among ethnicity. To elucidate genetic diversities in HCC genomes with regards to ethnic and epidemiological differences, we have conducted the trans-ethnic cancer genome research under the umbrella of the International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA).

We performed whole exome sequencing of 514 pairs of HCC, which include different ethnic populations (424 cases from the Japanese cohort and 90 from the US cohort) with various etiological backgrounds. Furthermore, whole exome data of 105 HCC cases from TCGA was included in the mutation signature analysis. Mutation call algorithms of three collaborating genome centers (National Cancer Center, Tokyo, Research Center for Advanced Science and Technology in the University of Tokyo, and Baylor College of Medicine, Houston) were adjusted and validated by the Ion Proton sequencer. In total, more than 100,000 somatic mutations were collected, and their signatures were significantly associated with ethnicity and gender, but not with the hepatitis virus status. In addition to TP53, WNT, and SWI/SNF pathways, aberrant activation of the TERT pathway by various mechanisms (promoter/coding mutations, gene amplification and viral genome integration) was found to play a central role in hepatocarcinogenesis.

Aggregation of the large cancer genome data by ICGC and TCGA has rapidly progressed. In addition to the cross-tumor analysis (Pan-Cancer study), population-based meta-cancer genome analysis would provide us unique and diverse landscapes of the cancer genomes on this planet.
Tetsuya Mitsudomi, M.D., Ph. D.

Kinki University

1980 M.D., Kyushu University, School of Medicine, Japan
1986 Ph.D., Kyushu University, Graduate School of Medical Science.
1986-1988 Department of Surgery, Matsuyama Red Cross Hospital
1988-1989 Instructor, Department of Surgery II, Kyushu University
1989-1991 Postdoctoral Fellow, NCI-Navy Medical Oncology Branch, National Cancer Institute, National Institute of Health
1991-1994 Assistant professor, Department of Surgery II, University of Occupational and Environmental Health, Japan
1994-1995 Assistant professor, Department of Surgery II, Kyushu University
1995-2012 Chief, Department of Thoracic Surgery, Aichi Cancer Center Hospital
2012-present Professor, Department of Surgery, Kinki University Faculty of Medicine

Specialty and Research Field of Interest
Thoracic Surgery, Molecular Biology of Lung Cancer, Molecular Targeted Therapy

Selected Publications
Acquired resistance in targeted therapy against driver gene mutation in lung cancer

Tetsuya Mitsudomi¹, Kenichi Suda¹, Hiroshi Mizuuchi¹, Yoshihisa Kobayashi¹, Kazuto Nishio², Yasushi Yatabe³

Department of Thoracic Surgery¹ and Genome Biology², Kinki University Faculty of Medicine, Department of Pathology and Molecular Diagnostics³, Aichi Cancer Center Hospital, Japan

Discovery of activating mutation of the EGFR gene in adenocarcinoma of the lung in 2004 opened the era of personalized therapy in thoracic oncology. These tumors are highly dependent on the EGFR pathway and EGFR-tyrosine kinase inhibitors (TKI) significantly prolong progression free survival in these patients compared with chemotherapy. In 2007, EML4-ALK translocation was found and these tumors are very sensitive to ALK-TKI. However, acquired resistance inevitably develops usually after a median of 10 months. The mechanisms for this resistance can be classified into 1) target gene alterations (T790M mutation in EGFR-TKI or L1196M and other mutations in ALK, 2) activation of additional kinases (e.g., MET, HER2 for EGFR, and KIT, EGFR, SRC for ALK) bypassing the inhibition of the original kinases, and 3) other mechanisms including epithelial-mesenchymal transition, small cell lung cancer transformation, etc.

To overcome T790M gatekeeper mutations, so-called third generation EGFR inhibitors that selectively inhibit EGFR-T790M while sparing the wild-type EGFR are being actively developed. Likewise, ALK-TKIs of a newer generation are active at least for some of the secondary mutations found in crizotinib-resistant tumors. Tumor resistance caused by the bypass track can be coped with by combination of the inhibitors for the original kinase and the bypassing kinases.

However, even with these strategies, cancer cells are smart enough to escape from the therapy using other mechanisms. Heterogeneities in terms of resistant mechanisms within a single patient become evident when specific therapeutic pressure persists. Therefore, we also need to have armamentarium that utilizes other mechanisms to cure lung cancer. Recent advances of immunotherapy targeting PD-1/PD-L1 appear attractive in this respect. These mechanism-driven therapeutic approaches will convert this fatal disease into a more chronic disorder, and eventually into a curable disease with the least patient burdens.

Nick Barker, Ph.D.
A*STAR Institute of Medical Biology, Singapore

1995-2001 Postdoctoral Fellow, University Medical Center Utrecht, the Netherlands
2001-2005 Senior Research Scientist, Semaia Pharmaceuticals BV, the Netherlands
2006-2010 Staff Scientist, Hubrecht Institute, Utrecht, the Netherlands
2010-present Senior Principal Investigator, Institute of Medical Biology, Singapore & Chair of Tissue Regeneration (Visiting) University of Edinburgh, UK

Specialty & Research Field of Interest
Epithelial Stem Cells, Tissue Engineering, Cancer

Selected Publications
Lgr5+ stem cells in epithelial self-renewal and cancer of the stomach and ovary

Nick Barker, Marc Leushacke, Annie Ng

A*STAR Institute of Medical Biology, Singapore

The availability of robust cell-surface markers for identifying and isolating adult stem cells is essential for studying both their normal in-vivo function during tissue renewal and for evaluating their contribution to cancer. Lgr5, a Wnt target gene expressing a 7-TM receptor that functions as facultative component of the Wnt receptor complex, has been shown to selectively mark stem cells in a range of rapidly renewing tissues, including the small intestine, colon, stomach, hair follicle and developing kidney. Clonal fate mapping employing the stem cell-specific Lgr5-CreERT2 line has been used to further dissect how these adult stem cell pools maintain tissue homeostasis and contribute to tissue repair following damage. Additionally, targeted in-vivo mutation of the Lgr5+ve adult stem cell pools using the same Lgr5-CreERT2 model has been used to determine the contribution of stem cells to tumor initiation and progression in various epithelia. A summary of the latest findings in the stomach and ovary will be presented here.

Hideyuki Saya, M.D., Ph.D.

Keio University

1981 M.D., Kobe University, School of Medicine, Kobe, Japan
1987 Ph.D., Kobe University, Graduate School of Medical Science, Kobe, Japan
1987-1988 Postdoctoral Fellow, University of California, San Francisco, CA, USA
1988-1994 Assistant Professor, The University of Texas, M. D. Anderson Cancer Center, Houston, TX, USA
1994-2006 Professor, Kumamoto University School of Medicine, Kumamoto, Japan
2007-present Professor, Keio University School of Medicine, Tokyo, Japan

Specialty & Research Field of Interest
Cancer Stem Cell, Cell Differentiation

Selected Publications
Regulation of cell differentiation by actin dynamics and its application in cancer treatment

Hideyuki Saya & Hiroyuki Nobuse

Division of Gene Regulation, Institute for Advanced Medical Research, School of Medicine, Keio University, Tokyo, Japan

Differentiation status is strongly associated with the behavior of cancer cells. Therefore, changes in the cellular context, which regulates the differentiation potential, may serve in novel therapeutic strategies in treating cancers.

We have established a mouse osteosarcoma (OS) model through overexpression of c-MYC in bone marrow stromal cells (BMSCs) derived from Ink4a/Arf (-/-) mice. In this model, we found that the loss of adipogenic potential was an essential event for OS development. Therefore, our understanding of regulatory mechanisms of adipocyte differentiation would greatly contribute to control OS tumorigenesis.

Adipocytic differentiation is accompanied by the adoption of a rounded cell shape that is characteristic of mature adipocytes. Cell shape is determined primarily by the actin cytoskeleton. We have recently found a novel regulatory mechanism of adipocyte differentiation, in which regulation of transcriptional coactivator MKL1 by actin cytoskeleton dynamics drives adipocyte differentiation mediated by PPARγ, a master transcriptional regulator of adipogenesis. Accordingly, adipocyte differentiation can be induced by the disruption of actin stress fibers through down-regulation of RhoA-ROCK signaling. Based on this concept, we attempted to induce adipocyte differentiation in OS cells, which resulted in a significant suppression of tumorigenesis. Induction of trans-differentiation in cancer stem cells by regulating actin cytoskeleton dynamics is a potential approach for some tumor types.
Masaki Inagaki, M.D., Ph.D.
Aichi Cancer Center Research Institute

1982 M.D., Faculty of Medicine, Mie University, Japan
1986 Ph.D., Faculty of Medicine, Mie University, Japan
1986-1991 Researcher, Laboratory of Experimental Radiology, Aichi Cancer Center Research Institute, Japan
1991-1992 Senior Researcher, Laboratory of Experimental Radiology, Aichi Cancer Center Research Institute
1992-1996 Head (Chief), Department of Neurophysiology, Tokyo Metropolitan Institute of Gerontology, Japan
1996-present Chief, Division of Biochemistry, Aichi Cancer Center Research Institute, Japan
2007-present Professor, Department of Cellular Oncology, Graduate School of Medicine, Nagoya University, Japan

Specialty and Research Field of Interest:
Biochemistry, Cell Biology, Oncology

Selected Publications:
Cancer research on the two noteworthy issues: tetraploidy and primary cilia

Masaki Inagaki

Division of Biochemistry, Aichi Cancer Center Research Institute and Department of Cellular Oncology, Nagoya University Graduate School of Medicine, Japan

Tetraploidy, a state in which cells have doubled chromosomal sets, is observed in ~20% solid tumors and considered to frequently precede aneuploidy in carcinogenesis. Tetraploidy is also detected during tissue differentiation and aging process. We generated knock-in mice featuring vimentin with mitotic phosphorylation-defective mutations to impair cytokinesis. Homozygotic (VIM<sup>SA/SA</sup>) mice presented with microophthalmia and cataracts, in which lens epithelial cells exhibited binucleation and aneuploidy, along with premature aging. We further analyzed the ability to repair wounds in the skin of VIM<sup>SA/SA</sup> mice, and found that some subcutaneous tetraploid fibroblasts caused by cytokinetic failure enter a new cell cycle and then develop into aneuploid fibroblasts in vivo, which promotes premature aging. We suggest that tetraploidy without the genetic alteration of cancer-related genes may be associated with premature aging rather than carcinogenesis.

Non-motile primary cilia are microtubule-based sensory organelles that regulate a number of signaling pathways during development and tissue homeostasis. Tumor cells are known to often lack primary cilia, but whether their loss is directly linked to tumorigenesis is completely unclear. We have recently found that ubiquitin-proteasome machinery removes trichoplein, a negative regulator of ciliogenesis, from mother centrioles and thereby causes Aurora-A inactivation, leading to ciliogenesis. We have identified KCTD17 as a substrate-adaptor for Cul3-RING E3 ligases (CRL3s) that polyubiquitylates trichoplein. Depletion of KCTD17 specifically arrests ciliogenesis at the initial step of axoneme (ciliary microtubule doublet) extension through aberrant trichoplein-Aurora-A activity. We would like to discuss the relationship between primary cilia and cancer stem cells, which may be implicated in drug resistance against cancer chemotherapy.
Session 3.
Strategies for Circumvention of Cancer Drug Resistance

Gianpietro Dotti, M.D., Ph. D.
Baylor College of Medicine, USA

1989  MD degree, University of Milan, Milan, Italy
1995  Hematology degree, University of Parma, Parma, Italy
1996-1999  Research Fellowship, Department of Hematology, Bergamo, Italy
1999-2000  Post-doctoral fellowship, CAGT, Baylor College of Medicine, Houston, Texas
2000-2001  Assistant professor, Department of Hematology, Bergamo, Italy
2002-2005  Instructor, CAGT, Baylor College of Medicine, Houston, Texas
2005-2007  Assistant professor, CAGT, Baylor College of Medicine, Houston, Texas
2007-2014  Associate professor, CAGT, Baylor College of Medicine, Houston, Texas
2014  Professor of Medicine with tenure, CAGT, Baylor College of Medicine, Houston, Texas

Specialty and Research Field of Interest
Hematology, Cancer Immunotherapy, Gene Therapy

Selected publications
T-cell therapy for cancer using gene modified T cells and strategies to overcome tumor escape or immunosuppression

Gianpietro Dotti

Center for Cell and Gene Therapy, Baylor Colledge of Medicine, Houston, TX, USA

T-lymphocyte-based treatments have enormous potential in cancer patients. Over the past decade, T cells modified to express chimeric antigen receptors (CARs) have had clinical success in B-lymphocyte derived malignancies. In the specific context of CAR-T cells therapies for B-cell malignancies we developed at Baylor a strategy aimed at achieving antitumor effects, but limiting the prolonged B-cell aplasia caused the infusion of CD19-CAR-specific T cells. We are currently targeting the κ-light chain of human immunoglobulins expressed on the cell surface of κ⁺ lymphoma cells in an effort to target lymphomas cells but spare normal λ⁺B-lymphocytes. An update of the clinical trial currently ongoing will be presented.

In contrast to B-cell malignancies, the clinical efficacy of CAR-T cells remains limited in solid tumors. This unfavorable outcome could be due to the insufficient migration of the infused T cells to the tumor site and to the immunosuppressive characteristics of the tumor environment, which inhibit the effector function and proliferation of those few T cells that do reach the tumor. We recently found that tumor-specific engineered T lymphocytes expanded ex vivo for adoptive T-cell therapy are defective in their capacity to degrade one critical component of the extracellular matrix. We also found that this defect can be however repaired by the ectopic expression of the enzyme heparanase. We also found that armed oncolytic viruses expressing RANTES and IL-15 can be used to favor the migration of CAR-T cells at the tumor site and promote the survival of CAR-T cells within the hostile tumor environment.

Masaaki Komatsu, Ph.D.
Niigata University

1995  B.A., Meiji University, Japan
1997  M.S., University of Tsukuba, Japan
2001  Ph.D., Juntendo University School of Medicine, Japan
2001-2002  Postdoctoral Fellow, Juntendo University School of Medicine, Japan
2002-2004  Postdoctoral Fellow, Tokyo Metropolitan Institute of Medical Science, Japan
2004-2007  Assistant professor, Juntendo University School of Medicine, Japan
2007-2008  Associate professor, Juntendo University School of Medicine, Japan
2008-2010  Principle Investigator, Tokyo Metropolitan Institute of Medical Science, Japan
2010-2014  Project Leader, Tokyo Metropolitan Institute of Medical Science, Japan
2014-present  Professor, School of Medicine, Niigata University, Japan

Specialty & Research Field of Interest
Biochemistry, Cell Biology, Protein Metabolism, Autophagy

Selected Publications
1. Ichimura, Y. et al. Phosphorylation of p62 activates the Keap1-Nrf2 pathway during selective autophagy. Mol Cell 51: 618 (2013)
Loss of autophagy causes metabolic changes through a transcription-factor pathway

Masaaki Komatsu

Department of Biochemistry, School of Medicine, Niigata University, Japan

Autophagy provides starved cells with amino acids, free fatty acids, and glucose for new protein synthesis energy production; autophagy also controls the quality and quantity of organelles such as mitochondria. Therefore, it is plausible that autophagy might be integrated with metabolic pathways. Indeed, suppression of autophagy causes myopathy, tumorigenesis, and metabolic disorders in mice and humans. However, the metabolic changes associated with deficiencies in autophagy are largely unknown. Furthermore, it remains unclear whether the major predisposing factor for the aforementioned diseases in the absence of normal autophagic activity is a simple deficit in supply of molecular building blocks, dysregulation of mitochondrial homeostasis, or some other cause. Here, we show that deficiencies in autophagy are associated with rearrangement of glucose and glutamine metabolism via a transcriptional regulatory mechanism.
Yasuaki Arai, M.D., Ph. D.
National Cancer Center Hospital, Tokyo, Japan

1979         M.D., Jikei University School of Medicine
1979         Residency, Internal Medicine, Tokyo National 2nd-hospital
1984         Staff, Diagnostic & Interventional Radiology, Aichi Cancer Center
1990         Doctor of Medical Science, Nagoya City University
             Graduate School of Medicine
1997         Chair, Diagnostic & Interventional Radiology, Aichi Cancer Center
2004         Chair, Diagnostic Radiology, National Cancer Center Hospital
2010         Deputy Director of the Hospital (Safety Management)
2012-present  Director, National Cancer Center Hospital
             (2014-present  President of Japanese Society of Interventional Radiology (JSIR))

Specialty and Research Field of Interest
Oncology, Interventional Radiology, Clinical Trial

Selected Publications
Interventional radiology in oncology

Yasuaki Arai

National Cancer Center Hospital, Tokyo, Japan

IR is a minimally invasive treatment modality in which small devices are percutaneously inserted into a patient’s body with minimum incision under image guidance.

There are two routes to access to the target lesion; trans-canal and direct puncture. The typical type of trans-canal approach is transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC), in which the feeding arteries are occluded with anticancer drug to kill tumor cells with stasis of blood flow. TACE could obtain total necrosis if the HCC tumor is hyper-vascular and less than 5cm in diameter. In a decade, microspheres with drug eluting and Yttrium-90 have been developed to treat HCCs with various stages. The other approach with percutaneous direct puncture is thermal ablation, such as radiofrequency ablation (RFA), microwave ablation, cryoablation for tumors in the liver, kidney, lung, etc. TACE and RFA are established as the standard treatment for early and intermediate stage HCC.

Moreover, there are novel IR treatments; high-intensity focused ultrasounds (HIFU) and irreversible electroporation (IRE). HIFU kills tumor cells with thermal ablation by high-intensity focused ultrasounds without needle puncture. IRE kills tumor cells with membrane with electroporation by high voltage pulse without the destruction of anatomical structures.

IR can be complementary with other treatment modalities because the mechanism of anti-tumor effect in IR is completely different from that of medical and radiation therapy.

On the other hand, IR is difficult to establish evidence by clinical trials, because the clinical results in IR greatly depend on the operator’s skills and equipment. We started to conduct many multi-institutional clinical trials in Japan more earlier than western countries, however, still it is very challenging for us to establish IR as one of the standard treatments in the oncology field.
Shigekazu Nagata, Ph.D
Kyoto University

1977 Ph.D., The University of Tokyo, Graduates School of Science, JAPAN
1977-1981 Postdoctoral Fellow, Institute of Molecular Biology I, University of Zürich, Switzerland.
1982-1987 Assistant Professor at the Institute of Medical Science, University of Tokyo, Japan
1987-1998 Head, Department of Molecular Biology, Osaka Bioscience Institute, Suita, Japan
1995-2007 Professor, Department of Genetics, Osaka University Medical School, Suita, Japan
2007-present Professor, Department of Medical Chemistry Graduate School of Medicine, Kyoto University, Japan

Specialty and Research Field of Interest
Biochemistry, Molecular Biology, Cell Biology,

Selected Publications
Apoptosis and exposure of phosphatidylserine

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Apoptotic cells are swiftly engulfed by macrophages. If this process does not occur properly, materials released from dead cells activate the immune system, leading to systemic lupus erythematosus-type autoimmune disease. Phospholipids in plasma membranes are asymmetrically distributed between inner and outer leaflets, and phosphatidylserine (PtdSer) is exclusively localized in the inner leaflet. The asymmetrical distribution of phospholipids is maintained by an ATP-dependent phospholipid translocase or flippase. When cells undergo apoptosis, or platelets are activated, the asymmetrical distribution of phospholipids is disrupted by scramblase, leading to PtdSer-exposure. The PtdSer exposed on dead cell surface is recognized by macrophages as an “eat me” signal, while PtdSer on activated platelets provides the scaffold for clotting factors. We recently identified two membrane proteins (TMEM16F and Xkr8) as phospholipid scramblases, and a pair of membrane proteins (ATP11C and CDC50A) as a flippase. TMEM16F, a protein with 8 transmembrane regions, requires Ca\(^{2+}\) to support phospholipid scrambling, and plays an essential role in the PtdSer-exposure in activated platelets. Xkr8 is a protein carrying 6 transmembrane regions, and caspases cleave off its C-terminal tail to promote the scramblase activity. ATP11C is a P4-type ATPase at plasma membrane, and CDC50A works as a chaperone to transport ATP11C from endoplasmic reticulum to plasma membranes. ATP11C translocates PtdSer from outer to inner leaflets of plasma membranes in an ATP-dependent manner. When cells undergo apoptosis, ATP11C is inactivated by caspase-mediated cleavage, indicating that in addition to the caspase-mediated activation of scramblase, inactivation of flippase is required to expose PtdSer during apoptosis. Lymphoma cells that lack the flippase constitutively expose PtdSer, are engulfed by macrophages, and can not develop tumors in nude mice. These results indicate that PtdSer is necessary and sufficient as an “eat me” signal to be recognized by macrophages, and the PtdSer-expressing tumor cells can be killed by being engulfed by macrophages.